FOGSI FOCUS

OCTOBER 2018

Women Health Wellness & EmpoWerment

Womb to Renaissance

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FOGSI FOCUS

FOGSI Focus is a regular and update series of review articles on current developments in the field of Obstetrics and Gynaecology by National and International team of academicians who are experts in their specialities.

This edition is totally dedicated to the Women of India and deals with Women Health, Wellness and Women Empowerment. Major Social, Spiritual, Legal, Medical, Gynaecological and Health aspects have been very well covered. It has brief yet comprehensive knowledge and opinion on a wide range of subjects.

Extremely well written, easy to read and informative.
A must for all clinicians involved in Women Health Care.

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FEDERATION OF OBSTETRICS & GYNECOLOGICAL SOCIETIES OF INDIA

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From the desk of Chief-Editor

Dr Meera Agnihotri

In the capacity of Organizing Chairperson, it is a matter of proud privilege and great honour for me, to be bestowed upon with the honour of holding this prestigious FOGSI International Conference **WWWCON 2018 (Women Health, Wellness for Women Empowerment).** We are overwhelmed because it is for the first time our President of India Honorable Shri Ramnath Kovind Ji has very kindly consented to bless and inaugurate the Congress. We are very grateful to him for sparing his precious time. To commemorate this prestigious event the book, FOGSI FOCUS on Women Empowerment is prepared for one and all.

The issue of women empowerment is a global concern and one of the prime agendas of WHO (World Health Organization) and it is one of the greatest concern of our country. The global scenario of women health wellness is well-known; it needs a U-Turn to empower our women with the different health agendas including Medical Health, Maternal Diet & Nutrition, Empowering Women with Motherhood, Spiritual Evolution, making them disease free, Vaccination against Preventable Diseases, Improving Reproductive Health of Women and many more.

In India although a number of policies are provided by Central & State Government and many more are in pipe line will be met, yet Women in our country are still looked upon as 2nd grade in the man dominated (patriarchal society).

SIX "S" ARE BASICALLY NEEDED TO EMPOWER THE WOMEN

1) Shiksha = Education
2) Swasthya = Health
3) Swavlamban = Self Reliance
4) Samajik Nyay = Justice
5) Samvedan = Sensitivity
6) Samta = Equality

Social obstetrics is one of the most important 7th tool empowering women. It can change the basic concept of all the SIX "S" needed to Empower Women. This book covers each and every aspect right from Womb to Tomb. The journey of humanity in Womb starts right from two different cells ovum from Mother and sperm from Father, zygote implanting in utero and the transformation into a

complete human being in short span of nine months is most fascinating. Fetus is our second patient who is privileged with "Right of Unborn Child". It is entirely the jurisdiction of obstetricians to protect the unborn legally, Medically, Socially and Spiritually.

Therefore, The face of antenatal care has undergone a revolutionary change and a paradigm shift in the last couple of decades with the advent of Fetal Medicine. Obstetrics has now diversified into a dual care pathway addressing the needs to mother and the fetus as two different patients rather than a common entity. It needs further Empowering Mother.

In this book efforts are made to include and discuss the latest concepts in Health issues related to Women in an attempt to empower them as it carries all the issue of obstetrics gynecology including social obstetrics.

It's indeed a great honor and proud privilege for me as Organizing Chairperson, to extend a warm welcome to the delegates, distinguished faculty, dignitaries and all the participants to National Conference of **WWWCON 2018 (Women Health, Wellness for Women Empowerment)** at prestigious GSVM Medical College Kanpur who have come from far and wide.

Our team extends special thanks with the welcome applause to Prof Jaideep Malhotra, President FOGSI, who is the chief architect and great visionary for framing the blue print of this academic extra bonanza without her dreams this Congress would have not seen today's dawn. We extend a hearty welcome to you Madam!

Dr Meera Agnihotri
(M.S. DGO, MAMS, FICOG, FICS, FICMCH)
Prof. & Head Obst. & Gynae. GSVM Medical College, Kanpur (Ex)
Professor Indian College of Maternal and Child (IC MCH)
Director, Institute of Infertility Management (IIM), KANPUR
Chairperson NOWW, National Organization Of Women & Family Welfare
Chairperson Ethical Committee State Medical Colleges

From the desk of Editors...

Dr. Rita Mittal

Dr. Renu Tandon

WOMAN-THE ANCHOR OF LIFE

Woman is the Goddess of Knowledge SARASWATI, the GODDESS of Wealth LUXMI and the Goddess of POWER the Adishakti JAGDAMBA. The creation and purpose of the world without Women is beyond imagination. Woman is the most beautiful creation of GOD, it is the masterpiece. Women are magical, mystical and spiritual loving beings whose true value is not celebrated in the society. In fact their delicacy and sacrifices are often perceived as their weaknesses.

She is the nucleus of the whole family a sister, daughter, wife and above all a divine mother and plays a pivotal role everywhere. It is very unfortunate that, even though, our civilization has progressed immensely, the attitude towards women in INDIA is still a matter of concern. They are bound by a lot of superstitions beliefs and social customs.

A woman is a full circle, within her is the power to create, nurture and transform. Someone has rightly described a woman.

”A woman has a strength that amazes men. She can hold heavy burdens. She smiles when she actually feels like screaming, she sings when she feels like crying, she cries in happiness. She stands up against injustice. She gives herself wholly so that her family can thrive and her love is unconditional. There is one thing innate in her nature, she forgets what she is worth..... ”

“Women's empowerment is the process in which women elaborate and recreate what it is that they can be, do and accomplish in a circumstance that they previously were denied”. Entire nations, businesses, communities and groups can benefit from the implementation of programs and policies that adopt the notion of women empowerment. It is by this tool of Women Empowerment that we can make her proud and feel important and thus change the future of our families and the NATION.

It is we FOGSIANS only who can accomplish this project as we are in so much contact with these women. In this FOGSI FOCUS we have tried to bring together authors who count among the best minds in India. This compilation is a step forward to achieve our goals. We hope you are provoked and enthralled by it, but most of all enriched by it.

empowered women,
empower women.

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Message from President FOGSI

Dear Friends and Colleagues,

Greetings...

More than 70 years after Independence and being the biggest Democracy in the World, with fastest growing Economy, what is the status of the women of our country? A country, where from times immemorial women were always on a pedestal, respected, worshipped and always held high esteem, when did we reach where we are today? Who is responsible and how can we resurrect it, needs a nation wide debate and my heartiest congratulations to Team Kanpur especially Prof. Meera Agnihotri for taking a lead and bringing to a National platform for discussion on the theme given by the President FOGSI.

"Give HER Wings and let HER Soar" and where HER stands for "Health, Empowerment and Respect" for the women of our country to be provided by QED (Quality, Ethics and Dignity) by us.

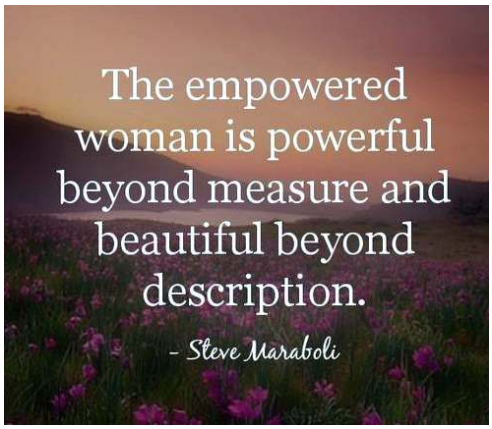
"We cannot succeed, when half of us are held back" Malala Yousafzai

No Family, Organisation or Nation can develop, if half of its population is held back, Womens' contribution to mankind cannot be measured and calculated, their contributions are indispensable and only thing required is to acknowledge them, support them and empower them and see the pace they set for development.

"Women are the largest untapped reservoir of talent in the world" Hillary Clinton

This Conference is unique and is touching upon the various issues related to women empowerment that will show us the way to move forward and hopefully we will live to see a Nation of women where each one is empowered and each one is beautiful as Steve Maraboli puts it,

"The Empowered woman is powerful beyond measure and beautiful beyond description"



I wish the conference all the best and eagerly looking forward to being with you all and the President of India Shri Ram Nath Kovind Ji.

Prof Jaideep Malhotra

MD, FICS, FICOG, FMAS, FRCOG, FRCPI

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INDEX

WOMEN EMPOWERMENT

LEGAL ISSUES

REPRODUCTIVE HEALTH

SOCIAL AND SPIRITUAL ISSUES

PREVENTIVE CARE

GENERAL HEALTH

INFERTILITY

DEDICATED TO

THE WOMEN OF INDIA

ACKNOWLEDGMENTS

There are many wonderful people to be thanked for helping us with this compilation 'FOGSI FOCUS'. Thanks to the Hony President of India Shri Ram Nath Kovind Ji who has very kindly accepted to grace and bless the great event. January 22, 2019 “Women Empowerment Award “was presented to Prof. Meera Agnihotri and then the organising Committee decided to assign the first International Conference Summit to the Awardee and the KOGS.

This was the sowing of the seed of this WWWCON 2018 and a platform to increase the Power of women. Our regards and love to the dynamic and enthusiastic President FOGSI Dr. Jaipdeep Malhotra who has undertaken this project on the theme of Women Health, Women Wellness and Women Empowerment, the dream of our Prime Minister Sri Narendra Modi Ji . Prof. Meera Agnihotri needs special appreciation for fulfilling this project and her diligent and painstaking assistance throughout the editing process and guiding the manuscript to the form in which it is before you all.

In this endeavour Dr. Renu Tandon my hard working partner was an invaluable support, digging up the documents and the academic material from all the contributors. Three tireless friends, Dr. Shubha Agarwal, Dr. Amita Tewari and Dr Manisha Bajpai kept themselves involved in the preparation of the manuscript including cross checking its pages. Thanks to the organisimg team of this WWWCON 2018 who took me into undertaking this project - a decision I made to accept rashly without fully realizing how much work it would involve.

Not the least, my heartfelt thanks and gratitude to all the learned authors for their unfailing courtesy, ideas and the substance of the book and bestowing upon us this great knowledge. The thought of documentation of the sweet memories of this great Conference initiated us to bring out this book FOGSI FOCUS for the glory of our biggest association FOGSI. Thanks to the staff of the Kratika Printers who whole heartedly supported us at any hour of the day and my family members for being so cooperative and backing me up.

Dr. Rita Mittal

Why Women Empowerment ?

Prof. Jaideep Malhotra
& Ms. Simran Bindra

- **Empowerment of women is essentially the process of upliftment of economic, social and political status of women, the traditionally underprivileged ones, in the society. It involves the building up of a society wherein in women can breathe without the fear of oppression, exploitation, apprehension, discrimination and the general feeling of persecution which goes with being a woman in a traditionally male dominated structure.**
- **We have to relate empowerment at three levels: empowerment on the individual, group, and societal/ community- level and the interaction between these.**
- **Pandit Jawaharlal Nehru first Prime Minister of India once remarked, "To awaken the people, it is women who must be awakened; once she is on the move, the family moves, the village moves and the nation moves". So there is a greater need of bringing women into mainstream of development of India.**

Kofi Annan, the former Secretary-General of the United Nations, once stated: **"There is no tool for development more effective than the empowerment of women."** Indian women are treading toward empowerment to make conscious, progressive decisions for themselves.

Is the above statement true? How many women in our country with a population of more than 7 Billion are making informed decisions for themselves??

Women in Indian society have come a long way from the days of being worshipped as goddesses to being molested and harassed - gruesome domestic violence cases, acid attacks and rapes.

A gradual change is now visible in modern-day India, and this can be seen in large cities. Women now have diverse professions as doctors, engineers, entrepreneurs, pilots, taxi drivers and police officers. They have found employment in fields that have been traditionally considered male-dominated.

Only 39% of women are formally employed in India. According to the gender diversity benchmark 2011, India has one of the world's lowest female employment rates. The lack of female participation in the workforce results in a "cultural" vicious cycle. It has an adverse economic impact, dampening productivity and growth as fewer young girls aspire to full time work because there are less female role models they can take the lead from.

Geeta Rao Gupta, the president of the International Centre for Research on women, offers a solution to this, saying, "you can trigger social and cultural change in a woman's status by giving her increased economic opportunities."

Empowerment of women is essentially the process of upliftment of economic, social and political status of women, the traditionally underprivileged ones, in the society. It involves the building up of a society wherein in women can breathe without the fear of oppression, exploitation, apprehension, discrimination and the general feeling of persecution which goes with being a woman in a traditionally male dominated structure.

Different Levels of Empowerment in line with most theorists on empowerment one has to view empowerment as taking place on different levels and that change on all levels is necessary if the empowerment of women is really to occur. We have to relate empowerment at three levels: empowerment on the individual, group, and societal/ community- level and the interaction between these. The **individual level** deals with individual women's abilities to take control over their lives, their perceptions about their own value and abilities, their abilities to identify a goal and work towards this goal. The **group level** deals with the collective action and sense of agency that woman experience together, in a group. The **societal level** deals with the permissiveness of the political and social climate, the societal norms and the public discourse on what is possible and impossible for women to do, how women should behave etc. The different levels are seen as interconnected and mutually reinforcing, e.g. when empowerment on individual level occurs, this will have effect on the group and societal level. Women who are empowered on an individual level will most likely go on and affect the other levels. Empowerment on a group level e.g. women organizing around a particular need is likely to have effect on the individual empowerment of women in the form of increased self-esteem and sense of agency.

Indian women are discriminated and marginalized at every level of the society whether it is social participation, political participation, economic participation, access to education, and also reproductive healthcare. Women are found to be economically very poor all over the India. A few women are engaged in services and other activities. So, they need economic power to stand on their own legs at par with men. On the other hand, it has been observed that women are found to be less literate than men. According to 2001 census, rate of literacy among men in India is found to be 76% whereas it is only 54% among women. Thus, increasing education among women is very important in empowering them. It has also being noticed that some of women are too weak to work. They consume less food but work more. Therefore, from the health point of view, women folk who are weaker are to be made stronger. Another problem is the workplace harassment of women. There are so many cases of rape, kidnapping of girls, dowry harassment, and so on. For these reasons, they

require empowerment of all kinds in order to protect themselves and to secure their purity and dignity. To sum up, women empowerment cannot be possible unless women come with and help to self-empower themselves. There is a need to formulate reducing feminized poverty, promoting education of women, and prevention and elimination of violence against women. Pandit Jawaharlal Nehru first Prime Minister of India once remarked, "To awaken the people, it is women who must be awakened; once she is on the move, the family moves, the village moves and the nation moves". So there is a greater need of bringing women into mainstream of development of India.

The status of Women in India has been subject to many great changes over the past few millenniums. In early Vedic period Women enjoyed equal status with men. Rigved & Upanishads mention several names of women sages and seers notably Gargi & Maitrey. However later the status of women began to deteriorate approximately from 500 B.C., the situation worsened with invasion of Mughals and later on by European invaders. Some reformatory movements by Guru Nanak, Jainism, Raja Ram Mohan Roy, Ishwar Chandra Vidyasagar, Pandita Ramabai and others did give some relief. It is not that Britishers didn't do anything for improving the condition of women. Some laws were enacted such an "Abolition of practice of Sati", Widow Remarriage Act 1856 etc. The real change came after Independence. Constitution of India guarantees equality to women (Article 14). There are other articles too which ensure rights of women e.g. no discrimination by the state [article15 (1)] equality of opportunity (Article16) etc. Feminist activism picked up momentum in India during later 1970's. Later on many groups and NGO's have been working for the Empowerment of women. We are proud that in India Women got voting right much before USA and some other European countries.

BUT THERE ARE THINGS WE NEED TO ADDRESS WITH URGENCY…

- Did you know that according to the World Bank, women account for 66% of the world's working hours but only 10% of the world income?
- Did you know that women produce 50% of the world's food yet possess only 1% of it's wealth?
- And of the 900 million adults worldwide who cannot read or write, about two thirds are women!?

THEREFORE SOME OF OUR LEADING CHALLENGES AHEAD ARE :

1. **How can we grant all women access to their basic needs?**
2. **How can we empower women to strive through education and employment with equal opportunities?**
3. **How can we break down gender stereotypes, inequality and violence against women?**

Our aim? Mobilise a maximum number of people to find solutions all around the world.

The political sphere of the country is, by and large, reserved for men alone. The place of women in society is also relegated to contributing minimally to the social development of the country. In addition, women's rights are not properly being protected in order for women to participate in various issues of their country but are subjected to abysmal violations. Moreover, women are highly

affected by environmental problems, and less emphasis is given to their participation in protecting the environment. Unless women are empowered and gender equality is achieved so that women can play their role in economic, social, political, and environmental areas, the country will not achieve sustainable development with the recognition of only men's participation in all these areas. The fact that women constitute half the entire population of the country makes empowering them to be an active part of all development initiatives in the country a compelling circumstance.

1. Violence against Women The lives of Indian women are full of sorrow and anxiety. There are various types of crimes like rape, molestation, dowry harassment, wife-battering, kidnapping, female children to be sold into brothel homes, forcible embracement etc. Problems faced by Indian women.

2. Gender Discrimination Gender discrimination refers to "the practice whereby one sex is given preferential treatment over the others. After overpopulation second number greatest problem in India is the female foeticide and discrimination. The practice of giving social importance to the biological differences between men and women is everywhere. In some societies, these differences are very much pronounced while in others, they are given less importance.

3. Negligence and Poor Health Indian women are the most exploited in the world. Socially, psychologically, politically and economically she is always on the secondary position. Improper hemoglobin, different medical problems, malnutrition and high death rate are the feathers of Indian women

4. Unequal Sex Ratio Normally, in the population of any country, male- female ratio remains more or less the same. That is 50:50. In India as the census reports reveal female population has been steadily declining ever since 1901.This is serious indicator in society. Efforts should be taken place for identification and sorting out this problem.

5. Negligence of Female Education Since ancient times it has been seen that generally women are ignored from the education.**'Ladki to paraya dhan hoti hai'** is common tendency observed among the Indians. Accordingly, much attention has been paid to the education of women after Independence. The female literacy level is also increasing steadily. It has increased from 18.7% in 1971 to 39.42% in 1991 and to 64% in 2001. In spite of this change in the trend towards literacy, some problems are still cropping up.

6. Dowry a curse At the time of marriage ceremony, the gift or amount given by the parents of girl is general trend in India. In later stage it became problem called dowry. Every year so many cases of dowry exposed in India. It is a very serious problem faced by Indian women and their parents.

7. Violence against Women Sexual Exploitation, Female Foeticide, Dowry, Domestic Violence etc are the common practices which we can see in Indian society. The rate of such problems is high in rural society. Main cause of it is that spoilt mentality with old customs and traditions.

8. Sexual Harassment - Now-a-days so many cases are exposing related to sexual harassment of women. Delhi gang rape and so many incidents' taking place in India. Child abuse, sexual

exploitation, human trafficking, child labour etc are the various problems are present in Indian society.

9. Organizational Problems - In working place, women face a lot of problems regarding various matters. May be sometimes sexual harassment and other conflicts can be created at working place. Excessive bossing, unequal shifts, unwanted demands by high authority etc are the factors responsible for women exploitation in organization.

Swami Vivekananda, one of the greatest sons of India, quoted that, **"There is no chance for the welfare of the world unless the condition of women is improved, It is not possible for a bird to fly on only one wing. "** Thus, in order to achieve the status of a developed country, India needs to transform its colossal women force into an effective human resource and this is possible only through the empowerment of women.

WHAT IS WOMEN EMPOWERMENT?

Women empowerment means emancipation of women from the vicious grips of social, economical, political, caste and gender-based discrimination. It means granting women the freedom to make life choices. Women empowerment does not mean 'deifying women' rather it means replacing patriarchy with parity.

Some of the key areas and types of empowerment needed for women is as follows:

Social Women Empowerment - A critical aspect of social empowerment of women is the promotion of gender equality. Gender equality implies a society in which women and men enjoy the same opportunities, outcomes, rights and obligations in all spheres of life.

Educational Women Empowerment - It means empowering women with the knowledge, skills, and self-confidence necessary to participate fully in the development process. It means making women aware of their rights and developing a confidence to claim them.

Economic And Occupational Empowerment - It implies a better quality of material life through sustainable livelihoods owned and managed by women. It means reducing their financial dependence on their male counterparts by making them a significant part of the human resource.

Legal Women Empowerment - It suggests the provision of an effective legal structure which is supportive of women empowerment. It means addressing the gaps between what the law prescribes and what actually occurs.

Political Women Empowerment - It means the existence of a political system favouring the participation in and control by the women of the political decision-making process and in governance.

MAJOR LANDMARK STEPS TAKEN FOR WOMEN EMPOWERMENT -

Provisions made under the Constitution of India such as :

- Right to equality under Article 14 of the Indian Constitution guarantees to all Indian women equality before law.
- Equal pay for equal work under Article 39(d), guards the economic rights of women by

guaranteeing equal pay for equal work.

- Maternity Relief under Article 42, allows provisions to be made by the state for securing just and humane condition of work and maternity relief for women.
- Acts like the Dowry Prohibition Act, 1961, prohibits the request, payment or acceptance of a dowry. Asking or giving dowry can be punished by imprisonment as well as fine.
- Protection of Women from Domestic Violence Act, 2005, provides for a more effective protection of the rights of women who are victims of domestic violence. A breach of this Act is punishable with both fine and imprisonment.
- Sexual Harassment of Women at Work Place (Prevention, Prohibition, and Redressal) Act, 2013, helps to create a conducive environment at the workplace for women where they are not subjected to any sort of sexual harassment.

Panchayati Raj Institutions : As per the 73rd and 74th Constitutional Amendment Act, all the local elected bodies reserve one-third of their seats for women. Such a provision was made to increase the effective participation of women in politics.

Women's Reservation Bill: It is a pending Bill in India which proposes to reserve 33% of all seats in the Lok Sabha and in all State Legislative Assemblies for women. If passed, this Bill will give a significant boost to the position of women in politics.

VARIOUS GOVERNMENT POLICIES AND SCHEMES -

The Government of India is running various welfare schemes and policies, both at State and Central levels for the empowerment of woman. Some of the major programs and measures include Swadhar (1995), Swayam Siddha (2001), Support to Training and Employment Programme for Women (STEP-2003), Sabla Scheme (2010), National Mission for Empowerment of Women (2010) etc. All such policies and programs focus on social, economic and educational empowerment of women across various age groups.

Thus, there has been no dearth of social, economic, political, legal and Constitutional efforts made for the empowerment of women both prior to and post-Independence. However, women in India continue to face atrocities such as rape, dowry killings, acid attacks, human trafficking, etc. According to a global poll conducted by Reuters, India is the "fourth most dangerous country in the world for women".

WOMEN EMPOWERMENT — CHALLENGES

Perspective - The most widespread and dehumanizing discriminations against women are on the basis of the biassed perspective. The discrimination against the girl child begins from the birth itself. Boys are preferred over girls; hence, female infanticide is a common practice in India. The ordeal that an Indian girl faces at birth is only the beginning of a lifelong struggle to be seen and heard.

Patriarchate Bottlenecks - The traditional Indian society is a patriarchal society ruled by the diktats of self-proclaimed caste lords who are the guardians of archaic and unjust traditions. They put the burden of traditions, culture, and honor on the shoulders of women and mark their growth.

The incidences of "honor killing" reveal the distorted social fiber in the male-dominated society.

Economic Backwardness: Women constitute only 29% of the workforce but forms majority of the destitute in the country. There has been a failure in transforming the available women base into human resource. This, in turn, has hampered not only the economic development of women but also of the country' as a whole.

Implementation Gaps - Through all these years, the attention is only on developing and devising new schemes, policies and programmes and have paid less attention to the proper monitoring system and implementation short-sightedness, for e.g. despite the presence of The Pre-Natal Diagnostic Technologies Act and various health programmes like Janani Suraksha Yojana and National Rural Health Mission (NHRM), our country has a skewed sex ratio and a high maternal mortality rate (MMR).

Loopholes in the Legal Structure - Although there are a number of laws to protect women against all sorts of violence yet there has been a significant increase in the episodes of rapes, extortions, acid, attacks etc. This is due to delay in legal procedures and the presence of several loopholes in the functioning of a judicial system.

Lack of Political Will : The still- pending Women's Reservation Bill underscores the lack of political will to empower women politically. The male dominance prevails in the politics of India and women are forced to remain mute spectators.

MEASURES

Way ahead starts with bridging the deep-rooted biases through sustained reconditioning. It is only possible by promoting the idea of gender equality and uprooting social ideology of male child preferability. This concept of equality should be first developed in each and every household and from there, it should be taken to the society. This can be achieved by running sustained awareness programs with the help of Nukkad Natak or dramas, radio, television, Internet, etc. across the country.

Replacing 'Patriarchy' with Parity: A strong patriarchate society with deep- rooted socio-cultural values continues to affect women's empowerment. The need of the hour is an egalitarian society, where there is no place for superiority. The Government should identify and eliminate such forces that work to keep alive the tradition of male dominance over its female counterpart by issuing inhumane and unlawful diktats.

Education is the most important and indispensable tool for women empowerment. It makes women aware of their rights and responsibilities. Educational achievements of a woman can have ripple effects for the family and across generations. Most of the girls drop out of schools due to the unavailability of separate toilets for them. The recently launched 'Swachh Bharat Mission' focusing on improving sanitation facilities in schools and every rural household by 2019, can prove to be very significant in bringing down the rate of girls dropping out of school.

Political Will: Women should have access to resources, rights, and entitlements. They should be given decision-making powers and due position in governance. Thus, the Women Reservation Bill

should be passed as soon as possible to increase the effective participation of women in the politics of India.

Bridging Implementation Gaps: Government or community-based bodies must be set up to monitor the programs devised for the welfare of the society. Due importance should be given for their proper implementation and their monitoring and evaluation through social audits.

Justice delayed is justice denied. Efforts should be made to restructure the legal process to deliver fair and in- time justice to the victims of heinous crimes like rapes, acid attacks, sexual harassment, trafficking and domestic violence. The idea of fast-track courts, devised to impart speedy justice to the victims of rapes and other crimes against women, is a good initiative taken by the judiciary and the Government of India.

CONCLUSION

Empowering women socially, economically, educationally politically and legally is going to be a Herculean task. It is not going to be easy to change the culture of disregard for women which are so deep-rooted in Indian society. But it does not mean that it is implausible. Only revolutions bring changes in a day, but reforms take their time. This one, in particular, will take its time as well. The idea of women empowerment might sound hard by the yard, but by the inch, it is just a cinch. All we need is a concentrated effort focused in the right direction that would rest only with the liberation of women from all forms of evil.

"I raise up my voice - not so I can shout, but so that those without a voice can be heard...we cannot succeed when half of us are held back." —Malala Yousafzai

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W.E.E.E.E.P.
Women Education Employment Environment and Empowerment Problems

Prof. Narendra Malhotra **Dr. Neharika M. Bora**

"Women are not dying because of the diseases we cannot treat, they are dying because societies have yet to make the decision that their lives are worth saving" - Prof Fathallah.

These lines and words still echo in our minds and heart and even though we have managed to reduce maternal mortality to half of what it was in India when Prof Fatahallah spoke this, still we are way behind our target of M.D.G. (Millennium Development Goals) and also we are very less likely to achieve the S.D.G. (Sustainable Development Goals). The sole reasons of this underachievement is W.E.E.E.E.P.

Yes ! for women WEEP has 4 "E"Its WEEEEP-

Women education, employment, environment and empowerment problems .Only **BETI BACHAO** will not save women and tackle all HER '4-E' problems at the same time. Lets see what we can do about these 4 'E's'!

EDUCATION Government of India, NGO's and many others are working overtime on the projects of educating women in India. Primary school education is free, secondary school education is free for girls or highly subsidized and lots of scholarships are available, yet we appear to have failed –She is educated now even in villages but SHE still does not matter in the society and SHE still cannot decide and HER problems of W.E.E.E.E.P. are still the same in 2018. All her problems are being improved these days but yet below par.

FOGSI in 2008 realised that just academics updating is not enough to bring about a change in MMR hence the slogan **BETI BACHAO BETI PADAO** was coined and was FOGSI's theme with the FOGSI daughter parked with 7 ribbons to highlight the problems of girls and women in India.

Today we FOGSIANS feel it is a great pride that Government of India under a very progressive, forward looking, dynamic leader Shri Narendra Modi Ji adopted this slogan as a National movement, So yes EDUCATE (first E) the girls we must.

EMPLOYMENT After education what? These girls of India even from rural backgrounds are now clearing graduation and pursuing post graduation courses, BUT! A very small percentage of these girls are working or get employment worth their education so the Govt of India has to provide ample jobs and equal opportunity to girls and women on all posts . Yes Indian air force now has women fighter pilot but only a handful (2-3to be exact), why not 30% at least .So the 2nd "E" of WEEEEP has to be addressed on a war footing if we want to be near S.D.Gs till 2030.

ENVIRONMENT The 3rd "E" of women 's WEEEEP problems is the environment . India still struggles for potable water, hunger, clean air, toilets; the list is endless. Yes we have started on many fronts and Swatch Bharat and Toilets India are two great initiatives BUT! It's the people of India who need to be educated on civic sense, clean water, hand hygiene, menstrual hygiene, toilet hygiene, environmental hygiene and food hygiene. Living CLEAN is our only hope of living HEALTHY. Diseases need to be prevented not treated, so tackling 3rd "E" of WEEEEP is very very important .

EMPOWERMENT The 4th "E" of WEEEEP is empowerment itself .What is empowerment is the question and how can we empower our women? Broadly women empowerment means there should be no discrimination between men and women.Women when they are born in India should be able to enjoy the same social rights when they grow up. Women need H.E.R. (Health Empowerment Respect) which is the FOGSI THEME OF 2018 depicting that a professional organisation is so sensitive to women's need and will go all out to work with all stake holders to empower women so that she remains healthy and can work and live with respect.

THE POINTS FOR TACKLING THE 4 E'

1. There should be Respect and Dignity towards woman.
2. Woman should have independence of their lives inside and outside their home and at work.
3. They should be able to make decision by their own choice.
4. Society should hold woman in high social respect.
5. Equal rights in society and equal legal rights.
6. No discrimination of any type in education .
7. Should be able to select their economic and financial choices on their own.
8. No discrimination in jobs and equal salary.
9. Safe and secure working location and environment with proper privacy.
10. Should be able to freely live their life with a sense of self worth respect and dignity.

HOW DO WE EMPOWER WOMEN?

1. Change the perspective towards women .
2. Overcome the patriarchate bottlenecks.
3. Implement the GAP`s.

4. Block the loopholes in legal structure.
5. Have a strong political will.

India has made considerable progress since Independence in the last 70 years, but still the struggle against many handicaps prevail and social evils and male dominated society has to be overcome.

We are the first Asian country to successfully complete Mars mission in the first attempt, but we are still 29th among 146 countries on the basis of gender equality index.

Indian women enjoyed a much more empowered position during Rig Vedic period which deteriorated to the level of denied right to inheritance, early child marriage, dowry, widow remarriage problems etc. During the British era many social reforms were initiated and in Independent India many laws were created to elevate woman's status in Indian society. Currently major efforts for women empowerment are being done and we all hope that the political will will continue to bring about a change in women status in India.

There is no chance for the welfare of the world unless the condition of women is improved, it is not possible for a bird to fly on one wing **"Swami Vivekanand".**

ABOUT THE AUTHORS

Prof. Narendra Malhotra and Prof. Jaideep Malhotra are practising obstetricians in Agra. They are the only couple in the world to head a professional organization. Dr. Narendra past president FOGSI in 2008 who gave the theme **बेटी बचाओ , बेटी पढ़ाओ** and WEEEEP.

Dr. Jaideep Malhotra is current president of FOGSI (2018) who has given the theme of HER (Health Empowerment Respect) to women with QED (Quality Ethics and Dignity)

Dr. Jaideep and Dr. Narendra are also the only couple in the world to have been conferred as Honorary FRCOG by the Royal College of London and FRCPI from Ireland.

Social service and working for women 's health is their passion and life mission.

Gender Disparity - From Womb to Tomb!!

Dr. Archna Tiwari **Dr. Meera Agnihotri**

We must ensure that we enable following six "S" for Women Empowerment:

1. **Shiksha = Education**
2. **Swasthya = Health**
3. **Swavlamban = Self-Reliance**
4. **Samajik Nyay = Justice**
5. **Samvedan = Sensitivity**
6. **Samta = Equality**

And, following four "S" for Women Survivors:

1. **Seeking Medical Aid**
2. **Seeking Police Protection**
3. **Seeking Shelter**
4. **Seeking Legal Advice**

Yatra Naryastu Pujyante tatra Ramante Devata,
"All men are equal, but some are more equal than others!!"

- George Orwell, Animal Farm

We as gynaecologists are the caretakers of the health of half the world's population. Most females do not access the health care system unless they have some issue with the menstrual cycles, or are pregnant. Hence, we are concerned about the fact that despite so much talk about equality, empowerment and empathy, there is still a wide gap between what is proposed and what actually happens with women's health.

"Beti Bachao, Beti Padhao" is one of our mantras- yet there is still preference for male child in many areas, and the gender ratio is skewed alarmingly in many states of our country.

Implementation of the PC-PNDT Act has had many hurdles and problems which we are all aware of. We are still facing the problem of vanishing girls who are never born. Our FOGSI Presidents down the years have been striving to address these issues and we are now seeing some light at the end of the tunnel!! Our website has the FOGSI policy statement on **VIOLENCE AGAINST WOMEN,** and guidance on procedure to be followed when a woman/ girl reports with alleged history of sexual assault.

If the girl child manages to be born, she now has to face the challenges of being low in priority in the food chain, and also struggle to get educated. Various health care schemes are being proposed but implementation at grass root level is the real challenge. As part of the health care system, we as gynaecologists must work hand in hand with the state and centre to do the needful.

Devi, Janani, Mata are words we use to pray to the Goddess….but what happens when we look at women in daily life?? Our country is fondly called "Bharatmata"- but what about the women of the country??? Domestic violence is happening in many places, down the ages. In fact in some of the ancient scriptures like the laws of Manu, beating the wife for misdemeanours was advised. The domestic violence act (2005) has been implemented and we should be aware that this gives an umbrella of protection. After the tragic case of Nirbhaya, there were amendments to the Rape Laws which make reporting mandatory, stringent punishments and expands the definition of sexual violence to include stalking and acid attacks. **"Maut ki Sazaa"** or capital punishment has now been proposed for the accused in cases of rape of minors below age of 12 years but there is much debate on whether this is really going to be a deterrent. The POCSO Act 2012 was a landmark which changed many things- child now includes upto age 18 years, and the act is gender neutral i.e. it recognizes that both boys and girls can be victims. It also recognizes that the accused may be a man or a woman and that anyone who is aware of sexual crime against children has to report it.

Third gender and LGBTQ (Lesbian, Gay, Bisexual, Transgender, Queer) community has often been marginalised and ignored - this bias is also changing. The recent landmark judgement of the Supreme Court regarding Section 377 has de-criminalised gay sex and hopefully will lead to more acceptance of personal choice.

What is truly required for our society is a change in mindset and ensuring respect for the girl child. **We must ensure we enable following six "S" for Women Empowerment:**

1. Shiksha = Education
2. Swasthya = Health
3. Swavlamban = Self-Reliance
4. Samajik Nyay = Justice
5. Samvedan = Sensitivity
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And, following four "S" for Women Survivors:

1. Seeking Medical Aid
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This International conference of WWWCON 2018 seeks to focus on Women's health and Wellness as the key to Women Empowerment and this special issue of the FOGSI Focus seeks to empower the readers by updating them on their role in this mammoth task.

"With great Power, comes great Responsibility" it has been said. As doctors we have to take this as our mantra, and do whatever is in our power and bridge the gaps in health care of the women who are our responsibility.

SOURCE REFERENCES & SUGGESTED READING

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The Story of Sakshi
Be the Witness of Struggle, Strength and Success

Ms. Sakshi Vidyarthi

- **We need not to empower a women we just have to make her realize the potential that she has inside . A woman can change the world, if she decides, with her strong will, she will fight out in all conditions. We all have to support her, not victimize her, neither socially neglect her nor boycott the family of that girl . As a part of our society we must come forward and help her.**
- **NGO named SAKSHI FOUNDATION, the motive of making this foundation is to provide social justice along with legal justice to the survivor. We motivate the victim to come forward and raise her voice, we provide legal assistance to her, provide her job and career security, and try to socially rehabilitate her.**

In the city of Kanpur known as Manchester of East, a girl named Sakshi was born in Vishnupuri in a middle class family. They were 5 members in the family Sakshi, father, mother and grandparents; Sakshi became the lifeline of her family. Being a single child she enjoyed all rights, her grandparents told her stories in the night and her mother prepared her for school. That girl's mind was full of many dynamic thoughts and her eyes were brimming with many dreams. When she saw the sky she imagined herself flying in the sky but she had a very struggling life from childhood. Once a time came at a very young age and she fell sick. Her parents approached everywhere to save her, and with the grace of Almighty GOD and family's love she was saved .

Since childhood she had keen interest in making aero models. She used to make small air crafts with paper and flew them in the air. Sometimes she used official papers too ,her innocent mind unable to read and write but was very curious about her dream. She always wanted to be like Kalpana Chawla and she wanted to design her own aircraft and fly it in air. At the age of 7 she made her first aircraft model with wood , scraps, spokes and threw it in the air but that model didn't stay for a long time in the air. That day she was happy but not satisfied because her efforts remained futile but she did not loose heart and kept trying. She went to her dad and shared her dream with her dad. He understood that she wanted to fly an aircraft model. He told her about basic concepts of flying and air craft designing. When she was in 6th standard she was studying in Air Force School Chakeri, Kanpur she made her model fly during Republic Day program on 26-1-2006 at Reserve police line Parade ground in the presence of Sukhram Singh, Chairman of UP Legislative Council who appreciated that girl and her devotional and dynamic thoughts for the Nation. When she was in the 7th standard she got a chance to meet Dr. APJ Abdul Kalam, former President who appreciated her and Sakshi was highly inspired by Kalam sir. His thoughts for students made her a big follower of Kalam sir . For her performance she got the "Youngest Aeromodeller award". Her skill achieved many appreciations from many renowned persons like Sri Prakash Jaiswal, former Coal Minister, who blessed her for her future. IIT Kanpur (department of aerospace engineering) appreciated her and she got many blessings and love from her family and people. She wanted to fly more in the sky, wanted to do more for the country, for her dreams but nobody knew what destiny had in store for her.

In 2010 Sakshi went to give her flying demonstration, people applauded for her flight, many police officials who were present there appreciated the girl. A person named Amarjit Singh also present there came to her and appreciated her, he gave his introduction as Deputy Superintendent of police and ex Major in Army. Since the girl's father was Chief Gliding officer in Indian Airforce that person made family relations with their family. He used to visit the girl's home frequently. One day in the month of November 2010 Amarjit came in the afternoon to Sakshi's home, she was all alone at home because both her parents had gone to the office. That person asked for a cup of tea, she went to the kitchen to make tea for him and when she came back and gave tea to him he asked for a glass of water. Again, she went to the kitchen for water. In the mean time he added some intoxicant to the tea and when she gave water he offered tea to the girl, while having tea she felt drowsiness. That person whom she used to call uncle abused her sexually, created obscene videos of her and also clicked vulgar photos. When she woke up she found her uncle was lying next to her. He showed Sakshi her

obscene videos and photos. He threatened her that if she told someone he could upload all pictures on the internet and give it to media to publish those photos and would spoil her bright future . She was shattered , she found herself in dilemma, her dreams were broken. That person used to come to her home while nobody was at home and abused her repeatedly. One day Sakshi decided to tell everything to her parents and she said the same to Amarjit .He used to beat her taking Sakshi at gun point. He forced her to write against her parents, he took signature of the girl on plain papers also because he was well versed with the law, he prepared fictitious papers to cover his heinous crime. After that day she was totally controlled by him she lost all sense of freedom except to take breath . Even after his transfer from Kanpur he and his people kept an eye on her . His consistent pressure left no way for her. This pressure forced her to commit suicide but fortunately was saved by her parents who asked her the reason behind that terrible step. Then the girl told the entire story to her parents who understood her pain, they supported her and refused to bow down and encouraged her to fight it out to expose the devil.

Her father approached competent authorities to lodge FIR but nobody helped them, many people advised to settle the case , many persons accused the family. Anyhow the FIR was lodged but the department was supporting Amarjeet as he was from the same department. Her family approached everywhere to get justice but all in vain. When they saw no hope the family sat on hunger strike. Then their protest was joined by many social activists, organizations, advocates. Then the former CM of Uttar Pradesh took cognisance and ordered to send the accused behind bars. Her family fought two battles simultaneously, first from the accused and system and second from the so called well wishers who frequently asked irrelevant questions from that girl. People advised to send her out of station , many relatives stopped talking to her, they accused her parents and raised many questions regarding freedom of girl child.

As the case went in the court the people of the accused chased the family, he particularly threatened the girl and her family of acid attack. After long judicial process the court found Amarjit guilty of abusing the innocent and sentenced him 10 year rigorous imprisonment in 2014. But between the period of 2 years many a times family sat on strike and went to the High court. Fabricated complaint was lodged against victim's father but victim's family was determined to get justice.

After the incident the girl decided to serve society and to save other victims. She made an NGO named **SAKSHI FOUNDATION,** the motive of making this foundation is to provide social justice along with legal justice to the survivor. Here we help those for whom nobody bothers whose relatives, parents and family neglect them .We work in slum areas to create awareness among people through organizing debates and workshops. We talk about gender equality, child rights , how to protect ourselves from all kinds of abuse, we emphasize on good parenting also because we believe it has a crucial role in making healthy and safe atmosphere for kids .We motivate the victim to come forward and raise her voices, we provide legal assistance to them, provide them job and career security, and try to socially rehabilitate them. We provide self defense training to victims or other girls for safety.

To raise the voice of women this NGO made a small film production house in which we made a documentary on Sakshi's horrific experience of life to give message to the victim and family to come forward and fight for justice because nobody will provide you justice and fight on your behalf.

For her bravery she was felicitated with SALAM INDIA AWARD by Hon. Home Minister Rajnath Singh, Ambedkar Ratna Award by Hon. Governor of UP Shri Ram Naik ji, Nari Ratna by Brinda Karat , Nari shakti Samman by Hon. Governor of UP Shri Ram Naik, Vishav Ratna Award by Laxmi Narayan Minister of UP, Mai Hoon Beti Award by MLC Raj Bahadur ji, Mata Savitribai Phule award , Indian Girl of Ambedkar Courage award, HT Women award by Hon.CM of UP Shri Yogi Aadityanath, Nirbhaya brave heart Award by FOGSI (Federation of Obstetrics and Gynecological Societies of India). She has not stopped, she is a law intern in High Court and took pledge to provide legal justice to victims. She is none other but the writer herself. It's me Sakshi who wants to see other victims to smile and help them to lead a dignified life.

I never left my dreams but I sacrificed for so many innocent souls to dream without fear. I am the witness of my traumatic life and struggle and like me many girls are facing the same situation but I request them to come forward, break the ice and raise their voice. Let the people see the strength of women. **We need not to empower a women we just have to make her realize the potential that she has inside . A woman can change the world, if she decides. With her strong will she will fight it out in all conditions. We all have to support her, not victimize her, neither socially neglect her nor boycott the family of that girl. As a part of our society we must come forward and help her.**

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Youth Today... Leaders Tomorrow... Lets Empower Them!!

Prof. Dr. Suchitra N. Pandit
& Dr. Priti Vyas

- **With the rising incidence of violence against women including all age groups ,there is an increasing need to empower women with knowledge about sexual and reproductive health rights , master the art of self defence, report violence and eventually become so strong that men are scared to make sexual overtures . The attitude of all women need to change . Women need to be in the position of strength and self reliance and not a vulnerable victim and so training has to start from childhood itself ! At the same time the micro environment has to change. We feel that boys have to be educated and taught to respect women.**
- **Empowering Youth Transforming Lives to make a difference.**
- **There is no tool for development more effective than empowering youth! So where should Youth empowerment occur ? It starts at Homes, Schools, Youth Organisations and Communities. Government Policy – making has to change to accommodate youth.**

India is a young country.. by 2020 will be the youngest country in the world where 64% of population will be in the working age group. Every third person in India will be a youth !!

India's secret weapon is its young population (CNBC)

Predictions of a growing economy…. addition of an extra 2% to GDP growth rate. India will have a dynamic transformation as a population burden of the past turns into a demographic dividend of tomorrow .There will be a greater political participation from the youth . They will be engaged at a policy level so it is imperative that improving the quality of life of the youth can ensure that India enjoys the benefits of this dividend .

Largest share of youth with formal skills are seen in Kerala, Maharashtra, Tamil Nadu, Himachal Pradesh and Gujarat and the lowest rates are seen in Bihar & Rajasthan.

Urban youth have 93% greater chance of acquiring training than someone in the rural areas. Currently 20% of youth lives on less than Rs.60 /day.

WHAT ARE THE CONCERNS ??

Health Concerns of youth both girls and boys - Urban girls are anemic, there is malnutrition either due to improper or inadequate food coupled with irregular eating hours. They have food fads and so instead of having nutritious food they end up having junk food. Girls from certain communities are still getting married young irrespective of socioeconomic strata. So naturally they are getting pregnant when they are teenagers. Anemia, malnutrition, ignorance and not accessing healthcare contributes to a high maternal morbidity. Young boys from the lower socioeconomic strata too have malnutrition .There are school dropouts and boys are more vulnerable to depression and substance abuse

Gender bias is prevalent in some communities and this also contributes to educational disparities with preferential education to boys. Youth face the challenge of unequal job opportunities which adds on to the confusion & stress amongst them. Unemployment very high in young men

Globalisation - Globalisation has definitely contributed to changes in access to technology but this is again is not for accessible for all. Many changes have occurred in the last decade World is changing rapidly, so are the youth. Education, awareness and knowledge have largely been responsible for this change. Given the exposure to explosion of information but with the lack of correct knowledge; youth have a lot of unanswered queries regarding their overall health and wellbeing.

Reproductive health is the ability to have a healthy, happy & fulfilled sexual relationship without fear of unwanted pregnancy & disease. It includes availability, accessibility & affordability of good antenatal natal & postnatal care. Adolescence is that period of life of an individual when ….A biological process which transforms a child into an adult.. a young adult. Period of sexual maturation, ie from biological immaturity to maturity. There is a conflict of values in the young minds but this is a situation of rights versus duties: they have a right to know about reproductive health and to make their own decisions. However the freedom of choice comes with the responsibility of the consequences of that choice. They need to learn and be able to say no !! Why No ? No to what ? This is obviously to casual and unprotected sex , alcohol , drugs and being abused !

A casual attitude towards reproductive health can otherwise can affect subsequent relationships and their lives in general too. Most common reason told by young people for not using any protection during intercourse is 'I was under emotional pressure, was scared of loss of the partner or not gaining approval of peers or was just curious' ! They succumb to these pressures and finally do what is not in the best of their interest.

The aftermath of this could lead to an unwanted teenage pregnancy with a physically and psychologically damaging effect. They are more susceptible to sexually transmitted infections including HIV and Herpes .

NEED TO WOMEN EMPOWERMENT

With the rising incidence of violence against women including all age groups ,there is an increasing need to empower women with knowledge about sexual and reproductive health rights , master the art of self defence , report violence and eventually become so strong that men are scared to make

sexual overtures . The attitude of all women need to change . Women need to be in the position of strength and self reliance and not a vulnerable victim and so training has to start from childhood itself ! At the same time the microenvironment has to change so we feel that boys have to be educated and taught to respect women.

MOGS YOUTH MELA

When I was the President of Mumbai Society of Obstetrics and Gynecology ,we conceptualized and initiated an informative & interactive program called "MOGS YOUTH MELA" for empowering the YOUTH - the future generation !!! 'Youth Mela was done with a group of committed doctors from our Youth council , as well as Mumbai society .We prepared a module and had videos and a powerpoint presentation .We piloted the program and finally had our first program at Sathye junior college , to reach out and impart scientifically correct information and knowledge, regarding health, safety and over all wellbeing. We had nearly 350 students and had a tremendous response from students .

We did forty Youth melas ,and we were encouraged by their popularity so we decided to spread our wings out of Mumbai . I was taking over as President of FOGSI in 2014 and I decided to roll these Youth melas all over India .We made more CDs and took some sessions for Training of Trainers in different zones of India .

FOGSI is one of the largest professional organization representing practitioners of Obstetrics and Gynecology in India. In 2014 we had 223 member societies and over 29,310 individual members spread over the length and breath of the country;

FOGSI's mission is to pilot and promote preventive and therapeutic services related to the practice of obstetrics and gynecology for betterment of the health of women and children in particular and the wellbeing of the community in general, to advocate the cause of reproductive health and rights.

Youth Mela was conceptualised by President MOGS & FOGSI ,Dr. Suchitra Pandit supported by Dr. Jayam Kannan Chairperson FOGSI Adolescent Health Committee, Dr. Priti Vyas & Dr. Sanket Pisat who were the National Coordinators .This is meant for both - boys & girls. Youth Mela is a 2-3 hours program, which includes the following topics:

- Self-Presentation Skills
- Nutrition & Prevention of Anemia and Staying Fit
- Physiology of the body
- Protecting oneself from
  - Unwanted Pregnancy & Sexually Transmitted Infections
  - Cervical Cancer
  - Physical & Sexual Abuse
- First Aid

These topics were taught to students by the way of lectures, interactive group discussions, live demonstrations and skits by our team of trained doctors . For the first fifty melas ,we had procured

an unconditional educational grant from Emcure pharma , but later the colleges itself sponsored them 2014 - 2016 .

We started the FOGSI YOUTH cell in 2015 after approval of the Managing committee and we are happy that now Dr. Shobha Gudi current President of Bengaluru Society has initiated a Youth cell in her society so they can carry on these activities regularly. Dr. Sampath Kumari current Chair of FOGSI Adolescent Health Committee and Dr. Charmila, Chair of Clinical research Committee are regularly doing the several programs related to youth.

We thought of involving Youth in community work and rallies were the best way to do that .We started with the Youth rally with help from Dr. Jayam and Dr. Sampath Kumari at our FOGSI flag hoisting at the AICOG at Chennai in 2015 .Students did role plays and carried health message on placards. Several Youth rallies were carried out by subsequently by both of them .We also did several Youth summits at Mumbai, Chennai, Trichy ,Kanpur in 2016 during Dr. Rishma Pai's year as President FOGSI. Here we had a two day program meant for schools and junior colleges .This had health exhibits handmade by our team which also included nursing staff. We had teams to demonstrate Self Defence.We had several games related to health issues.

Youth Leadership training is a life - skill building exercise . We have tried to create peer group leaders and encourage them to spread awareness and health messages that they have learnt during their training in Youth health melas to maximise the reach and have an impact.

YOUTH MELA - Faridabad 11th April 2014

EMPOWERING WOMEN - THE MOST EFFECTIVE TOOL

- We feel that 'Empowering Youth Transforming Lives to make a difference. ' Youth are going to be the next generation and our future is in their hands.
- Youth empowerment refers to Attitudinal, Structural & Cultural process whereby young people gain ability, authority and agency to make decisions & implement change in their own lives & accept responsibility for the consequences of those actions !
- There is no tool for development more effective than empowering youth !
- So where should Youth empowerment occur? It starts at Homes, Schools, Youth Organisations and Communities. Government policy – making has to change to accommodate youth.

- Parents play a temendous Role in shaping future of youth !! They can create a microenvironment wherein young people are allowed to think & take a decision. Parents can help but should not take decisions for youth. Expectations from a child are so high that in today's competitive world, children are burdened with this, the peer group performances plus competitions at all levels. This puts a tremendous pressure on students. I sincerely feel that parents must communicate with the child, show faith and interest in their child's progress and allow them to decide. They must reassure children as all may not be at the same scholastic level.

  Providing financial assistance where possible is important. If financial conditions are not conducive to supporting a child's dream parents can encourage children to get enrolled in scholarships, loans for studies and financial assistantships

  Children are keen observers They derive impressions by observing how their parents interact when talking amongst themselves or about their grandparents. Interpersonal relationships and mutual respect amongst parents influence the child's behavioural pattern so parents must take care of this.

THE CHALLENGES THAT YOUTH HAVE TO FACE

The challenges that youth have to face are varied & complex coping with the physical changes in their bodies, external appearance and changes of menarche in girls and boys may be unexpected for them. Having a strict environment at home with overbearing parents, abuse in school or home and there could be financial problem. Not getting admission in the right field. Many a times inability to cope with peer group pressure is often perceived as a failure and this may lead to loss of self esteem and depression. Some unfortunate students have to start working at an early age and can face unemployment. Girls often have the family pressures for marriage and young people may face failure in Love. Ill health, disability and psychiatric problems can contribute to an unhappy youth.

- Investing in young people by creating jobs and by building gateways into the labour market is a significant opportunity for business to invest in itself.
- Youth Leadership training is a life-skill building exercise
- Creation of peer group leaders
- Replicate amongst their peers in the community. The youth also replicate all that they have learnt from the training in schools to maximise the reach and impact.

SPECTRUM OF ATTITUDES YOUTH AS PARTNERS !

Youth recognizes that technology will not solve the problems of the developing world, but it can help to bridge social and economic obstacles. Adults respect young people as having something significant to offer, recognizing the greater impact youth bring to a project. Youth are encouraged to become involved.

TIPS TO ADULTS WHILST DEALING WITH YOUTH

- It is better to be open & nonjudgmental and ensuring that they are treated as individuals.

- One should take advantage of expertise and ensure youth participate in meaningful Ways. Youth schedules will be different so be honest about expectations & accommodate them.
- Working together can be fun and a word of encouragement always helps.
- Avoid assumptions about youth and remembering that Youth have the right to say " No "
- The young people too must remember that most adults have good intentions & criticism does not mean condescension.
- Adults may be unaware of the capabilities of youth & often feel responsible for the success or failure of the project.
- Adults may be just as uncertain as youth but hide it better so communication should improve and assumptions on both sides must be avoided.
- Involving youth helps in community activities helps them feel more connected with their communities and leads to a positive feelings about belonging. It promotes a community ownership. Programs get more effective when youth are involved (teaching, mentoring)
- Youth excitement can energize & synergise the community involving young people in decision making …

OUTCOMES - YOUTH DEVELOPMENT PROGRAM

- Increased academic achievement & motivation to succeed
- Increased self esteem, popularity & personal control
- Increased development of leadership, communication & decision skills
- Increased dependability & job responsibility
- Social skills & Increased communication in the family
- Decreased psychosocial problems (i.e., loneliness, shyness)
- Positive health decisions
- Decreased involvement in risky behaviors (tobacco,alcohol & drug use)
- Youth are uniquely qualified to say what works for them

WHAT HAS FOGSI DONE FOR THE YOUTH IN THE PAST

Young Talent Promotion Committee started by - Prof. Rajan President FOGSI in 1997. Dr. Hafiz Rehman, myself, Dr. Parag Biniwale, Dr. Bhaskar Pal, Dr. Geeta Balsarkar & now Dr. Vineeta have chaired this committee. In my year as Chairperson all our published books research projects, articleship, workshops & CMEs had 80% youth involvement.

KISHORI - Adolescent Empowerment Project of FOGSI in 2002 in the slums of Dharavi with LTMG hospital, Unicef, ICDS & Sneha initiated in Dr. Duru Shah 's year as President FOGSI, I was the Secretary and Dr. Daksha Pandit & Dr. Fernandez were the pillars of the project Promoting

reproductive health, having an adolescent friendly clinic & helping adolescent girls (school droputs) to develop a skill which helps them to be self reliant.

YUVA FOGSI conferences initiated by Dr. Kamini Rao where youth are given a scientific platform and 70 % of the faculty are under the age of forty years.

YOUTH WING - Some societies have also initiated a Youth wing so the young doctors are mentored by Mumbai society, Jaipur, Delhi, Jabalpur & Pune.

MOGS Youth Council given responsibility during conferences which develops their organisational skills, gives a boost to their talent & gives them the sense of responsibility.

Youth Talent Search - Dr.Rishma Pai did a Youth Talent search at all the Yuva FOGSI conferences to encourage talent and winners were felicitated at the main AICOG.

YOUTH CELL -

FOGSI now has a YOUTH CELL since 2015 to help in formulating plans and encourage youth activities. Other FOGSI committees like Adolescent Health, Young Talent, Sexual medicine, Public awareness are also involved with Youth cell activities.

By investing in youth and their parents, there can be a positive impact on the future of India's growth.
Youth today are leaders tomorrow so lets empower them !!

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Sexual Violence and Domestic Violence 'Challenges and Concerns'

Dr. Reena Wani
& Dr. Toral Dhokia

- **The United Nations defines violence against women as "any act of gender-based violence that results in, or is likely to result in, physical, sexual, or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life."**
- **In India, Rape is one of the most common crimes against women in India.**
  - **A woman is raped every 29 minutes.**
  - **India's average rate of reported rape cases is about 6.3 per 100,000 of the population.**
  - **About 99% of cases of sexual violence go unreported. If true, this would put India among the nations with highest levels of crimes against women.**
- **We must ensure to enable following six "S" for Women Empowerment:**
  1. **Shiksha = Education**
  2. **Swasthya = Health**
  3. **Swavlamban = Self-Reliance**
  4. **Samajik Nyaya = Justice**
  5. **Samvedana = Sensitivity**
  6. **Samta = Equality**
- **SDG Goal 3 of good health and well-being, and Goal 5of gender equality will be achieved only if we work towards identifying, managing and hopefully preventing continued violence against women and children.**

INTRODUCTION

The United Nations defines violence against women as "any act of gender-based violence that results in, or is likely to result in, physical, sexual, or mental harm or suffering to women, including

threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life." [1]

Sexual violence is "any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic, or otherwise directed, against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting, including but not limited to home and work." [2]

Domestic violence (also named domestic abuse or family violence) is violence or other abuse by one person against another in a domestic setting, such as in marriage or cohabitation. It may be termed intimate partner violence when committed by a spouse or partner in an intimate relationship against the other spouse or partner, and can take place in heterosexual or same-sex relationships, or between former spouses or partners.[3]

FACTS ABOUT SEXUAL VIOLENCE

Worldwide

- 1 in 3 (35%) of women worldwide have experienced either physical and/or sexual intimate partner violence or non-partner sexual violence in their lifetime. [4]
- Almost 750 million women and girls alive today were married before their 18th birthday.[5]
- Around 120 million girls worldwide (slightly more than 1 in 10) have experienced forced intercourse or other forced sexual acts at some point in their lives.[6]

In India, Rape is one of the most common crimes against women in India.

- A woman is raped every 29 minutes. [7]
- India's average rate of reported rape cases is about 6.3 per 100,000 of the population. [7]
- About 99% of cases of sexual violence go unreported. If true, this would put India among the nations with highest levels of crimes against women. [7]

SCOPE OF THE PROBLEM

India's average rate of reported rape cases is about 6.3 per 100,000 of the population [7], which is not very high when compared with the rest of the world, suffers from under-reporting. According to a recent report by the Livemint[4], about 99% of cases of sexual violence go unreported. If true, this would put India among the nations with highest levels of crimes against women.

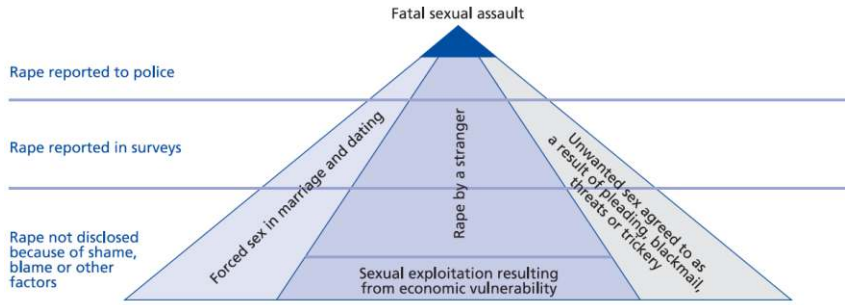


Figure 1. Magnitude of the problem of sexual violence (WHO 2013) [2]

Even if one excludes marital rape and assault from the analysis, the extent of reporting sexual violence is still small. Only about 15% of sexual violence committed by others (someone other than the current husband) is reported to the police[9]. This suggests that the absence of a strong law against marital rape and assaults is not the only factor behind the low reporting. There are other factors at play, including low trust in the police, lack of awareness and low conviction rates in such crimes that prevent women from reporting sexual assaults.

The conviction rate for all crimes against women stands at a measly 19% across India (compared with an average conviction rate of 47% for all crimes) [10]. A troubling observation is that while cases being reported have increased over the last five to six years, conviction rates, unfortunately, have remained stagnant to slightly falling [10].

HEALTH CONSEQUENCES

Sexual violence, in addition to being a violation of Human Rights, is an important public health issue as it has several direct and indirect health consequences. Survivors of sexual violence may present to health care services with varying signs and symptoms. For those survivors who do not reveal a history of sexual violence, the following signs and symptoms should prompt one to suspect the possibility of sexual abuse/assault

Physical	Psychological
Abdominal pain	Fear and shock
Burning micturation/ UTI	Physical and emotional pain
Menstrual disorders	Intense self-disgust, powerlessness
Dyspareunia	Worthlessness
Unwanted pregnancy	Apathy
Pelvic inflammatory disease	Denial
Mutilated genitalia	Numbing
Risk of sexually transmitted infections including HIV	Withdrawal

LEGAL SUPPORT :

What was the remedial measures before Domestic Violence Act?

There was Act 498 A but there were limitations. Husband or relative of husband of a woman subjecting her to cruelty shall be punished with imprisonment for a term of one year extend to three years and shall also be liable to fine.

The Act covers women who are or in a relationship with the abuser

1) By Marriage - or adoption; in addition relationship with family members living together as a joint family are also included.

2) **Sisters, Widows, Mothers, Single Women or living with the abuser** are entitled to get legal protection under the proposed Act.

DOMESTIC VIOLENCE ACT – HIGHLIGHTS

include the following important features - The Act provides for the woman's right to secure housing and woman's right to reside in the matrimonial or shared household, whether or not she has any title or rights in the household.

(a) Habitually assault or make the life of the aggrieved person miserable by cruelty of conduct.

(b) Forces the aggrieved person to lead an immoral life; or

(c) Otherwise injures or harms the aggrieved person

(d) "Economic Abuse" deprivation of all or any economic or financial resources, household necessities for the aggrieved person and her children.

Power of the court to pass protection orders that prevent the abuser from

- Entering the workplace or residence of the victim
- Any other place frequented by the abused, attempting to communicate with the abused

LAWS PERTAINING TO SEXUAL VIOLENCE

Recent incidents have led the Government of India to reform its penal code for crimes of rape and sexual assault.

- **The Criminal Law (Amendment) Act, 2013 (Nirbhaya Act)** is an Indian legislation which provides for amendment of Indian Penal Code, Indian Evidence Act, and Code of Criminal Procedure, 1973 on laws related to sexual offences.This new Act has expressly recognised certain acts as offences which were dealt under related laws. These new offences like, acid attack, sexual harassment, voyeurism, stalking have been incorporated into the Indian Penal Code.
- **Assault or criminal force to woman with intent to outrage her modesty -** Section 354 of the IPC criminalises any act by a person that assaults or uses criminal force against a woman with the intention or knowledge that it will outrage her modesty. Such an act is punishable with either simple or rigorous imprisonment of up to 2 years, or a fine, or both. Indian courts have ruled that the essence of a woman's modesty is her sex, i.e: a woman possesses modesty by virtue of being a woman.
- **Sexual Harassment -** Sexual harassment is defined under S. 354 A of the IPC as a man committing any of the following acts -

  (i) Physical contact and advances involving unwelcome and explicit sexual overtures

  (ii) A demand or request for sexual favours

  (iii) Showing pornography against the will of a woman

  (iv) Making sexually coloured remarks

The punishment for (i), (ii) and (iii) as given above is rigorous imprisonment for a term that may extend to 3 years, or a fine, or both while the punishment for (iv) is either simple or rigorous imprisonment for a term which may extend to 1 year, or a fine, or both.

- **Assault or use of criminal force to women with intent to disrobe -** Section 354B of the IPC criminalises assault or use of criminal force against a woman with the intention of disrobing her, i.e. with the intention of depriving her of her clothing or forcing her to be naked. Such an act is punishable with either simple or rigorous imprisonment of 3 to 7 years and a fine. Aiding such a crime also carries the same punishment. While this may sound similar to outraging modesty, it isn't. It is considered an offence whether or not the man intended to outrage the modesty of the woman.
- **Voyeurism -** Section 354C of the IPC criminalises the act of voyeurism. It defines it as a man watching or capturing the image of a woman engaged in a private act in circumstances where she would usually not expect to be observed by the perpetrator or by any other person on the orders of the perpetrator or the distribution of an image so captured by the perpetrator. The punishment for committing this offence is simple or rigorous imprisonment of 1 to 3 years and a fine. Repeated offenders are punished with simple or rigorous imprisonment of 3 to 7 years and a fine.
- **Stalking -** Section 354D of the IPC criminalises stalking of a woman by a man. It defines the Act to include continuous following or contacting a woman by a man or attempts to contact a woman to build a personal relationship with that women even when the woman has shown a clear lack of interest. It also include acts of monitoring a woman's electronic communication, i.e. communication over emails, social media etc. First time offenders are punished with either simple or rigorous imprisonment of upto 3 years and a fine while repeated offenders are punished with simple or rigorous imprisonment of upto 5 years and a fine.
- **Human Trafficking -** Section 370 of the IPC defines human trafficking as the action or practice of transporting people illegally or without their consent across areas mainly to be used in the labour or commercial sex industry. The Immoral Traffic (Prevention) Act, 1956 is the law regulating human trafficking in India.
- **Rape -** Section 375 of the IPC defines rape to include any or all of the following acts, by a man against a woman :

o Penetration of a man's sexual organ (penis) into a woman's mouth, vagina, urethra or anus or making her do so with him or someone else; or

o Inserting any object, not the penis, into a woman's vagina, urethra or anus or making her do so with him or someone else; or

o Manipulating any body part of the woman to cause penetration into her vagina, urethra, anus or any other body part or making her do so with him or someone else; or

o Applying his mouth to a woman's vagina, urethra or anus or making her do so with him or someone else.

Under the following circumstances :

- Against her will;
- Without her consent;
- With her consent, if such consent is obtained by causing her fear of death or hurt for herself or for someone she knows;
- With her consent, if she believes the man she is engaging with sexually is her husband;
- With her consent, where due to unsoundness of mind or intoxication, the woman is not able to fully understand the nature and consequences of the act she consents to;
- With or without the consent of a woman who is below 18 years if age;
- When the woman is unable to communicate consent.

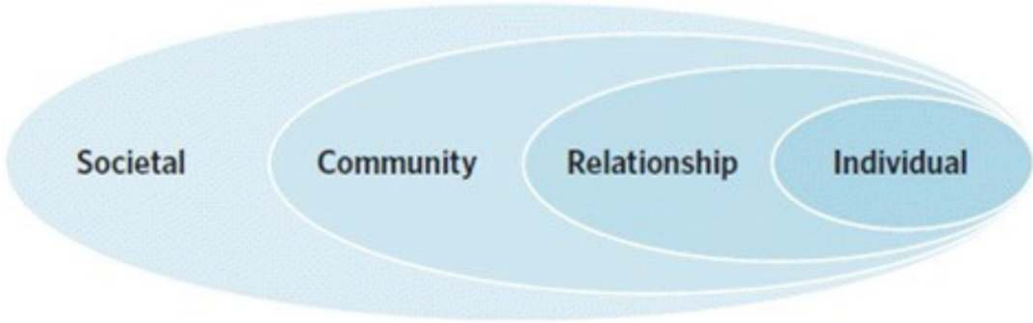
The punishment is rigorous imprisonment of 7 years to life and the person will also be liable to pay a fine.

FOCUSING ON PREVETION TO STOP THE VIOLNCE AGAINST WOMEN

Given the devastating effect violence has on women, efforts have mainly focused on responses and services for survivors. However, the best way to end violence against women and girls is to prevent it from happening in the first place by addressing to its root and structural causes.

The World Health Organization (WHO) recently published a strategic framework for preventing and reducing violence against women[11]. In doing so, WHO drew on an 'ecological model' of factors (below, Figure 2), which illustrates the intersecting determinants of intimate partner violence (IPV) that can influence the likelihood that men will abuse women and women will become victimized[11].

FIGURE 2.THE ECOLOGICAL MODEL (WHO, 2010)[11]



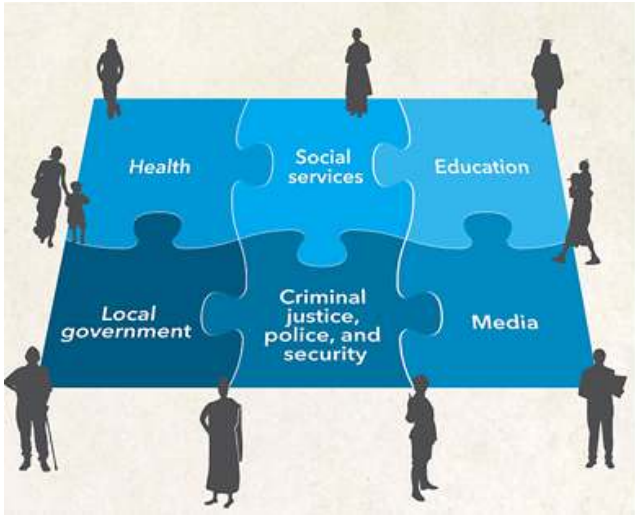
The factors related to both victimization and perpetration, and therefore to finding solutions to IPV, are located at the level of the individual (for example, witnessing abuse as a child; drinking alcohol at harmful levels), the relationship (for example, men controlling financial resources or having multiple partners); the community (high poverty or unemployment levels, weak community sanctions) and society (for example, norms of masculinity including dominance and aggression; the absence of legal sanction or redress against gender-based violence) [12].

Programs to reduce intimate partner violence need to address risk factors at multiple levels [13].

Level	Risk Factor	Intervention
Individual	History of violence in childhood	Parenting programmes to prevent child maltreatment
Relationship	Male control over women	Programmes targeting men and boys to promote gender equitable attitudes and behaviours
Community	Unequal gender norms that condone violence against women	Programmes promoting equitable gender norms through media, community mobilization, schools, and religious institutions
Societal	Male partner's harmful use of alcohol Women's lack of access to education and employment	Reducing availability and access to alcohol Laws, policies, and programmes that promote women's access to employment and microcredit, girls' access to education, and that ban or prohibit violence against women

Source: WHO[13]

To prevent and respond to violence against women, multiple sectors of society must work together.



The health sector plays a key role in preventing and responding to violence against women.

A role for the health sector [13]:

Provide comprehensive health services for survivors

Collect data about prevalence, risk factors, and health consequences

Inform policies to address violence against women

Prevent violence by fostering and informing prevention programmes

Advocate for the recognition of violence against women as a public health problem

CONCLUSION

As health care professionals we must understand that providing emotional support is as important as taking care of the medico-legal aspects of rape.

The physical wounds will heal but unless the survivor is given adequate psycho-social support in the right way from the first contact, the emotional trauma can last life-long.

If possible a mental health professional like clinical psychologists and or counselors should form part of the team in the initial stage itself.

If not possible they should at least be involved and referred to, for long term rehabilitation of the survivor

We must ensure to enable following six "S" for Women Empowerment

1. Shiksha = Education
2. Swasthya = Health
3. Swavlamban = Self-Reliance
4. Samajik Nyaya = Justice
5. Samvedana = Sensitivity
6. Samta = Equality

And, following four "S" for Women Survivors:

1. Seeking Medical Aid
2. Seeking Police Protection
3. Seeking Shelter
4. Seeking Legal Advice

SDG Goal 3 of good health and well-being, and Goal 5of gender equality will be achieved only if we work towards identifying, managing and hopefully preventing continued violence against women and children [14].

ACKNOWLEDGMENTS

Special thanks to Dr. Mandakini Megh and Dr. Meera Agnihotri who have been guiding lights in the work being done nationally in these areas, for their valuable inputs for this article.

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Sexual Violence : Examination of Survivors

Dr. Mandakini Megh

Dr. Reena Wani

- **Sample preservation is necessary if survivor is brought for examination within 7 days of last sexual assault. However within 96 hours is advisable.**
- **Preserve following samples -**
  - **Air dried swabs and smears from vagina, cervix, vulva, anus or any suspicious stain over body for detection of sperm/semen.**
  - **Preserve clothes for detection of seminal/blood/mud stains; if any visible to naked eye. (if she has not changed her clothes)**
  - **Preserve the blood for grouping 2 cc in EDTA bulb.**
  - **Preserve the blood for chemical analysis 5 cc in fluoride bulb.**
  - **Preserve the pubic hairs (20 cut hairs) for matching.**
  - **Nail clipping for detection of epithelial cells/ foreign body.**

Increased attention in the media and awareness among both Indians and the outside world is bringing attention to the issue of rape in India and helping empower women to report the crime. This year, incidents of rape cases in Kathua (J&K) and Unnao (UP) have once again drawn our attention towards the security and social well-being of women and protecting them from sexual and domestic violence. Despite the public support and open acknowledgement of violence against women through global movements like ME TOO CAMPAIGN; and Indian celebrities raising their voice against their partner's domestic violence, India still has a long way to go in terms of making women feel safe in the society.

It's really creditable that FOGSI has been taking the initiative in this area, from 2015 when under the Violence against women cell, guided by national convenor Dr. Duru Shah, the STAR Program was formulated which provides training modules, updates on laws, forensic evidence collection and medical/ psychological management of survivors. Under the guidance of our FOGSI Presidents

down the years, Dr Alka Kriplani, Dr RishmaPai and now Dr Jaideep Malhotra we have been conducting sensitization programs and distributing literature and guidelines on a standardized format. More details can be got from the FOGSI Office and website.

Gender-based violence is an increasing problem- it has been there since years but probably now more people are talking about it and there has been increasing media coverage and social debate on these issues. In fact, the on going # ME TOO CAMPAIGN on Facebook has made many people of different genders come out into the open and talk about their past experiences on social media.

Things have changed down the years with one key word- shift from being a **"victim"** to a **"survivor"** of abuse. The POCSO (Protection of Children from Sexual Offences) Act 2012 has also changed the definition of child from 12 years to 18 years. Although as gynecologists we focus on Women's health, boys (and transgenders) too are also vulnerable to sexual violence. In fact young boys are subjected to unnatural sex and are often unable to speak up about it.

A lot of doctors used to feel that such cases have to be referred to the nearest public hospital- this is no longer acceptable as per International guidelines **(FIGO Policy statement)** and Indian Law. Everyone may not have access to one-stop centers – in fact even in a Metropolitan city like Mumbai there are very few, if any, which fit the ideal criteria! Yet we have to do our best within the given circumstances, with one clear objective- that the evaluation process should not be an additional burden or trauma to the survivor, and should give useful and accurate information if legal action is contemplated later on.

We present herewith a simplified checklist to be followed by private practitioners in such cases:

If a case of alleged sexual assault brought for examination in private hospital then: Do your legal duties in following chronological order -

1) If case is brought by police then see vitals of survivor first; if vitals are stable then you can start your examination with consent of the survivor.
2) If case is brought by any one other than police like relatives or survivor came herself for examination then you can examine the survivor even without police requisition with consent of survivor as per guidelines by Ministry of Health and Family Welfare, Govt. of India (PDF file of guidelines is available over website of same dept.)
3) If vitals are not stable then first stabilize the case.
4) Do not refuse to give the treatment to the survivor. Treat survivor free of cost.
5) Failure to give treatment or its refusal is a punishable offence under section 166b of Indian Penal Code with one year imprisonment or fine or both.
6) If survivor came on her own but she does not want to lodge the police complaint then examine her and treat her. Also inform her that you are going to inform the police as it is your mandatory duty to inform each and every case of sexual assault.

7) Failure to inform police will make you responsible for any legal complications in future. Hence you must phone the nearest police station and inform, document in your records.

8) Consent: if she is less than 12 yrs or of unsound mind or intoxicated then take consent from parents/ guardian/ officer in charge of your hospital in absence of above. Under POCSO Act now age below 18 years consent of guardian/ parents is necessary.

9) If she is more than 12 yrs; she can also give consent (Assent Form). Age proof Xerox copy (ID card/ aadhar card/ birth certificate should be asked for, can be submitted subsequently- if not available, Forensic opinion to establish age advisable).

10) If person refuses to give consent then document informed refusal in the proforma.

11) Take consent in presence of disinterested witness with name and signature of witness.

12) Take consent in the language that survivor understands or with help of interpreter if necessary.

13) If survivor is female and she is less than 18yrs; then examination should be done by the female doctor as per **Section 27 Sub Section 2 of POCSO Act.** If female doctor not available ensure female attendant and document reason

14) Use Proforma Issued By Ministry of Health and Family Welfare, Govt. of India (Pdf File of guidelines is available over website of same dept.)

15) Sample preservation is necessary if survivor is brought for examination within 7 days of last sexual assault. However within 96 hours is advisable.

16) Preserve following samples

- Air dried swabs and smears from vagina, cervix, vulva, anus or any suspicious stain over body for detection of sperm/semen.
- Preserve clothes for detection of seminal/blood/mud stains; if any visible to naked eye. (if she has not changed her clothes)
- Preserve the blood for grouping 2 cc in EDTA bulb.
- Preserve the blood for chemical analysis 5 cc in fluoride bulb.
- Preserve the pubic hairs (20 cut hairs) for matching.
- Nail clipping for detection of epithelial cells/ foreign body.

13) Forward samples to FSL in sealed condition by filling the form no 2 with seal (form is available in forensic science lab at Mumbai. This is via police station/ constable.

14) Take due receipt of samples in the same form from police with his/her buckle no, date, time, mobile no, police station. Usually female PC is deputed in such cases.

15) Inform police before discharge if victim was admitted

16) Prepare 4 copies of your report. Sign each page of the report: Give one copy to police, one to victim with due receipt. One copy is for Forensic science Lab, and one for hospital records

17) Give treatment for emergency contraception and for prevention of STD as per history given by her. Consider PEP for HIV.

18) MTP can be done if victim is pregnant as a result of sexual assault as per guidelines given in MTP act. If age is less than 18 yrs then take consent from parents/guardians for MTP.

19) Preserve the product of conception for DNA analysis by filling form no 2. Send the product of conception in sealed condition to FSL through police with due receipt.

20) Preserve the medicolegal documents for 30 years or till final disposal of the case in court of law as per Civil Medical Code of Maharashtra.

21) Do not charge the police or victim for issuing MLC documents.

Document based on MOHFW Guidelines 2014,updated 2017; Inputs by: Dr Shailesh Mohite, (Prof & HOD FMT) & Dr. Chaitanya Kulkarni (Asst Prof. FMT), TNMC & BYL Nair Ch Hospital, Mumbai Friends, it's not difficult…we need to change our mind set and help the person who has approached us. Remember that we are shifting the focus from collection of evidence and medical examination to care, treatment and maintaining the dignity of the survivor!

Problems in the current response of the medical profession to sexual assault in India have been listed by CEHAT in 2012 to include

- Overemphasis on presence of injuries in medical examination. Absence of injuries interpreted as sexual assault did not take place.
- Poor history taking: non-recognition of non-penovaginal assaults.
- Mandatory police requisition for examination of sexual assault.
- Doctors' attitudes- fear of appearing in court, avoidance, stereotypes about rape.
- Inadequate update on current situation and laws

We need to be aware of our duties and legal implications of these situations and do the best we can.

Finally we will leave you with the words of Yehuda Bauer:

"Thou shalt not be a victim,

Thou shalt not be a perpetrator

But, above all,

Thou shalt not be a bystander."

Ministry of Health & Family Welfare Government of India

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Right to Information Act 2005

Mr. Rajesh Mehtani

"Right to information" means the right to information accessible under this Act which is held by or under the control of any public authority and includes the right to -

(i) Inspection of work, documents, records.

(ii) Taking notes, extracts or certified copies of documents or records.

(iii) Taking certified samples of material.

(iv) Obtaining information in the form of diskettes, floppies, tapes, video cassettes or in any other electronic mode or through printouts where such information is stored in a computer or in any other device.

Right of information is an extension of freedom of speech, a fundamental human right. **Article 19 of Universal Declaration of Human Rights, 1948 declares, "everyone has the right to freedom of opinion and expression; this right includes freedom to hold opinion without interference and to seek, receive and impart information and ideas through any media and regardless of frontiers"**

The Supreme Court of India right from 1975 onwards has consistently held that right to receive information or the right of being informed is implicit in Article 19(1)(a) of the Constitution of India.

Let us have a look on some of the important provisions of the Right to Information Act, 2005.

APPROPRIATE GOVERNMENT

"Appropriate Government" means in relation to a public authority which is established, constituted, owned, controlled or substantially financed by funds provided directly or indirectly –

(i) By the Central Government or the Union territory administration.

(ii) By the State Government.

COMPETENT AUTHORITY

(i) The Speaker in the case of the House of the People or the Legislative Assembly of a State or a

Union territory having such Assembly and the Chairman in the case of the Council of States or Legislative Council of a State.

(ii) The Chief Justice of India in the case of the Supreme Court.

(iii) The Chief Justice of the High Court in the case of a High Court.

(iv) The President or the Governor, as the case may be, in the case of other authorities established or constituted by or under the Constitution.

(v) The administrator appointed under article 239 of the Constitution.

INFORMATION

"Information" means any material in any form, including records, documents, memos, e-mails, opinions, advices, press releases, circulars, orders, logbooks, contracts, reports, papers, samples, models, data material held in any electronic form and information relating to any private body which can be accessed by a public authority under any other law for the time being in force

PUBLIC AUTHORITY

"Public authority" means any authority or body or institution of self- government established or constituted—

(a) By or under the Constitution.

(b) By any other law made by Parliament.

(c) By any other law made by State Legislature.

(d) By notification issued or order made by the appropriate Government, and includes any -

(i) Body owned, controlled or substantially financed.

(ii) Non-Government organisation substantially financed, directly or indirectly by funds provided by the appropriate Government.

RIGHT TO INFORMATION

"Right to information" means the right to information accessible under this Act which is held by or under the control of any public authority and includes the right to -

(i) Inspection of work, documents, records.

(ii) Taking notes, extracts or certified copies of documents or records.

(iii) Taking certified samples of material.

(iv) Obtaining information in the form of diskettes, floppies, tapes, video cassettes or in any other electronic mode or through printouts where such information is stored in a computer or in any other device.

THIRD PARTY

"Third party" means a person other than the citizen making a request for information and includes a public authority.

ELIGIBILITY FOR INFORMATION

Subject to the provisions of this Act, all citizens shall have the right to information.

DEEMED PIO

The Central Public Information Officer or State Public Information Officer, as the case may be, may seek the assistance of any other officer as he or she considers it necessary for the proper discharge of his or her duties.

SECTION 5(4)

Any officer, whose assistance has been sought under sub-section 5(4), shall render all assistance to the Central Public Information Officer or State Public Information Officer, as the case may be, seeking his or her assistance and for the purposes of any contravention of the provisions of this Act, such other officer shall be treated as a Central Public Information Officer or State Public Information Officer, as the case may be.

TRANSFER OF APPLICATION

Where an application is made to a public authority requesting for an information,—

(i) Which is held by another public authority; or

(ii) The subject matter of which is more closely connected with the functions of another public authority, the public authority, to which such application is made, shall transfer the application or such part of it as may be appropriate to that other public authority and inform the applicant immediately about such transfer:

Provided that the transfer of an application pursuant to this sub-section shall be made as soon as practicable but in no case later than five days from the date of receipt of the application.

FORM OF INFORMATION

An information shall ordinarily be provided in the form in which it is sought unless it would disproportionately divert the resources of the public authority or would be detrimental to the safety or preservation of the record in question.

EXEMPTIONS

(a) Information, disclosure of which would prejudicially affect the sovereignty and integrity of India, the security, strategic, scientific or economic interests of the State, relation with foreign State or lead to incitement of an offence.

(b) Information which has been expressly forbidden to be published by any court of law or tribunal or the disclosure of which may constitute contempt of court.

(c) Information, the disclosure of which would cause a breach of privilege of Parliament or the State Legislature.

(d) Information including commercial confidence, trade secrets or intellectual property, the disclosure of which would harm the competitive position of a third party, unless the competent

authority is satisfied that larger public interest warrants the disclosure of such information.

(e) Information available to a person in his fiduciary relationship, unless the competent authority is satisfied that the larger public interest warrants the disclosure of such information.

(f) Information received in confidence from foreign Government.

(g) Information, the disclosure of which would endanger the life or physical safety of any person or identify the source of information or assistance given in confidence for law enforcement or security purposes.

(h) Information which would impede the process of investigation or apprehension or prosecution of offenders.

(i) Cabinet papers including records of deliberations of the Council of Ministers, Secretaries and other officers: Provided that the decisions of Council of Ministers, the reasons thereof, and the material on the basis of which the decisions were taken shall be made public after the decision has been taken, and the matter is complete, or over provided further that those matters which come under the exemptions specified in this section shall not be disclosed.

(j) Information which relates to personal information the disclosure of which has no relationship to any public activity or interest, or which would cause unwarranted invasion of the privacy of the individual unless the Central Public Information Officer or the State Public Information Officer or the appellate authority, as the case may be, is satisfied that the larger public interest justifies the disclosure of such information provided that the information which cannot be denied to the Parliament or a State Legislature shall not be denied to any person.

SEVERABILITY

(1) Where a request for access to information is rejected on the ground that it is in relation to information which is exempt from disclosure, then, notwithstanding anything contained in this Act, access may be provided to that part of the record which does not contain any information which is exempt from disclosure under this Act and which can reasonably be severed from any part that contains exempt information.

(2) Where access is granted to a part of the record under sub-section (1), the Central Public Information Officer or State Public Information Officer, as the case may be, shall give a notice to the applicant, informing—

(a) That only part of the record requested, after severance of the record containing information which is exempt from disclosure, is being provided.

(b) The reasons for the decision, including any findings on any material question of fact, referring to the material on which those findings were based.

(c) The name and designation of the person giving the decision.

(d) The details of the fees calculated by him or her and the amount of fee which the applicant is required to deposit.

(e) His or her rights with respect to review of the decision regarding non-disclosure of part of the information, the amount of fee charged or the form of access provided, including the particulars of the senior officer specified under sub-section (1) of section 19 or the Central Information Commission or the State Information Commission, as the case may be, time limit, process and any other form of access.

THIRD PARTY INFORMATION

(1) Where a Central Public Information Officer or a State Public Information Officer, as the case may be, intends to disclose any information or record, or part thereof on a request made under this Act, which relates to or has been supplied by a third party and has been treated as confidential by that third party, the Central Public Information Officer or State Public Information Officer, as the case may be, shall, within five days from the receipt of the request, give a written notice to such third party of the request and of the fact that the Central Public Information Officer or State Public Information Officer, as the case may be, intends to disclose the information or record, or part thereof, and invite the third party to make a submission in writing or orally, regarding whether the information should be disclosed, and such submission of the third party shall be kept in view while taking a decision about disclosure of information provided that except in the case of trade or commercial secrets protected by law, disclosure may be allowed if the public interest in disclosure outweighs in importance any possible harm or injury to the interests of such third party.

(2) Where a notice is served by the Central Public Information Officer or State Public Information Officer, as the case may be, under sub-section (1) to a third party in respect of any information or record or part thereof, the third party shall, within ten days from the date of receipt of such notice, be given the opportunity to make representation against the proposed disclosure.

(3) Notwithstanding anything contained in section 7, the Central Public Information Officer or State Public Information Officer, as the case may be, shall, within forty days after receipt of the request under section 6, if the third party has been given an opportunity to make representation under sub-section (2), make a decision as to whether or not to disclose the information or record or part thereof and give in writing the notice of his decision to the third party.

(4) A notice given under sub-section (3) shall include a statement that the third party to whom the notice is given is entitled to prefer an appeal under section 19 against the decision.

FIRST APPEAL

(1) Any person who, does not receive a decision within the time specified in sub-section (1) or clause (a) of sub-section (3) of section 7, or is aggrieved by a decision of the Central Public Information Officer or State Public Information Officer, as the case may be, may within thirty days from the expiry of such period or from the receipt of such a decision prefer an appeal to such officer who is senior in rank to the Central Public Information Officer or State Public

Information Officer as the case may be, in each public authority provided that such officer may admit the appeal after the expiry of the period of thirty days if he or she is satisfied that the appellant was prevented by sufficient cause from filing the appeal in time.

(2) An appeal under sub-section (1) or sub-section (2) shall be disposed of within thirty days of the receipt of the appeal or within such extended period not exceeding a total of forty-five days from the date of filing thereof, as the case may be, for reasons to be recorded in writing.

SECOND APPEAL

A second appeal against the decision of first appellate authority shall lie within ninety days from the date on which the decision should have been made or was actually received, with the Central Information Commission or the State Information Commission:

Provided that the Central Information Commission or the State Information Commission, as the case may be, may admit the appeal after the expiry of the period of ninety days if it is satisfied that the appellant was prevented by sufficient cause from filing the appeal in time.

PENALTIES

(1) Where the Central Information Commission or the State Information Commission, as the case may be, at the time of deciding any complaint or appeal is of the opinion that the Central Public Information Officer or the State Public Information Officer, as the case may be, has, without any reasonable cause, refused to receive an application for information or has not furnished information within the time specified under sub-section (1) of section 7 or malafidely denied the request for information or knowingly given incorrect, incomplete or misleading information or destroyed information which was the subject of the request or obstructed in any manner in furnishing the information, it shall impose a penalty of two hundred and fifty rupees each day till application is received or information is furnished, so however, the total amount of such penalty shall not exceed twenty-five thousand rupees.

Provided that the Central Public Information Officer or the State Public Information Officer, as the case may be, shall be given a reasonable opportunity of being heard before any penalty is imposed on him:

Provided further that the burden of proving that he acted reasonably and diligently shall be on the Central Public Information Officer or the State Public Information Officer, as the case may be.

(2) Where the Central Information Commission or the State Information Commission, as the case may be, at the time of deciding any complaint or appeal is of the opinion that the Central Public Information Officer or the State Public Information Officer, as the case may be, has, without any reasonable cause and persistently, failed to receive an application for information or has not furnished information within the time specified under sub-section (1) of section 7 or malafidely denied the request for information or knowingly given incorrect, incomplete or misleading

information or destroyed information which was the subject of the request or obstructed in any manner in furnishing the information, it shall recommend for disciplinary action against the Central Public Information Officer or the State Public Information Officer, as the case may be, under the service rules applicable to him.

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      and many others...

Corrected

Women Rights in India
Constitutional Rights and Legal Rights

Extracted from the Internet for ready reference by team | August 3, 2017

Dr. Rita Mittal

COMMENT

The rights available to Woman in India can be classified into two categories, namely as constitutional rights and legal rights. The constitutional rights are those which are provided in the various provisions of the constitution. The legal rights, on the other hand, are those which are provided in the various laws (acts) of the Parliament and the State Legislatures.

Constitutional Rights to Women : The rights and safeguards enshrined in the constitution for women in India are listed below:

1. The state shall not discriminate against any citizen of India on the ground of sex [Article 15(1)].
2. The state is empowered to make any special provision for women. In other words, this provision enables the state to make affirmative discrimination in favour of women [Article 15(3)].
3. No citizen shall be discriminated against or be ineligible for any employment or office under the state on the ground of sex [Article 16(2)].
4. Traffic in human beings and forced labour are prohibited [Article 23(1)].
5. The state to secure for men and women equally the right to an adequate means of livelihood [Article 39(a)].
6. The state to secure equal pay for equal work for both Indian men and women [Article 39(d)].
7. The state is required to ensure that the health and strength of women workers are not abused and that they are not forced by economic necessity to enter avocations unsuited to their strength [Article 39(e)].
8. The state shall make provision for securing just and humane conditions of work and maternity relief [Article 42].
9. It shall be the duty of every citizen of India to renounce practices derogatory to the dignity of women [Article 51-A(e)].
10. One-third of the total number of seats to be filled by direct election in every Panchayat shall be reserved for women [Article 243-D(3)].
11. One-third of the total number of offices of chairpersons in the Panchayats at each level shall be reserved for women [Article 243-D(4)].
12. One-third of the total number of seats to be filled by direct election in every Municipality shall be reserved for women [Article 243-T(3)].

13. The offices of chairpersons in the Municipalities shall be reserved for women in such manner as the State Legislature may provide [Article 243-T(4)].

Legal Rights to Women : The following various legislation's contain several rights and safeguards for women:

1. Protection of Women from Domestic Violence Act (2005) is a comprehensive legislation to protect women in India from all forms of domestic violence. It also covers women who have been/are in a relationship with the abuser and are subjected to violence of any kind—physical, sexual, mental, verbal or emotional.
2. Immoral Traffic (Prevention) Act (1956) is the premier legislation for prevention of trafficking for commercial sexual exploitation. In other words, it prevents trafficking in women and girls for the purpose of prostitution as an organised means of living.
3. Indecent Representation of Women (Prohibition) Act (1986) prohibits indecent representation of women through advertisements or in publications, writings, paintings, figures or in any other manner.
4. Commission of Sati (Prevention) Act (1987) provides for the more effective prevention of the commission of sati and its glorification on women.
5. Dowry Prohibition Act (1961) prohibits the giving or taking of dowry at or before or any time after the marriage from women.
6. Maternity Benefit Act (1961) regulates the employment of women in certain establishments for certain period before and after child-birth and provides for maternity benefit and certain other benefits.
7. Medical Termination of Pregnancy Act (1971) provides for the termination of certain pregnancies by registered medical practitioners on humanitarian and medical grounds.
8. Pre-Conception and Pre-Natal Diagnostic Techniques (Prohibition of Sex Selection) Act (1994)prohibits sex selection before or after conception and prevents the misuse of pre-natal diagnostic techniques for sex determination leading to female foeticide.
9. Equal Remuneration Act (1976) provides for payment of equal remuneration to both men and women workers for same work or work of a similar nature. It also prevents discrimination on the ground of sex, against women in recruitment and service conditions.
10. Dissolution of Muslim Marriages Act (1939) grants a Muslim wife the right to seek the dissolution of her marriage.
11. Muslim Women (Protection of Rights on Divorce) Act (1986)protects the rights of Muslim women who have been divorced by or have obtained divorce from their husbands.
12. Family Courts Act (1984) provides for the establishment of Family Courts for speedy settlement of family disputes.
13. Indian Penal Code (1860) contains provisions to protect Indian women from dowry death, rape,

kidnapping, cruelty and other offences.

14. Code of Criminal Procedure (1973) has certain safeguards for women like obligation of a person to maintain his wife, arrest of woman by female police and so on.
15. Indian Christian Marriage Act (1872) contain provisions relating to marriage and divorce among the Christian community.
16. Legal Services Authorities Act (1987) provides for free legal services to Indian women.
17. Hindu Marriage Act (1955) introduced monogamy and allowed divorce on certain specified grounds. It provided equal rights to Indian man and woman in respect of marriage and divorce.
18. Hindu Succession Act (1956) recognizes the right of women to inherit parental property equally with men.
19. Minimum Wages Act (1948) does not allow discrimination between male and female workers or different minimum wages for them.
20. Mines Act (1952) and Factories Act (1948) prohibits the employment of women between 7 P.M. to 6 A.M. in mines and factories and provides for their safety and welfare.
21. The following other legislation's also contain certain rights and safeguards for women:
    - Employees' State Insurance Act (1948)
    - Plantation Labour Act (1951)
    - Bonded Labour System (Abolition) Act (1976)
    - Legal Practitioners (Women) Act (1923)
    - Indian Succession Act (1925)
    - Indian Divorce Act (1869)
    - Parsi Marriage and Divorce Act (1936)
    - Special Marriage Act (1954)
    - Foreign Marriage Act (1969)
    - Indian Evidence Act (1872)
    - Hindu Adoptions and Maintenance Act (1956).
22. National Commission for Women Act (1990) provided for the establishment of a National Commission for Women to study and monitor all matters relating to the constitutional and legal rights and safeguards of women.
23. Sexual Harassment of Women at Workplace (Prevention, Prohibition and Redressal). Act (2013)provides protection to women from sexual harassment at all workplaces both in public and private sector, whether organised or unorganized.

Modern Management of Anaemia in Pregnancy

Dr. Purnima Nadkarni
Dr. Vaibhav Nadkarni, Dr. Pooja Nadkarni Singh & Dr. Aditi Nadkarni

- **The fetal consequences of anaemia in pregnancy are well established and depend not only on the severity of anaemia but also on the duration. Maternal haemoglobin below 11.0 g/dl is associated with a significant rise in perinatal mortality rates and triples at maternal haemoglobin levels below 8.0 g/dl and increase by tenfold when anaemia is very severe (Hb < 4 mg/dl).**
- **The maternal outcomes in severe anaemia depend on level of decompensation. If not recognized early and corrected, the heart is unable to compensate for the severity of anaemia and eventual circulatory failure occurs leading to pulmonary oedema and death. The women are unable to tolerate third stage of labour and blood losses associated with delivery. When the anaemia is very severe, there is a steep rise in maternal deaths.**

INTRODUCTION

Anaemia is the most common medical disorder during pregnancy and is known for high maternal morbidity, mortality and perinatal deaths. The World Health Organization (WHO) prevalence of anaemia in South East Asia is 56% and as per NFHS 4 (2015-2016) Indian prevalence of anaemia in pregnancy is 23.6-61.4 %[1]. Out of which Iron Deficiency anaemia attributes to 50% of the cases of anaemia in pregnancy, low socioeconomic status, high parity, nutritional deficiency, phytates rich Indian diets, malaria, helminthic infection and inflammatory or infectious disease further increases the incidence of Iron Deficiency during pregnancy[2].

HAEMATOLOGICAL CHANGES IN PREGNANCY

Pregnancy is associated with physiological changes that assist foetal survival and prepares the mother for labour, delivery and breastfeeding. The changes start from 6 weeks of gestation and are largely as a result of progesterone and oestrogen. The total blood volume increases steadily from as early as 6 weeks of pregnancy to reach a maximum of 30-40% above the non-pregnant level at 30 to 34 weeks. The plasma volume increases by 40-50 % (1.25 L). Red blood cell mass increases by 20-

30% (approximately 350mg) due to increase in the production of erythropoietin. There is disproportionate increase in plasma volume and red blood cell mass resulting in relative fall of haematocrit and haemoglobin value, with peak haemodilution occurring at 32 weeks. This is termed physiological anaemia of pregnancy. This dilution picture is often normochromic and normocytic. In pregnancy, there is an additional demand of about 1000 mg iron. While the transferrin and total iron binding capacity rises, the serum iron falls. Thus women who enter pregnancy in an iron deficient state are then unable to meet the demands of pregnancy by diet alone and require iron supplementation.

EPIDEMIOLOGY OF ANAEMIA IN PREGNANCY

Anaemia has been found to be associated with poverty and underdevelopment and is one of the most common disorders globally. The incidence of anaemia varies from place to place even within the same country and depends on the socioeconomic status and level of development. The World Health Organization reports anaemia among the top ten most important contributors to global ill health and deaths. It estimated that about a third of the world's population of 7 billion have haemoglobin levels below the WHO criteria for diagnosis of anaemia. The majority of these persons reside in Sub-Saharan Africa and South East Asia. Pregnant women are particularly considered to be the most vulnerable group because of the additional demands that are made on maternal stores during pregnancy. The average global prevalence of anaemia in pregnancy is reported to be 51%. Like anaemia in the general population the prevalence of anaemia in pregnancy varies from 17% in Europe to 52 % and 60% respectively in Africa and Asia. In sub-Saharan Africa it is estimated that 20% of maternal deaths are associated with anaemia. It is also a major risk factor for infant iron deficiency which has been shown to be associated with adverse behavioural and cognitive development of children and low birth weight, which is one of the main risk factors for infant mortality.

DEFINITION OF ANAEMIA

The term anaemia refers to the reduction in the oxygen-carrying capacity of the blood due to fewer circulating red blood cells than normal or a reduction in the concentration of haemoglobin. WHO has defined Anaemia during pregnancy as Haemoglobin concentration of < 11 gm % and haematocrit of <33%[3]. CDC (centre for drug control) proposes cut off point of 11 gm% in 1st and 3rd Trimester and 10.5 gm % during 2nd trimester.

Severity of Anaemia is graded as per ICMR

Degree of severity	Haemoglobin Concentration (gm%)
Mild	10-10.9
Moderate	7-10
Severe	<7
Very Severe	<4

CLASSIFICATION OF ANAEMIA

A. Physiological

B. Acquired

1. Nutritional Anaemia

i. Iron deficiency

ii. Folate deficiency

iii. B12 deficiency

2. Blood loss

a. Acute

i. Antepartum haemorrhage (Eg: placenta praevia, abruptio- placenta)

ii. Intrapartum haemorrhage

iii. Postpartum Haemorrhage (PPH)

b. Chronic

i. Hookworm infestation

ii. Bleeding haemorrhoids

iii. Peptic Ulcer Disease

3. Bone marrow failure

a. Aplastic anaemia

b. Isolated secondary failure of erythropoiesis

c. Drugs (Eg: Chloramphenicol, Zidovudine)

d. Chemo radiation

4. Haemolytic

a. Inherited

i. Haemoglobinopathies (Eg: Sickle cell disorders, Thalassemia)

ii. Red cell Membrane defects (Eg: Hereditary spherocytosis, elliptocytosis)

iii. Enzyme deficiencies (Eg: G6PD deficiency, Pyruvate kinase defeciency)

b. Acquired

i. Immune Haemolytic anaemias. eg autoimmune, alloimmune, drug induced

ii. Non- Immune Haemolytic anaemias

a. Acquired membrane defects. eg: Paroxysmal nocturnal Haemoglobinuria

b. Mechanical damage. eg: Microangiopathic haemolytic anaemia)

iii. Secondary to systemic disease (eg renal diseases, liver disease)

iv. Infections (Malaria, TB, Sepsis, HIV)

AETIOLOGY

The causes of anaemia in the general population are generally same as for anaemia in pregnancy. The causes of anaemia in pregnancy are often multifactorial. In developing countries, the major causes of anaemia in pregnancy are nutritional deficiencies, infections and infestations, haemorrhage and haemoglobinathies. Anaemia is also seen in some chronic medical disorders like renal and hepatic diseases.

Nutrition - The World health Organization ((WHO) estimates, that about half of all pregnant women globally suffer from nutritional anaemia which is mainly due iron and folate deficiency in diet.

1. **Increased Demand:** The demand of Iron and folic acid is markedly increased during pregnancy.
2. **Diminished Intake:** apart from socioeconomic factor faulty dietary habits, loss of appetite and vomiting of pregnancy.
3. **Diminished Absorption:** Acidic environment favours Iron absorption on the hand antacids Inhibits iron absorption.
4. **Disturbed Metabolism:** presence of infections markedly interferes with erythropoiesis.
5. **Infestation**
   i. Hook worm infestation is another cause of iron deficiency anaemia in the tropics. The folic acid requirement is also increased two fold in pregnancy. Normal body stores can only last for 3- 4 months. Folate deficiency in pregnancy often develops as a result of poor dietary intake which is often the case in developing countries as well as excess utilization. Sources of folate include liver, egg yolk, and leafy green vegetables. Folate deficiency results in ineffective erythropoesis. Folate deficiency can be further exacerbated in pregnant women with hemoglobinopathies as well as in those residing in areas of high malaria endemicity as increased haemolysis leads to high red cell turnover and increased folate demand. Vitamin B12 deficiency is rare during pregnancy as the daily requirement is as low as 3- 5µg and liver stores last for as long as 2 years.

Infections - Pregnant women are more prone to infections as a result of depressed immunity. Anaemia due to infections is usually as a result of products from the infecting organisms causing ill health, fever, red cell destruction and/ or reduced red cell production. Bacterial infections used to be a leading cause of anaemia, however in the tropics and developing countries, malaria and more recently, HIV/AIDS are leading contributors to anaemia in pregnancy.

Malaria - Anaemia resulting from malarial infection is caused by the destruction of infected and uninfected red blood cells as well as bone marrow suppression. Red blood cells infected with malaria parasites also accumulate and sequester in the placenta. Macrophages and cytokines (e.g. Tumor necrosis factor alpha, Interferon gamma and interleukin 1), enhance red cell destruction, splenic clearance capacity, and depress bone marrow erythropoesis.

HIV/AIDS - The aetiology of HIV associated anaemia is multifactorial and may include the infiltration of the bone marrow by tumour or infection, bone marrow suppression by the virus itself, the use of myelosuppressive drugs like Zidovudine or drugs that prevent the utilization of folate like cotrimoxazole. Other aetiologies include decreased production of erythropoietin, red cell

destruction as a result of autoantibodies to red blood cells, and nutritional deficiencies. Apart from iron and folate deficiency, other reported vitamin deficiencies in HIV infection include vitamin B12, vitamin B6 and vitamin A.

Haemoglobinopathies - Haemoglobinopathies are inherited disorders affecting haemoglobin structure (Sickle cell disorders) or synthesis (thalassemias). They are usually seen in individuals from Africa, the Middle East, the Mediterranean, Asia and the Far East. The haemoglobinopathies that cause anaemia in pregnancy are sickle cell disorders- HbSS, HbSC and HBS- beta thalassemia. Haemoglobinopathies cause a chronic haemolytic anaemia. In sickle cell disorders, the abnormal haemoglobin S sickles in hypoxic states, predisposing the structurally damaged cells to early destruction hence affected persons are chronically anaemic. Folate demands are increased and concurrent infections will worsen anaemia.

Haemorrhage - Acute blood loss in cases of ectopic pregnancy, antepartum haemorrhage and abortions are common causes of anaemia in pregnancy. Chronic blood loss from worm infestations, gastrointestinal ulcers and hemorrhoids results in depletion of iron stores and ineffective erythropoesis. [6.7]

Red Cell Aplasia - This is a rare cause of anaemia in pregnancy and results from a selective failure of erythropoesis. In most cases, the cause is unknown The identified causes of pure red cell aplasia include autoimmune diseases (e.g. SLE,) drugs, and infection with parvovirus B19.

CONSEQUENCES OF ANAEMIA IN PREGNANCY

Fetal - The fetal consequences of anaemia in pregnancy are well established and depend not only on the severity of anaemia but also on the duration. Maternal haemoglobin below 11.0 g/dl is associated with a significant rise in perinatal mortality rates and triples at maternal haemoglobin levels below 8.0 g/dl and increase by tenfold when anaemia is very severe (Hb < 4 mg/dl). Similar findings have also been noted for both infant birth weight and preterm delivery rates and intrauterine growth restriction.

Maternal - Women with moderate anaemia tend to experience higher rates of morbidity during pregnancy as compared to those with mild anaemia. Evidence has shown that a large percentage of maternal deaths due to antepartum haemorrhage, pre-eclampsia and infections occur in women with moderate anaemia. The maternal outcomes in severe anaemia depend on level of decompensation. If not recognized early and corrected, the heart is unable to compensate for the severity of anaemia and eventual circulatory failure occurs leading to pulmonary oedema and death. The women are unable to tolerate third stage of labour and blood losses associated with delivery. When the anaemia is very severe, there is a steep rise in maternal deaths.

CLINICAL FEATURES

The clinical features of anaemia in pregnancy are dependent on rapidity of onset and severity of anaemia. In general, symptoms occur with moderate to severe anaemia and are more severe when anaemia has been rapidly progressive. Anaemia may be asymptomatic. Where the patient is symptomatic, symptoms may be those of vague ill health, headaches, light headedness, tinnitus, intermittent claudication, or symptoms of angina. However, as decompensation ensues, there may be palpitations, easy fatigability and patients can present in heart failure.

The signs of anaemia can be general or specific. General signs of anaemia include pallor of the mucous membranes, hyperdynamic circulation with tachycardia, a bounding pulse, cardiomegaly

and a apical systolic flow murmur (haemic murmur). The specific signs are associated with particular types of anaemia e.g painless glossitis, angular stomatitis, ridged or spoon shaped nails, unusual dietary cravings for non-food substances(pica) in iron deficiency, jaundice in haemolytic and megaloblastic anaemias, neuropathy, widespread melanin pigmentation in B12 deficiency. Hepato-splenomegaly (may be difficult to elicit when pregnancy is advanced) may be features of chronic haemolytic disorders, megaloblastic anaemia, or other haematologic pathologies. The findings of anaemia with fever and spontaneous bruising may be indicative of bone marrow failure.

DIAGNOSIS OF CAUSE(S) OF ANAEMIA

A detailed history, physical examination and appropriate investigations are necessary for the identification of the cause(s) of anaemia. Except in very severe anaemia where there is an urgent need to treat the pregnant woman to avoid death, the cardinal rule is to establish the cause of anemia before commencing treatment.

History - A detailed history including diet, gynaecological, obstetric, drug and social history should be taken. Symptoms of decompensation and possible predisposing factors are to be taken into consideration.. Previous history of postpartum haemorrhage or abortion as well as numbers of pregnancies and birth spacing and drug ingestion should be sought. Ideally, the history should address all possible aetiology of anaemia, features and its complications.

Physical examination - A good physical examination should confirm the presence of anaemia, possible aetiology and signs of decompensation. Where anaemia has been chronic, physical examination may reveal cardiomegaly, bounding pulses and a systolic flow murmur (haemic murmur). In acute blood loss the patient can present in shock. On examination the presence of pallor, jaundice, spleen and liver size should be documented.

INVESTIGATIONS

Investigations for anaemia are general and specific. Complete Blood Count provides information about haemoglobin levels, packed cell volume, white cell and platelet counts.

Red cell indices include mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) and classify anaemia into either microcytic (MCV 100fL) and normocytic (MCV80-100fL) or hypochromic or normochromic (MCH and MCHC).

A peripheral blood smear provides information about red cell morphology, variations in size, and shape, the reticulocyte count provides information on the marrow response. In the presence of anaemia a reticulocyte count less than 2-3 times normal indicates inadequate bone marrow response.

Elevated neutrophil counts may suggest an infection and peripheral smears that reveal a pancytopenia is suggestive of marrow failure. Hyper segmentation of neutrophils is suggestive of Vit. B12 deficiency

RDW - Red cell distribution width.

Stools should also be examined for colour, consistency, occult blood, ova and parasites. It is also important to note that in the tropics most of the causes may coexist.

Other specific tests are often dictated by suspected cause of the anaemia. In the tropics, it is usual to screen for malaria as it is a well-documented cause of anaemia in pregnancy.

Table for specific Investigation

1. Iron deficiency a. Serum ferritin b. Total iron binding capacity c. Transferrin saturation d. Marrow iron stain	**2. Haemoglobinopathics** a. Hb electrophoresis **3. HIV infection** a. Detection of antibody to HIV using ELISA or Western blot assays.
4. Chronic medical disorders a. Liver function tests b. Serum electrolyte, urea and creatinine c. Screening for autoimmune diseases	**5. Antepartum haemorrhage** a. Ultrasonography

TREATMENT

It is of utmost importance to establish the cause of anaemia prior to definitive management. The goal of treatment of anaemia in pregnancy is to maintain wellbeing, identify and correct the underlying cause(s) within shortest time possible and improve patient quality of life and survival. By and large, the management of anaemia in a pregnant woman depends on the duration of pregnancy, severity of the anaemia and complication (obstetric, medical or both). In cases of decompensation, very severe anaemia and acute blood loss immediate red cell transfusion is required.

Mild and moderate anaemia in pregnancy as a result of iron deficiency should be carefully assessed for the cause and the patient placed on iron therapy apart from the treatment of the aetiology. The preferred route of iron replacement is oral route as there is no benefit in giving parenteral iron as opposed to oral iron.

Oral Iron Therapy - Ferrous sulphate (200mg per tablet containing 67mg elemental iron) is the least expensive and best absorbed form of Iron.

Ferrous glutamate (300mg per tablet containing 37mg elemental iron)

Ferrous fumarate can also be used where iron sulphate is not tolerated. The optimal doses are 120-200mg daily of elemental iron in divided doses.

Oral iron should be given for long enough to correct the anaemia and to replenish iron stores which usually means for at least 6 months. Haemoglobin should rise at the rate of approximately 2g/dl every 3 weeks. Side effects of oral iron include gastrointestinal symptoms such as diarrhoea, nausea, constipation, abdominal pain.

Parenteral Iron may be indicated in cases of poor adherence, intolerable side effects or malabsorption of oral iron. In such situation parenteral iron such as iron dextran or sorbitol may be administered by the intravenous or intramuscular route. The hematological response to parenteral iron is not faster than adequate dosage of oral iron but the stores are replenished faster.

Ferric hydroxide –sucrose (Venofer): is the safest form and is administered by slow intravenous injection or infusion usually 200mg in each infusion.

Iron dextran (Cosmofer): can be given but not used due to severe anaphylaxis

Iron sorbitol (Jectofer)(50mg/ml) Intramuscular Injections: should be given deep into the gluteal muscle. The drawbacks of intramuscular iron include pain and staining of the skin at the injection site,myalgia, athralgia and injection abscess.

Total Dose Iron (Ferric Carboxy Maltose): 500/1000 mg single dose can be safely given during 2nd & 3rd Trimester without anaphylactic reaction.

Severe or very severe anaemia requires the immediate hospitalization of the woman, management of heart failure and transfusion of packed cells. Once the emergency is averted, the iron replacement is as in mild to moderate anaemia.

Treatment of anaemia from **folate deficiency** is with folic acid 5mg daily for 4 months and is usually given throughout pregnancy.

Vitamin B12 deficiency is rare in pregnancy and is treated with intramuscular injections of hydroxocobalamin 1000ug . Initial doses are 6 injections over 2-3 weeks then 100ug every 3 months.

Erythropoietin is beneficial in patients -with marrow suppression . 100-200U/Kg 3times a week until normalization of the red cell and then once a weekly to maintain haemoglobin of approximately 12g/dl.

Treatment of malaria with artemisin combination therapy, bacterial infections with appropriate antibiotics, hookworm infestation with mebendazole or Albendazole and use of highly active antiretroviral therapy according to treatment guidelines in HIV infection. Other co-morbidities e.g. diabetes, hypertension should also be managed.

PREVENTION

Approximately 1000 mg of iron is required during a normal pregnancy. Up to 600mg of iron is required for the increase in maternal red cell mass, and a further 300mg for the foetus. These requirements exceed the iron storage of most young women and often cannot be met by the diet. Therefore, few women avoid depletion of iron reserves by the end of pregnancy.

Folate requirements are increased approximately twofold in pregnancy (800ug/day vs 400ug/day because of transfer of folate to the growing fetus and if diet is insufficient, may exceed the body's stores of folate(5-10mg). To prevent anaemia in pregnancy the following are necessary.

Routine screening for anaemia in adolescence, nutritional education about foods rich in iron (meat, liver, leafy green vegetables, legumes) and folate (liver, egg yolk, yeast and leafy green vegetables) to encourage consumption, early as well as regular antenatal clinic attendances, iron, folate supplementation in pregnancy and early treatment of concomitant infections. In areas of high malaria endemicity, intermittent prophylactic therapy with pyrimethamine sulphodoxine for malaria should also be given at 16-17 weeks and 4 weeks later. A third dose is given in HIV infection.

CONCLUSION

Anaemia in pregnancy is a major public health problem in developing countries and is associated with an increased risk of maternal and perinatal morbidity and mortality. Fortification of foods with iron and folate, routine screening for anaemia from adolescence, health education, and prompt treatment of infections and attendance of antenatal facilities by pregnant women can reduce this burden

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Prediction and Prevention of Preterm Labor

Dr Pratap Kumar **Dr Akhila Vasudeva**

- **Presently, none of the common late-pregnancy complications including preterm labor can be predicted with sufficient accuracy (sensitivity and specificity) using a single biochemical marker7. For this reason, the simultaneous use of multiple risk-factors, that may include demographic/risk-factor(s), cervical length and biochemical markers.**
- **Preventing teenage pregnancy, preventing sexually transmitted infections, providing adequate diet, maintaining optimal weight gain in pregnancy, maintaining optimal inter pregnancy interval are the general measures as part of good antenatal care.**
- **Metronidazole is commonly used for the treatment of BV and because AV does not respond well to metronidazole, clindamycin is considered to be a better choice for treating pregnant women with an unconfirmed diagnosis of abnormal vaginal microbiota because it is able to eradicate both AV and BV-associated bacteria.**

INTRODUCTION

Spontaneous Preterm Labor (PTL) is the leading cause of perinatal mortality/morbidity. In addition, this is a significant contributor to long term neurological sequel in the offspring. The incidence of Spontaneous Preterm Birth (SPTB) varies between countries with a range of 5-13%, resulting in 15 million preterm deliveries worldwide each year. The highest rates are found in South-eastern and South Asia where 13.4% of the children are born preterm1.

Once PTL sets in, complete cessation of labor is difficult to achieve. Tocolytics may help prolonging the pregnancy in order to facilitate in utero transfer to a tertiary center and to buy time for steroids and Magnesium Sulphate to act. Incidence of PTL continues to increase, as a result of increasing number of multiple pregnancies resulting from Assisted Reproductive Technologies. In addition, infection contributes significantly to raising incidence of PTL and Preterm Premature Rupture of Membranes(PPROM). Appropriate timely prediction followed by institution of preventive measures seem to be the best strategies against this important public health problem.

PREDICTION OF PTL:

As discussed earlier, biophysical processes responsible for initiation of labor are difficult to be reversed, once woman is symptomatic. Hence appropriate prediction strategies must focus on asymptomatic women reasonably early in pregnancy, in order to institute effective preventive measures at the right time.

There are certain known risk factors for preterm labor, which are identifiable at the time of booking itself or during the course of pregnancy2.

1. Previous history of Spontaneous preterm birth/PPROM
2. Previous second trimester miscarriage
3. Assisted reproductive technology
4. History of excisional surgery for cervical intraepithelial neoplasia
5. Congenital uterine anomaly
6. Antepartum hemorrhage
7. Multifetal gestation
8. Polyhydramnios
9. Genito-urinary infections (Urinary Tract Infection, asymptomatic bacteruria, Lower genital infections, especially Bacterial Vaginosis with prior preterm labor)
10. Periodontal disease
11. Extremes of maternal age (<18>35 years), low socio-economic status, poor prenatal care, lifestyle factors including smoking/alcohol.
12. Poor pre-pregnancy weight and poor pregnancy weight gain

Although above mentioned risk factors are well known, a significant proportion of preterm births occur among women with no known risk factors2. Therefore, it is important to be vigilant towards the possibility of PTL/PPROM in any pregnant woman. During routine ante-natal visits, symptoms and clinical examination findings may suggest the possibility of PTL. Suggestive symptoms include low backache, increased vaginal discharge, show, menstrual-like cramps, feeling of pelvic pressure and increased frequency of micturition etc. On obstetric examination, premature engagement of fetal presenting part may suggest the possibility of PTL. Such clinical clues heighten the clinician's suspicion towards PTL leading to prompt necessary action, thus improving outcome.

Certain specific investigations and imaging techniques have been developed as predictive tools for PTL, among which cervical length measurement by Trans Vaginal Scan (TVS) - is the best studied and most commonly practiced during antenatal visits.

A) Cervical length measured by TVS - Short cervix (most common cut off 25 mm) as measured by TVS has been proven to be one of the important predictive factors for preterm labor. Cut –off cervical length for intervention – depends upon the pre-existing risk factors and gestational age. This ranges between 15-25 mm. In addition, funneling at the internal os predicts PTL. It is reasonable to repeat cervical length measurements in pregnancy. Shortening of cervix over a period

of time may be observed among those who deliver preterm.[2] A shortening of more than 10% of the cervical length at 3-week interval is associated with an increased risk of preterm birth3. However, cervical length may remain stable for a period of time, and shorten rapidly over a short period prior to onset of symptoms4. Also, the gap between two measurements should be adequate in order to overcome observer errors. Presence of sludge in the amniotic fluid in the region of cervix, also increases the risk of preterm labor/PPROM.

1. **Pregnancies at low risk for preterm labor -** Among these women, general incidence of preterm labor is low which results in low positive predictive value of TVS detected short cervix. Also, there have not been enough research or literature to prove the beneficial effects of cervical encerclage for short cervix detected among low risk obstetric population. Hence, among low risk obstetric population, currently there are no recommendations to measure the cervix by TVS[2,1]. Nevertheless, detection of short cervix during mid -trimester significantly increases the risk of PTL. Commonly, this finding prompts the clinician to employ remedial actions including bed-rest, progestogens and /or cervical cerclage; depending on their clinical judgement.
2. **Pregnancies at high risk for preterm labor, but asymptomatic -** Those at a higher risk of preterm labor due to any of the several risk factors would benefit by TVS cervical length assessment in pregnancy. The predictive value of cervical assessment is higher in these women[2]. Gestational age at previous preterm labor must be born in mind while deciding the timings for such a screening. Cervical encerclage may be beneficial if short cervix is found at mid-trimester. If short cervix is found in this group beyond 24 weeks, certain interventions may help including rest, progestogens, relocating closer to a tertiary center, and corticosteroids for fetal lung maturity.

B. Cervical Elastography - It is well known that the cervix undergoes biochemical changes/biomechanical changes in advance of morphological change during pregnancy, leading to change in stiffness. Thus, there is clearly a clinical need for cervical elastography in the evaluation of biochemical factors in combination with cervical length, which only assesses morphological changes. Studies have shown the predictive value of cervical strain elastograhy of cervix, albeit with several limitations. Improved technique and the combination with measurement of cervical length will make it possible to assess the uterine cervix of pregnant women more precisely[5]. This technique is not available universally and needs further standardization and validation.

C. Combination of cervical length and fetal fibronectin among those at high risk - Again, they have good predictive value when used among those at high risk of preterm delivery[2]. However, there is not enough data to support the use of fetal fibronectin as a predictive tool routinely among high risk but asymptomatic women[3]. True value of fetal fibronectin assay lies in its negative predictive value among symptomatic women, to reduce unnecessary interventions[6]. There is no hard evidence endorsing the clinical value of fetal fibronectin tests in asymptomatic singleton pregnancies so far1.

D. Serum markers - Several biomarkers have been studied in the body fluids including serum,

urine, cervico-vaginal secretions, saliva, and amniotic fluid – in order to predict the occurrence of PTL in asymptomatic and symptomatic women. However, none have shown the predictive ability to be useful as a screening tool recommended for asymptomatic obstetric population, both low and high risk.

It is now clear that single biomarker based screening for the early detection of PTL (in the absence of infection) may never achieve the desired diagnostic efficiency[7]. Such an approach poses a significant challenge due to the heterogeneity of clinical presentations and of the biochemical mechanisms involved in preterm birth. Presently, none of the common late-pregnancy complications including preterm labor can be predicted with sufficient accuracy (sensitivity and specificity) using a single biochemical marker[7]. For this reason, the simultaneous use of multiple risk-factors, that may include demographic/risk-factor(s), cervical length and biochemical marker(s), and the development of multivariate prediction models represent a promising approach to improving diagnostic efficiency.

In a retrospective cohort study of ten year referrals to Preterm Labor Clinic in Australia, Fetal fibronectin and serum alkaline phosphatase were independent predictors of preterm birth <34 weeks and <37 weeks[8].

Many other serum markers have been tried with varying degrees of success in prediction of preterm labor. Examples include CRP, Hs-CRP, IGF, IGFBP-1, IGFBP-3 etc. But none has proven useful enough to be incorporated into routine clinical practice[9].

In asymptomatic women with cervical insufficiency or a short cervix, the risk of Intra Amniotic Infection (IAI) can be predicted fairly and non-invasively by measurements of serum CRP. Overall, this non-invasive parameter appears to have similar accuracy to the Amniotic Fluid WBC counts for predicting IAI[10]. Several biomarkers are studied in the cervicovaginal fluid non -invasively and proven to be efficient in predicting preterm delivery <32 weeks[11]. Highly Sensitive CRP levels in serum are known to correlate well with funisitis and early onset neonatal sepsis among women with SPTB/PPROM[12]. However, attempts at predicting preterm labor using HS-CRP assessment in the first trimester, have been unsuccessful[13].

Screening and treatment of infections - Microbial infections, such as bacterial vaginosis, have one of the strongest associations with SPTB. Bacterial vaginosis is associated with the development of chorioamnionitis, an intra-amniotic infection found in placentas of 40% of all SPTBs, and is particularly prevalent when births occur before 35 weeks of gestation. Sequential changes in the microbiota during the pregnancy likely are important in either initiating inflammation or suppressing protective factors, resulting in rupture of membranes; however, our understanding of the role of microbiota in SPTB is rather limited. Therefore, research to characterize the entire microbiome present in vaginal and placental tissues is important and may lead to a better understanding of the role of bacteria in SPTB[14].

The etiology of preterm birth is multifactorial but there is overwhelming evidence to implicate infection as a major cause. Abnormal genital tract flora in early pregnancy is predictive of preterm birth so it is logical to screen for Lower Genital Tract Infections (LGTIs) and accordingly consider the use of antibiotics for the prevention of preterm birth[15]. A focused systematic review/meta-

analysis, which targeted the use of clindamycin before 22 weeks' gestation, in women with objective evidence of abnormal genital tract flora, demonstrated that clindamycin produced a significant decrease in late miscarriage and preterm birth[15].

Matrix metalloproteinase (MMP)-8 and its inducer extracellular MMP inducer (EMMPRIN) is a key trigger to weaken the cervix and allows ascending commensal or potential pathogenic microorganisms, most often associated with bacterial vaginosis (BV), to cause intra-amniotic infection to occur. BV refers to an alteration in the composition of the vaginal microbiota whereby lactobacilli are either greatly reduced in number or totally absent and there is a large increase in concentration of anaerobic and facultative bacteria. In most cases of BV, Gardnerella vaginalis, Prevotella and Bacteroides spp., and Mycoplasma hominis are present in high concentrations. Other than BV, LGTI due to 'intermediate flora' are also linked to ascending infections and PTL. This includes partial BV, Aerobic Vaginitis(AV) and other abnormalities. In AV, lactobacilli are replaced predominantly by Staphylococcus species, group B streptococci, Escherichia coli and Enterococci. These are responsive to Clindamycin and not to metronidazole. Intermediate flora represents a situation that is intermediate between a Lactobacillus-dominant microbiota and one dominated by BV-related bacteria. AV and partial BV may pose a greater risk for the pregnancy than full blown BV16. Hence it does not come as a surprise that meta-analyses have failed to show the beneficial effects of metronidazole in prevention of pre-term birth. Besides Lactobacillus. iners (A species in the genus lactobacillus) and Gardnerella vaginalis being general surrogate markers of BV, Mobiluncus and Atopobium vaginae are even stronger indicators of full-blown BV (Nugent score above 8), and are, remarkably, not responsive to metronidazole. Although they are notorious lactic acid producers, both organisms are independently linked to an increased preterm birth risk[16].

Hence it appears that there are large gaps in our understanding of vaginal microbiome and LGTI in pregnancy. Specific diagnosis of LGTI appropriately early in pregnancy, followed by targeted antibiotic therapy may help reduce the burden of PTL.

Having understood many predictive tests and their prediction modules, it has not been possible to bring down the incidence of preterm delivery, even among those countries with high human development index. It has been found that about two thirds of preterm birth within such country lacks a plausible biologic explanation, and similarly difference between incidence of preterm births among these countries cannot be explained with known risk factors[17]. Therefore, research must focus on biological explanations for preterm birth, so as to identify efficacious preventive measures.

PREVENTION OF PRETERM LABOR:

A. General measures - Preventing teenage pregnancy, preventing sexually transmitted infections, providing adequate diet, maintaining optimal weight gain in pregnancy, maintaining optimal inter pregnancy interval are the general measures as part of good antenatal care, which are known to reduce the likelihood of SPTB. Identification and treatment of periodontal disease may reduce the risk of preterm labor, although the evidence is conflicting. Cessation of smoking/alcohol helps reduces the risk1. Treatment of asymptomatic and symptomatic bacteruria

reduces the associated risk of SPTB. Although treatment of asymptomatic bacteruria is recommended in pregnancy, a recent RCT showed no difference in the risk of PTD between treatment and placebo arms1. A reduction in environmental stress by modifying the work and home environment result in the prolongation of gestation. It may be helpful to provide bed rest in high risk population including previous SPTB/short cervix.

B. Screening and treatment of LGTI - The pioneering studies of Hoyme and Saling have clearly demonstrated that self-detection of an elevated vaginal pH at early pregnancy stages followed by treatment with antibiotics or probiotic lactobacilli in cases of absence or scarcity of lactobacilli or an elevated vaginal pH, significantly reduces the rate of preterm birth16. However, antibiotic treatment of BV in pregnant women remains controversial. A Cochrane review concluded that while antibiotics can eradicate BV it did not reduce the risk of a subsequent SPTB[16].

There is no consensus opinion on whether to screen and treat asymptomatic Bacterial Vaginosis in pregnancy, as the evidence is unclear whether this practice reduces the risk of preterm labor1. Inappropriate antibiotics used in inappropriately selected women at inappropriately late gestations do not reduce preterm birth. Conversely, a focused systematic review/meta-analysis, which targeted the use of clindamycin before 22 weeks gestation, in women with objective evidence of abnormal genital tract flora, demonstrated that clindamycin produced a significant decrease in late miscarriage and preterm birth[15,16].

The prevalence of BV varies extraordinarily by ethnic and / or geographical origin (4-58%). The link between BV and SPTB is low with odds ratios between 1.5 and 2 in the most recent studies. Metronidazole or clindamycin are effective in treating BV. It is recommended to prescribe one of these antibiotics in cases of symptomatic BV (professional agreement). Routine screening followed by treatment of BV in general obstetric population has not shown any benefit in preventing the risk of SPTB. However, risk of SPTB depends upon the previous history of SPTB and whether previous SPTB was associated with genital tract infection or not. Although routine screening is not consistently proven beneficial even among high risk population in the subpopulation of patients with a history of preterm birth in the context of maternal-fetal bacterial infection, there may be a benefit in early and systematically identifying and treating the specific lower genital infection (professional agreement)[18].

The American College of Obstetricians and Gynecologists, the Centers for Disease Control and Prevention, and the US Preventive Services Task Force recommend against routinely screening asymptomatic pregnant women for bacterial vaginosis (BV). Although asymptomatic BV has been associated with preterm birth, there is insufficient evidence demonstrating that treatment of asymptomatic BV improves outcomes. Conversely, women who have symptomatic BV should be treated to relieve their symptoms.

The prophylaxis and treatment of AV and BV differ. Metronidazole is commonly used for the treatment of BV and because AV does not respond well to metronidazole, clindamycin is considered to be a better choice for treating pregnant women with an unconfirmed diagnosis of abnormal vaginal microbiota because it is able to eradicate both AV and BV-associated bacteria 19. There is a clear indication that, even when asymptomatic, AV may represent a risk factor for preterm delivery

and other complications of pregnancy such as ascending chorioamnionitis and PPROM.

Infection-related SPTB is more common at early gestational ages and is associated with major neonatal mortality and morbidity due to late miscarriage and early PTB. Accordingly, it is logical to consider antibiotics as an intervention. Unfortunately, the conclusions of systematic reviews and meta-analyses do not support routine screening and treatment of LGTI, as there are no benefits demonstrated. While individual studies have found benefit of antibiotic intervention for the prevention of PTB, in meta-analyses these effects have been negated by large methodologically flawed studies with negative results. As a result, no recommendations suggest routine screening and treatment of LGTI in pregnancy. However it is likely that antibiotics active against BV-related organisms, used in women whose risk of PTB is solely due to abnormal microflora, and used early in pregnancy before irreversible inflammatory damage has occurred, can reduce the rate of PTB.

A Cochrane review in 2015 studied one trial involving 4155 pregnant women and concluded that LGTI infection screening and treatment programs for pregnant women before 20 weeks' gestation reduce preterm birth and preterm low birth weight[20].

C. Restoring normal vaginal flora and normal vaginal pH - Treatment with lactic acid in cases with a disturbed lactate D over lactate L ratio could be an option to help prevent preterm birth that requires further attention. However, preventive or curative non-antibiotic treatment options are not limited to the use of lactic acid gel and/or glycogen. Antiseptics, pH-lowering devices such as vitamin C, or probiotic agents can also restore normal vaginal flora and are currently being studied in low resource countries. These non -antibiotic-based approaches to infection control during pregnancy require only low-cost nonperishable items, and are biologically plausible protocols to improve pregnancy outcomes in disadvantaged areas[16].

1. LOW RISK ASYMPTOMATIC WOMEN WITH A SINGLETON PREGNANCY AND SHORT CERVIX IN THE MIDTRIMESTER :

Progesterone supplementation - Supplemental progesterone is administered in one of several forms, intramuscularly (17-Alpha Hydroxy progesterone Caproate) or intravaginally /orally (Natural micronized Progesterone). Among general obstetric population with no pre-existing risk factors for PTD, a subgroup of women with short cervix (defined variously as <10-25 mm in the midtrimester), may benefit from progesterone therapy[6]. Hence, there may a role of routine cervical length assessment in low risk population as well. Use of vaginal Progestogens have definitely proven beneficial in reducing the risk of PTD among this group of women[1].

Cervical encirclage - Studies have not shown a consistent beneficial effect of encirclage procedure in this group. Hence there are no recommendations for cervical encirclage for this group of women with no prior preterm delivery but short cervix on a routine scan[1].

Cervical Pessary - The Arabin pessary is a cervical pessary used to prevent PTB.It is a flexible silicon ring with a smaller inner diameter that encompasses the cervix, aiming to tilt it posteriorly and provide cervical support. It is usually inserted at around 18–22 weeks of gestation, and is removed by 36 weeks. Again, beneficial effects of cervical pessary has not been consistently proven across studies in the literature. Hence in this group of asymptomatic women with no prior

preterm delivery, pessary is not recommended as yet, for the management of short cervix[1].

2. HIGH RISK WOMEN WITH PREVIOUS HISTORY OF SPTB, SINGLETON PREGNANCY -

Role of Progesterone: Role of progesterone is proven with benefit in this group of women, hence it is recommended to offer women with a prior spontaneous preterm birth either vaginal progesterone (gel capsules 200 mg daily or vaginal gel 90 mg daily) or 17a-hydroxyprogesterone caproate intramuscular (250 mg weekly) starting between 16 and 24 weeks of gestation, until 36 or 37 weeks of gestation1. Benefit of progesterone continues if they are found to have short cervix (1.5 -2.8 cm between 24-34 weeks) as measured by TVS [(2,6)]. Remarkably, the effect is most pronounced in patients with prior very preterm (<32 weeks) deliveries.

In addition, this group of high risk women benefit from routine monitoring of cervical length by TVS starting from around 16 weeks, at regular intervals. Active search for LGTI/urinary infections is recommended followed by aggressive treatment. Bed rest, although not proven beneficial, is often employed by obstetricians.

3. HIGH RISK WOMEN WITH PREVIOUS HISTORY OF SPTB, SINGLETON PREGNANCY, FOUND TO HAVE SHORT CERVIX IN THE MIDTRIMESTER:

Cervical encirclage - Procedure has been proven beneficial among asymptomatic women with prior spontaneous preterm delivery, when mid trimester (at or prior to 24 weeks) cervical length is < 2.5 cm by TVS 2. Published data suggests the benefit of emergency cerclage in this group, even when membranes are bulging at or beyond the external os[2].

In this group of asymptomatic women who have pre-existing risk factors for preterm delivery, there are two approaches generally employed to prevent preterm labor. One is elective cervical encirclage based on clinician's discretion; other is serial cervical length assessment followed by encirclage when indicated by short cervix. It is unclear which is the best policy as a preventive measure.

Pessary - There is not enough literature to support the use of pessary to prevent PTD among these high risk women with previous PTD. However, this is an attractive non-surgical option which if employed early, may be of benefit.

4. HIGH RISK GROUP; WOMEN WITH HISTORY SUGGESTIVE OF CERVICAL INSUFFICIENCY:

History indicated/ Primary cerclage, also known as elective cerclage, is considered to be effective in the prevention of preterm birth in women with a cervical insufficiency. Cervical insufficiency is characterized by progressive shortening and dilatation of the cervix before 24 weeks of gestation without signs of preterm labour, and is associated with mid-trimester pregnancy loss. An elective history indicated cerclage should be limited to patients with a history of one or more unexplained second-trimester deliveries in the absence of painful cervical dilation or labour.

5. MULTIPLE PREGNANCY

Considering that they belong to high risk group for SPTB, predictive tests are routinely employed

starting from early midtrimester; including TVS cervical measurements at regular intervals, active look out for genito-urinary infections followed by prompt treatment. In addition, bed rest is often employed by clinicians, although not well supported by evidence.

Encirclage: A Cochrane review in 2014 and a meta-analysis in 2015 failed to show a benefit from routine or ultrasound indicated cervical encirclage in women with twin pregnancy1.

Pessary: There are conflicting results from the literature1, when it comes to the benefit of pessary for twin gestation, to prevent preterm labor. In general, there seems to be a benefit among those with short cervix, and pessary inserted earlier in gestation. However, in a systematic review and meta-analysis, Saccone et al in 2017 concluded that use of the Arabin pessary in twin pregnancies of women with a short cervix may not prevent PTB or improve perinatal outcome[21]. The cervical pessary is not currently routinely used in clinical practice outside of the research setting.

Progesterone: There are conflicting results on benefit of progestogens in preventing preterm labor among twins and multiple gestations. Therefore, there are no standard recommendations for starting Progesterone therapy in twin gestation. However, there seems to be a benefit for those with short cervix, as indicated by some studies[1,6]. A systematic review and meta-analysis published in 2017[22] concluded that administration of vaginal progesterone to asymptomatic women with a twin gestation and a sonographic short cervix in the mid-trimester reduces the risk of preterm birth occurring at < 30 to < 35 gestational weeks, neonatal mortality and some measures of neonatal morbidity, without any demonstrable deleterious effects on childhood neurodevelopment.

In summary, SPTB is a major public health problem. Process of PTL once sets in, is difficult to halt or reverse. Predictive tests should focus on early pregnancy on asymptomatic women. Therefore, scientific research must focus on the several basic mechanisms initiating PTL which are yet unknown. There is growing evidence to suggest some of these triggers may also be related to stress and environmental conditions. Alteration of physiological milieu that results in such a process needs to be studied, in order to effectively predict and prevent SPTB.

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Antiphospholipid Antibody Syndrome in Recurrent Miscarriage

Dr. Abha Majumdar

- **The acquired thrombophilia also known as APLA syndrome or APS, is the only proven thrombophilia that is associated with early pregnancy adverse outcomes. APS is an autoimmune disease with the presence of antiphospholipid autoantibodies formed against the person's own tissues. These autoantibodies interfere with coagulation.**
- **In presence of APS, the hypercoagulable state of pregnancy worsens and this may increase the risk of thromboembolism in the patient not only during pregnancy but in the postpartum period as well.The placental circulation is comparable to venous circulation with its low pressure and low velocity flow rendering it susceptible to thrombotic events at the maternoplacental interface, reducing the blood flow to the fetus with resultant abortions, intrauterine fetal growth retardation (IUGR) and/ or intrauterine fetal losses.**
- **All women with recurrent first trimester miscarriage and with one or more second trimester miscarriage should be screened before pregnancy for APS as per recent recommendation by RCOG.**
- **According to RCOG Greentop guidelines, there is good and adequate evidence that pregnant women with APS should be treated with low dose aspirin and low molecular weight heparin to prevent fetal loss.**

INTRODUCTION

Recurrent pregnancy loss (RPL)is a very traumatic experience for the expectant couple and continues to be one of the most difficult areas to treat in reproductive medicine. There has been a lot of research ranging from etiology to management of RPL yet it remains to be one of the most debated topic amongst clinicians and academicians. The ideal management is still unanswered.It is estimated that 15% to 20% of all clinically recognized pregnancies result in miscarriage.

Approximately 2% of pregnant women experience two consecutive miscarriages and 0.4 to 1% of fertile women have three consecutive pregnancy losses[4]. This is approximately twice the incidence

that would have been expected by chance alone, and indicates that an abnormality is likely to be present[5].

DEFINITION

Recurrent miscarriage (RM) is defined as three or more consecutive pregnancy losses occurring before 20 weeks by the European Society for Human Reproduction and Embryology (ESHRE)[1]. However, most countries including the United States now agree to start investigations for recurrent miscarriage after two pregnancy losses [2,3].

WORK UP IN PATIENTS OF 'RM'

Even after extensive investigations, in approximately 50% of cases no cause can be found to explain the occurrence of RPL[6]. Parental chromosomal translocation defects, maternal thrombophilia disorders especially the acquired anti-phospho-lipid antibody (APLA) syndrome (APS) and structural uterine anomalies like septate uterus have been directly associated with recurrent miscarriage. Therefore, recommendations made for basic investigations for RM, based on the data of recently published large randomized controlled trials (RCTs) and meta-analyses, include only testing for APLA, parental karyotype, pelvic ultrasound and/or hystero-salpingogram apart from noting the woman's age and body mass index (BMI). A detailed obstetric and medical history is also an important part of work up in such couples especially history of exposure to toxins or of chronic inflammatory diseases and endocrinopathies such as diabetes. Other investigations should be limited to specific cases and used within research programs only. If parental chromosomal abnormalities are found these couples should be counselled regarding the chance of successful pregnancy naturally vs the use of preimplantation genetic testing (PGT) with in vitro fertilization (IVF). The presence of uterine septum requires surgical correction hysteroscopically, with only a small chance of successful obstetric outcome if left untreated[7]. In the remaining women, 15-20% of patients with recurrent miscarriage are found to have anti phospholipid antibodies[8]. Fetal loss rate in these patients if left untreated is approximately 90%[9].

Both thrombophilias, hereditary as well as acquired are important research avenues in the field of RPL. The acquired thrombophilia also known as APLA syndrome or APS, is the only proven thrombophilia that is associated with early pregnancy adverse outcomes. APS is an autoimmune disease with the presence of antiphospholipid autoantibodies formed against the person's own tissues. These autoantibodies interfere with coagulation.

Research involving inherited thrombophilia and recurrent miscarriage is limited to only small observational studies within small and heterogeneous populations and do not warrant investigation for early pregnancy losses[10] . This association is stronger for fetal deaths, such as stillbirths after 20 weeks' gestation than for recurrent early losses. Other large prospective cohort studies have not shown significant associations between hereditary thrombophilia and sporadic and recurrent early

pregnancylosses[11,12] .

HEMATOLOGIC CHANGES DURING NORMAL PREGNANCY:

Normal pregnancy is a hypercoagulable state with a trend toward thrombosis, in order to be prompt for the hemostatic challenge of delivery[13,14] . There is increase in clotting factors like factor VII, VIII, X, vWF and fibrinogen. Other markers of a hypercoagulable state like D-dimer and/or prothrombin fragments are also increased during pregnancy[15]. However, this thrombogenicity is not balanced by simultaneous increase in natural anticoagulant proteins. Rather levels of protein S decreases by 40 to 50% and levels of protein C and anti-thrombin III remain unchanged, resulting in loss of homeostasis. Further fibrinolytic activity is decreased, with progressively increasing levels of plasminogen activator inhibitor-1 (PAI-1) produced by endothelial cells and plasminogen activator inhibitor-2 (PAI-2) produced by trophoblasts during pregnancy leading to hyper coagulable state in pregnancy.

Platelet activation and increased production of thromboxane, as well as decreased sensitivity to the anti-aggregation effects of prostacyclin, increase the prothrombotic state of pregnancy. Vasorelaxation and resulting stasis of the venous blood flow further favors coagulation.

THROMBOPHILIA AND ITS IMPACT ON PREGNANCY:

Obstetric complications of thrombophilia are attributed to affection of uteroplacental blood flow. Many recurrent miscarriages are characterized by defective placentation and microthrombi in placental vasculature. The most established thrombophilia correlating with recurrent miscarriage is APLA syndrome.

According to the Royal College of Obstetricians and Gynecologist (RCOG) APLA syndrome is the most important or possibly the only medically treatable cause of RPL[16]. It is the only autoimmune condition in which pregnancy loss is part of the diagnostic criteria. A large variety of autoantibodies towards clotting factors are found in APS[17] but the exact role of these autoantibodies is yet to be defined. However, now it is clear that antibodies do not primarily recognize phospholipid, but rather proteins that bind to the phospholipid, hence assays have been developed to measure antibodies that specifically recognize those cofactors. In a nutshell during pregnancy, clotting factors I, VII, VIII, IX, and X rise, and protein S and fibrinolytic activity diminishes. When compounded by autoantibodies as in presence of APS, the hypercoagulable state of pregnancy worsens and this may increase the risk of thromboembolism in the patient not only during pregnancy but in the postpartum period as well. The placental circulation is comparable to venous circulation with its low pressure and low velocity flow rendering it susceptible to thrombotic events at the materno placental interface, reducing the blood flow to the fetus with resultant abortions, intrauterine fetal growth retardation (IUGR) and/ or intrauterine fetal losses.

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TABLE 1.
DIAGNOSTIC CRITERIA TO DETECT ANTIPHOSPHOLIPID SYNDROME

Clinical Criteria (Vascular thrombosis of arterial and/or venous vessels in any tissue or organ) Pregnancy morbidity	Laboratory Criteria
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation	Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart. detected according to the International Society of Thrombosis and Haemostasis (ISTH)
One or more unexplained deaths of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe eclampsia or placental insufficiency	Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or in plasma present in medium or high titer on two or more occasions at least 12 weeks apart
Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation	Anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or in plasma present on two or more occasion at least 12 weeks apart

LAB DIAGNOSIS

All women with recurrent first trimester miscarriage and with one or more second trimester miscarriage should be screened before pregnancy for APS as per recent recommendation by RCOG. The clinical and laboratory criteria for the diagnosis of APS, also referred to as the "Sydney Criteria" were given after consensus meeting at international conference in Sydney, Australia13. History of vascular thrombosis and pregnancy complications due to placental vascular insufficiency were included in clinical criteria whereas laboratory assays of presence of lupus anti-caogulant (LA), anti-cardiolipin antibody (ACA) of IgG and IgM type, and anti-beta 2 glycoprotein1(Anti- β2 GPI) of IgG and IgM constituted the laboratory criteria. To diagnose APLA syndrome only one of the above tests are required to be abnormal but it must be reproducible on repeat testing after a period of at least 12 weeks from the initial positive test. Laboratory testing for antibodies for APS should generally be limited only to patients who present with the thrombotic events and/or the pregnancy losses. Some experts might consider patients with SLE and perhaps other autoimmune disorders to be an exception to this rule because they are at increased risk for having APL antibodies and for experiencing thrombosis related complications[19].

IMMUNOASSAYS

ACAassays - Most patients with APS are identified by elevated levels of anti-cardiolipinantibodies, a test with high sensitivity but poor specificity. ACA antibodies can be high in infective conditions like syphilis, Lyme disease, Ebstein Barr Virus (EBV), Cytomegalovirus (CMV) and Human Immunodeficiency Virus (HIV) but in these conditions, it will not be associated with elevated LA or anti β2 GPI antibodies[20]. A recent meta-analysis found significant association between recurrent

miscarriage and ACA.[21] This association was found with both IgM and IgG classes of anti-cardiolipin antibodies though IgM antibodies can be falsely elevated in presence of rheumatoid factors and cryoglobulins.

Anti- β2 GPI antibody assays - In literature the controversial results have been obtained when relationship between β2 GPI antibodies and recurrent miscarriage was studied. Since 2006 ELISAs for β2 GPI antibodies have been included in diagnosis of APS to identify patients who are at higher risk.ELISAs for β2 GPI antibodies are considered to be more specific but less sensitive to APS than ACA assays. It has high specificity for APS (98%), but β2 GPI antibodies alone cannot be relied upon for the diagnosis because of their low sensitivity (40 – 50%). Its inter-laboratory reproducibility is considered good and better than ACA antibodies[22].

Lupus anti-coagulant tests - Isolated prolongation of Activated Partial Thromboplastin Time (APTT) with normal PT may be secondary to the presence of lupus antibodies; which can be confirmed by Russel viper venom time (RVVT) or kaolin clotting time (KCT) mixing studies with normal plasma and phospholipid neutralization procedures. The various LA tests, all report the inhibition of phospholipid dependent blood coagulation reactions, but by different detection methods These include modifications of the APTT test with LA-sensitive and LA-insensitive reagents, the kaolin clotting time, the dilute RVVT, the tissue thromboplastin inhibition time, the hexagonal phase array test, and the platelet neutralization procedure. The inter laboratory reproducibility of LA tests is also very poor due to number of test available.[23] In absence of fully sensitive test the international consensus in 2006 recommended use of two or more positive test for the diagnosis of LA[13].

SOME IMPORTANT POINTS TO REMEMBER WHILE TESTING FOR APLA

1. Screening of APS should not be done in asymptomatic patients with the aim to identify those at risk for thrombosis, and pregnant women without histories of complications. These assays are associated with a significant false positive rate. Different studies have reported from 3% to almost 20% positive rate inimmunoassays in the asymptomatic "normal" population[24]. Such false positive results can lead to unwarranted anticoagulant prophylaxis with the potential of hemorrhagic complication in otherwise disease-free population.
2. Weak positive results in APLA immunoassays do not have clinical significance and should not be treated with prophylactic anticoagulation[25].
3. For LA a single negative test should not be relied upon and it should always be checked by two assays which is usually dRVVT, LA insensitive APTT or KCT.
4. In case of positive ACA assays, presence of recent infections should always be ruled out.
5. If there is a strong clinical suspicion of APS but APL immunoassays yield negative results consider seronegative APS. In such cases ACA and anti- β2 GPIIgA antibodies and antiphosphotidylserine antibodies can be done to clarify the picture.

TREATMENT OF ANTIPHOSPHPLIPID ANTIBODY SYNDROME

APS is the most medically treatable condition out of all clinically established causes of RPL.

Different mechanisms have been suggested by which APS affects pregnancy including inhibition of trophoblastic function and differentiation, activation of complement pathways leading to local inflammatory response at maternal-fetal interface and thrombosis of utero-placental vasculature[26,27,28]. According to RCOG Greentop guidelines, there is good and adequate evidence that pregnant women with APS should be treated with low dose aspirin and heparin to prevent fetal loss. Many studies have been conducted in past to find the ideal treatment of APS in patients with RPL. The different treatment options which have been tried for this group of patients are, low dose aspirin alone or with heparin, corticosteroids or intravenous immunoglobulins.

a) **Low Dose Aspirin Alone -** Aspirin has been commonly used to treat women with so called 'idiopathic' or unexplained RPL without thrombophilia. However, according to Cochrane Database Review (2005) aspirin alone has no benefit over placebo or supportive care in preventing fetal loss in patients with RPL.[30]

b) **Low Dose Aspirin with Heparin-** A recent meta-analysis (2010) involving 334 patients with APS and recurrent miscarriage compared treatment with aspirin alone versus aspirin and heparin. The live birth rates in the group receiving aspirin and heparin was 74% as compared to 56% in the group on aspirin alone.[31] Another systematic review and meta-analysis of three RCTs including 212 patients demonstrated better pregnancy outcomes when combined treatment with aspirin and unfractionated heparin was given as compared to aspirin alone in women with APS and recurrent miscarriage.[32] In Cochrane review of 13 trials also, it was found that treatment with unfractionated heparin and aspirin may reduce pregnancy loss by 54%. But the quality of studies included in this review was variable and there was problem of allocation concealment. Another recent cohort study in a recurrent miscarriage clinic compared low dose aspirin alone with combined low dose aspirin with low molecular weight heparin and found increase in live birth rate in combined group (53/67;79%) as compared to low dose aspirin alone(64/104; 62%)[33].

c) **Un-fractionated Heparin (UFH) Versus Low Molecular Weight Heparin (LMWH):** LMWH is favored over un-fractionated heparin for clinical use because it offers several advantages like longer half-life, once daily dosing, greater bioavailability and more stable dose-response relationship. As compared to unfractionated heparin, LMWH is also associated with fewer side effects like bleeding, thrombocytopenia and osteoporosis. However, one systematic review has shown in women with APS and recurrent miscarriage there was a significant increase in live birth rates when UFH and aspirin were given together as compared to LMWH with aspirin. This lead to a thought that probably UFH compared to LMWH has some properties beyond anticoagulation which help these women even though, the exact mechanism is yet to be discovered.[34] A multi-centered RCT (2011) comparing LMWH and aspirin versus UFH and aspirin in women with APS and recurrent miscarriage showed no statistical difference in live birth rates in the two groups.[35] Different doses of LMWH has been given in previous studies , 40 mg subcutaneously daily is usually the most commonly prescribed dose. A study comparing dose of 40mg/day to 20mg/day of LMWH in patients with

APS and recurrent miscarriage demonstrated no significant difference in live birth. They concluded that a dose of 20mg/day of LMWH can be used effectively to prevent miscarriage in women with APS.[36] Unfractionated heparin is usually given in dose of 5000 units twice daily. LMWH when given in prophylactic doses has to be stopped 24 hours prior to planned induction or cesarean section. In case of spontaneous labor/ emergency cesarean, regional anesthesia can be given after 12 hours of last dose of LMWH. UFH can be given up to 12 hours prior to induction or cesarean. Protamine is a known antidote for heparin but it is only 60% effective against LMWH.

d) **Role Of Corticosteroids:** Glucocorticoids should not be prescribed in APS without connective tissue disorder.[37] In presence of lupus low dose prednisolone can be given after consultation with rheumatologist. There is limited data on its efficacy and Cochrane review does not support use of corticosteroids in APS for prevention of fetal loss.[38] Their use during pregnancy are known to be associated with maternal side effects such as gestational hypertension and diabetes.

e) **Role of Intravenous Immunoglobulin (IVIG) Treatment:** IVIG is a fractionated blood product derived from human plasma. It was seen in experimental models that for pregnancy to establish and continue inhibition of local inflammatory mediators are beneficial and hence this effect was extrapolated to usage of IVIG in APS with recurrent miscarriage. However, evidence does not support use of IVIG to improve pregnancy outcome in women with APS and recurrent fetal loss. A RCT comparing IVIG with LMWH and aspirin in women with APS showed higher miscarriage rate in IVIG arm. The women on IVIG were also found to be at a two fold higher risk of preterm delivery.[39] A systematic review also has shown no benefit of IVIG in women with APS and recurrent miscarriage.[40]

CONCLUSION:

Recurrent miscarriage is one of most the widely researched areas in medicine. Apart from karyotypic translocations and mullerian septal defects,thrombophilias appear to be the only medically treatable cause of this distressing condition. The acquired thrombophilia also known as APLA syndrome or APS, is the only proven thrombophilia that is associated with early pregnancy adverse outcomes. APS is an autoimmune disease with the presence of antiphospholipid autoantibodies formed against the person's own tissues. These autoantibodies interfere with coagulation. 15-20% of patients with recurrent miscarriage are found to have anti phospholipid antibodies. Fetal loss rate in these patients if left untreated is very high. Many studies have concluded that treatment with aspirin and/or heparin in this group definitely improves the prognosis of subsequent pregnancy.

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  - Felicitated by Agra medical college for 'Outstanding contribution towards fields of specialty 2008
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  - Over 15 publications in indexed journals and 20 chapters in text books for Obs. & Gyn. and reproductive medicine.
  - Over 150 guest lectures and orations in national /international conferences.

Massive Obstetric Haemorrhage and Role of Blood Transfusion in the Management

Dr. Alpesh Gandhi

- **In case of massive Haemorrhage immediately start volume replacement with upto 1-2 litres of crystalloid. Follow plasma expanders until the blood is available. Dextran should be avoided as it has been associated with bleeding due to decreased platelet adhesions and dilution of clotting factors. It also interferes with subsequent cross match.**
- **It is a myth that when massive haemorrhage occurs, when patient loses whole blood ONLY whole blood should be given and it will take care of all. The fact is that the use of whole blood is an unscientific, inefficient, unhealthy and criminal waste of a valuable resource (WHO).**
- **MTP is known as Massive Transfusion Protocol. It is different in different institutes but it usually known as a rule of 4 or rule of 6. In patients likely to need massive transfusion, begin resuscitation with blood products as soon as possible to prevent dilution coagulopathy. Administer blood products in a ratio of 4 units PRBC: 4 units FFP: 4 units Platelets: 4 cryoprecipitate**
- **A blood transfusion should never be ordered unless it is worth the risk. We should ensure the rational use of blood components means right patient is getting right product in the right amount at the right rate at the right time.**

DEFINITION :

Major Obstetric Haemorrhage is defined as blood loss >2000ml or rate of blood loss of 150mls/min, or 50% blood volume loss within 3hrs. It may result in a decrease in haemoglobin (Hb) >4g/l, or an acute transfusion requirement of >4 units. Haemorrhage is a common complication of pregnancy. It further becomes complicated because of inaccuracy in determination of exact amount of blood loss.

CAUSES :

It is the first rank direct cause for maternal mortality and morbidity in our country. There are many causes which can lead to massive haemorrhage during pregnancy and child birth. Commonest

causes are Abruptio placenta, Uterine atony, Placenta previa, Placenta accreta, Retained placenta, PIH, Uterine rupture, Ectopic pregnancy, Coagulation disorders, Birth trauma, Operative Trauma, Amniotic Fluid Embolism, HELLP Syndrome etc. Pregnant women at term have hyper-coagulable state caused by excess of procoagulants. Pregnancy also shares the risk of exposure to thromboplastic material from abnormal or damaged placentas as well as from labour process which is also responsible for haemorrahge.

GOALS OF THERAPY FOR MASSIVE OBSTETRIC HAEMORRHAGE:

1. To restore intravascular volume
2. To maintain tissue oxygen delivery and
3. To eliminate the source of hemorrhage.

Immediately insert at least two large I.V. cannula. Take blood at the same time for urgent cross match (type specific), full blood count (FBC) and coagulation screen. Initiate volume replacement with Lactated Ringers or Normal Saline. Lactate Ringer's solution and 0.9% normal saline are the two most commonly used crystalloids solutions. Start volume replacement with up to 1-2 litres of crystalloid. Follow with plasma expanders until the blood is available. Dextran should be avoided as it has been associated with bleeding due to decreased platelet adhesions and dilution of clotting factors. It also interferes with subsequent cross match. Foley's catheter should be inserted to monitor urine output. Monitor central venous pressure (CVP) and arterial pressure. The recognition and removal of the underlying cause is an important part of the management of obstetric hemorrhage. To discuss the medical and surgical obstetric management of massive haemorrhage is not the aim or scope of this article. Besides that the main therapeutic endeavor remains replacement of massive blood loss. In most of the places in our country, factor replacement (Prothrombin complex, Fibrinogen concentrate, AT III etc.) is not easily available.

Blood transfusion practice is an essential and important aspect of high risk pregnancy and critical care in obstetrics. The WHO strategy for blood safety emphasizes the need to reduce unnecessary transfusions. The inappropriate transfusion rate is around 15-45%, either due to transfusion in non indicated cases or due to too late or too little transfusion in indicated cases. In the countries of the SEA Region, obstetric cases need blood the most. 10% of blood was utilized for surgery, 30% for obstetric cases, 24% for paediatric cases, 8% for trauma and 31% for miscellaneous cases. (WHO, 2010)

PURPOSE OF BLOOD TRANSFUSION IS REPLACEMENT AND/OR THERAPEUTIC.

1. To restore intravascular volume.
2. To restore the oxygen capacity of blood by replacing red blood cells.
3. To replace clotting factors and correction of anaemia.

INDICATIONS OF BLOOD TRANSFUSION IN ACUTE BLOOD LOSS:

a. Estimated or anticipated blood loss > 15% of total blood volume

b. Diastolic blood pressure < 60 mm Hg
c. Systolic blood pressure - decrease > 30 mm Hg
d. Oliguria/anuria.
e. Tachycardia (> 100 beats/minute)
f. Mental status changes
g. Shortness of breath, light headedness or dizziness with mild exertion

WHOLE BLOOD AND BLOOD COMPONENTS

350ml /450 ml of blood is collected from a donor into a plastic bag containing an anticoagulant. This is called 1 "unit" of whole blood. Whole blood can be separated into "blood components". Types of blood components are Red blood cell concentrate (packed red blood cells), Platelet concentrate, Fresh frozen plasma, Cryoprecipitate, separated by differential centrifugation. Others include Plasma proteins—IVIg, Coagulation Factors, albumin, Anti-D, Growth Factors, Colloid volume expanders. Apheresis may also be used to collect blood components.

It is a myth that when massive haemorrhage occurs, and the patient loses blood ONLY whole blood should be given and it will take care of all. The fact is that the use of whole blood is an unscientific, inefficient, unhealthy and criminal waste of a valuable resource (WHO). Storage Requirement for Blood Components is different.

- Whole Blood is stored at 4-6° C,
- Red Cells at 4°C,
- Platelets at 22-24° C (On Shaker), FFP at -30 to -40° C,
- Cryoprecipitate is stored at -30°to -40 C.

So when we give whole blood, FFP and Cryoprecipitate had already lost its functions. Similarly Shelf life of each component is also different. For Red cells it is- 35-40 days, for FFP/CPP - 1 year, for Platelets - 5days, for CRYO- 1 Year and for White blood cells- 2 days. **So when we give whole blood to a patient who requires only red cells, unnecessary FFP and Cryoprecipitate will be wasted which otherwise could have been separated, stored and used later on in a patient who requires it.** When we compare Packed Red Cells with Whole Blood, Packed RBC has low volume which is good to prevent overload and has low Citrate (ml), low Sodium, low Potassium, low Ammonia and low unwanted Plasma than whole blood which are responsible for more complications of B.T. Whole blood is also not rational for better patient management as concentrated dose of required components which are low in quantity, is also useful to avoid circulatory overload, to minimize reactions and to decrease cost of management.

When acute massive blood loss occurs, it can lead to four different problems-Hypovolemia, deficiency of clotting factors, deficiency of Platelets and Hypoxia. All these Problems have different solutions and allow us for different optimum time for it's correction. Plasma Expanders required for Hypovolemia, Packed RBCs for Hypoxia, FFP for Clotting Factors, Cryoprecipitate

for Clotting Factors deficiency and for low platelet -PRC / PRP is required. We need to correct Platelet deficiency as soon as possible within (<1 hr), coagulation defects within 2-4 hrs, hypovolemia within 6-12 hrs and hypoxia within 6-12 hrs.

For Blood Component Therapy in massive obstetric haemorrhage, we should take two I.V. lines.

Line A	**Line B**
	4 Cryoprecipitate
Red Cells transfusions	4 platelets, if Platelets <50 k/uL
(4-6) or till Hb >9.0 gm	Time: 30 minutes
	2-4 FFPs till PT is 6 + control value
Time: 6-8 Hours	Time: 6-8 Hours (continue to monitor Hb, Platelet, PT.)

MTP IS KNOWN AS MASSIVE TRANSFUSION PROTOCOL

It is different in different institutes but it usually known as a rule of 4 or rule of 6. In patients likely to need massive transfusion, begin resuscitation with blood products as soon as possible to prevent dilution coagulopathy. Administer blood products in a ratio of 4 units PRBC: 4 units FFP: 4 units Platelets: 4 cryoprecipitate

1. **Volume replacement & Clotting Factor Correction:** Fresh frozen plasma should be used for volume expansion so that replacement of clotting factor may be started early. Generally the initial volume required must be administered rapidly and that 600 ml to 2 litres should be infused over a period of 2-4 hours. Each unit of FFP generally contains 250 ml of volume. Untill FFPs are made available volume expanders should be used.
2. **Correction of Fibrinogen/Platelet deficits:** Platelet count should be maintained above 50000/uL, 1 unit of platelet rich concentrate (PRC) raises the platelet count by 8000-10000/uL and accordingly platelet transfusion should be planned as soon as possible. In addition, fibrinogen level should be maintained above 150 mg/dL. 4-8 units of Cryoprecipitate generally are sufficient to achieve this goal. In addition to platelets and cryoprecipitate as mentioned earlier fresh frozen plasma should be continuously infused. The replacement therapy is guided by laboratory assessment. The usual trigger value for transfusion need is platelet count of 50,000/ul or less, fibrinogen < 150 mg/L and prolonged PT by not more than 6 seconds.
3. **Correction of Anaemia (Hypoxia):** Hb should be maintained above 9.0 g/dL by transfusing red cells. One unit of red cells generally raises Hg by 1.0 g/dL. In general, once patient has DIC, requirement of 4-6 units of red cells is usual.
4. **Intravenous Tranexamic Acid :** Clinicians should consider the use of intravenous tranexamic acid (0.5–1.0 g), to reduce blood loss in women at increased risk of PPH.
5. **Role of Obstetric intervention/surgery:** Vaginal delivery makes less severe demand on the hemostatic mechanism than caesarean section. When a coagulation defect exists, severe

bleeding will occur at sites of surgical incisions and may not develop until after the operation. Therefore in obstetric patient, extensive bleeding can occur into the abdomen from caesarean section incision on the uterus. In exceptional circumstances, when surgical intervention is being necessary every effort should be made to correct the coagulation failure before and following operation. It is imperative to check platelet count /PT/APTT and Fibrinogen during antenatal visit prior to delivery. Prompt reference to a Hematologist is needed, if any of the above parameters are abnormal. In this attempt, quite a few abnormalities can be detected prior to labour and corrected, if possible.

6. **Follow-up Treatment:** Therapy should be planned for 4 to 6 hours time period. Vital signs and urine output should be monitored hourly. Hb, platelet count, PT/APTT should be repeated to define further treatment. Once patient stabilizes, these tests can be done at 12 hourly intervals and later once a day. Vitamin k, Folic Acid should be given to all patients.

Transfusion of FFPs, Platelets and Cryoprecipitates should not be given only on the basis of clinical suspicion unless there is delay in obtaining results of blood counts and coagulogram. FFPs and Cryoprecipitates should ideally be of same blood group of recipient. But if unavailable, FFPs of different blood group can be given provided. The unit does not have high anti A or B activity. Anti D prophylaxis is not required if Rh D negative women receive Rh D positive FFPs or Cryoprecipitates. The platelets should ideally also be ABO group compatible. Rh-ve women should receive Rh-ve platelets. Inj. Anti-D will be needed if the platelets are Rh+ve and the recipient Rh-ve.

DIC

The diagnosis of DIC is made based on clinical presentation plus laboratory manifestations. Laboratory tests which are most frequently abnormal in DIC are platelet count, FDP levels, prothrombin time, activated partial thromboplastin time (APTT), and fibrinogen. These tests show varying degree of abnormality and during early stage of DIC many of them can be normal and therefore, if DIC is strongly suspected, it is important to repeat this test 4-6 hours later. Diagnosis of DIC should be made based on clinical presentation as well as abnormalities of the above mentioned tests should be interpreted together and not in isolation. DIC essentially remains a clinical diagnosis.

There should be an understanding on the terminology to be used between blood bank staff and clinical staff to avoid any misinterpretation. Extremely urgent can be used when blood is required within 15 min, Very urgent means within an hour, Urgent means within 2-3 hour and on the same day for during the day.

Blood transfusion can be associated with many mild to fatal complications. There is a risk of transfusion transmitted diseases. Risk for Infection from Transfusion for Hepatitis C in 1:103,000, Hepatitis B in 1:64,000, HIV in 1:493,000. Disorders of Excessive neutrophil Function like ARDS, TRALI and MOF can occur which are fatal. Once patient is stable, the risks of transfusion far outweigh the benefits of transfusion and so transfusion should not be given.

In appropriate cases, it is advisable to keep blood ready rather than not keeping it. Separate and specific consent is to be taken for the same in advance. Prior to transfusion, we need to take written and informed consent from the patient as blood transfusion involves additional risk.

The blood bag which has been kept for > 4 hours at room temperature or pack that has been opened or shows any sign of deterioration should be discarded.

While choosing the donors our preference would never be 1st relation as 1st relation blood has 50% HLA match white cells especially lymphocytes. These cells remain viable in recipient circulation and develop their clones of cells, produce antibodies which act on recipient cells. Worst fatal rare complication graft versus host disease can take place in 3 weeks times which has nearly100% mortality.

Whenever it is possible, Fresh blood should not be used. Ultra fresh blood is the immediately unrefrigerated collected blood and Fresh blood is the blood stored within 24hrs to 48 hrs of collection. In any stored refrigerated blood for > 6 hrs, Platelets loose it's function. For >24hrs, all clotting factors loose their property to prevent bleeding. Before component therapy, whole blood. was the principal product available and it was known that components like platelets and coagulation factors were present in full for few hrs, so at that time fresh blood was justified. In fresh blood, proper screening of blood is not possible. Risk of disease transmission is more as intracellular pathogens (CMV, HTLV) can survive in leukocytes in fresh blood. Treponema Pallidum can survive for 72-96 hrs in stored blood, malarial parasite can survive up to 72 hrs in stored blood. If < 24hrs stored whole blood is transfused, there is risk of transmission of malaria and T. pallidum. This risk is eliminated if > 72 hrs stored blood is transfused. Fatal reactions are more with fresh blood because of presence of viable lymphocytes and granulocytes.

CMV screening is necessary in blood transfusion. Cytomegalovirus (CMV) seronegative red cells and platelets should be used for CMV seronegative pregnant women. Urgent transfusion should not be delayed if CMV seronegative components are not immediately available.

Use of rFVIIa may be considered as a treatment for life-threatening PPH. It should not be considered as a substitute for, nor should it delay the life-saving procedure such as embolisation or surgery, or the transfer of a patient. Factor VIIa has a pivotal role in initiating the process of blood coagulation. The introduction of rFVIIa has stimulated interest in its use in patients with intractable bleeding despite corrective measures, such as replacement of plasma coagulation factors, fibrinogen, platelets and red cells. The availability and use of rFVIIa is limited and owing to its financial cost, it is advisable to keep rFVIIa in the blood bank stock in case of any bleeding emergency. Pre-requisites for using rFVIIa before administering rFVIIa are Hb levels should be preferably above 7 g/dl, Platelet levels should be above 50 000/cumm and Fibrinogen level of a minimum of 100 mg/dl, preferable more than 150 mg/ dl must be ensured before administration of rFVIIa. In case these parameters are derranged, they must be corrected by using appropriate therapy before rFVIIa administration. Also, correction of the pH to $\geqslant$ 7.2 is recommended before rFVIIa

administration because efficacy of rFVIIa decreases at a pH ⩽ 7.1. If required, bicarbonate may be used to elevate the serum pH.

Warming blood or blood products is not normally necessary. It is often sufficient to keep patient warm during transfusion; however, when numerous units of blood are administered quickly, it may be necessary or desirable to warm the blood products. Warming of blood products should be done using a blood warmer device that is licensed for it which has visible thermometer and audible warning alarm. The device should not allow the temperature of blood to exceed 42ºC.

Donated blood is stored in bag containing anticoagulant Citrate. Citrate binds with calcium in the blood and thus depletes the concentration of free calcium in the blood. In adults rapid liver and kidney metabolism of citrate usually prevents this. If > 3 bags are given to a person in a row within a day, then body may not cope up with rate of decline of free calcium. Therefore, extra calcium is to be given for that purpose. Hypocalcemia with hypothermia and acidosis is dangerous and will decrease cardiac output, causes bradycardia and dysrhythmia, thus calcium gluconate administration is indicated here. (WHO)

For monitoring a patient when she is on transfusion, vital signs must be taken before the transfusion of all blood products. Vital Signs include temperature, pulse, respiration rate, blood pressure and O2 saturation. Vital Signs should be repeated at minimum 15 minutes after infusion has started, at every 30 min during transfusion and at the end of transfusion. Patient should be informed of possible adverse effects of transfusion.

The use of Intraoperative cell salvage (IOCS) in obstetric practice has been limited, owing to concerns about contamination by amniotic fluid, specifically the risks of amniotic fluid embolism, and by foetal blood cells, particularly the risk of anti-D formation. IOCS has a role in the management of patients who refuse allogenic blood transfusions who are at risk of significant intraoperative haemorrhage. The use of cell salvage in obstetrics remains controversial and that experience of its use remains limited. (RCOG Green-top Guideline No. 4 of 10 47)

COMMON TRANSFUSION COMPLICATIONS

It can be Immune mediated and Non-Immune mediated.

- Acute Transfusion Reactions (ATR's)
- Chronic Transfusion Reactions
- Transfusion related infections

Acute Transfusion Reactions

- Hemolytic Reactions (AHTR)
- Febrile Reactions (FNHTR)
- Allergic Reactions
- TRALI (Transfusion related acute lung injury)

- Coagulopathy with Massive transfusions
- Bacteremia

In Transfusion related Acute Lung Injury, patient develops shortness of breath and dyspnoea, mild-moderate respiratory distress, use of accessory muscles, hypotension, tachycardia, no evidence of volume overload, crepts bilaterally. Chest X-ray shows bilateral fluffy infiltrates. TRALI, a leading cause of transfusion-related death (30% of transfusion-related fatalities) and clinical syndrome is similar to ARDS. It occurs 1-6 hours after receiving plasma-containing blood products. In management of TRALI, Transfusion should be stopped immediately. It has high mortality and does not improve with diuretics, only supportive care is given, may need ventilatory support. Patient usually recovers quickly and steroids have not been shown to help.

Transfusion-Associated Circulatory Overload (TACO) occurs up to 1% of all transfusions. Patient may develop shortness of breath and dyspnoea, cough, tachycardia, hypertension, crepts bilaterally, JVP may be raised. Usually IV Diuretic is given and symptoms improve due to circulatory overload. Risk is high in those who are having cardiopulmonary compromise or renal failure.

Acute Hemolytic Transfusion Reactions (AHTR) occurs when incompatible RBCs are transfused. Antibodies activate the complement system, causing intravascular hemolysis. Symptoms occur within minutes of starting transfusion. This hemolytic reaction can occur with few cc of RBCs. It can happen with PRBC, FFP or platelets. Common signs and symptoms are high fever/chills, hypotension, back/abdominal pain, oliguria, dyspnea, dark urine and pallor. It can be fatal. Immediately transfusion should be stopped. Blood bag with B.T. set is separated. IV line is maintained and NS should be started with new I.V. set. Try to maintain B.P./pulse. Catheterization is done and Diuretic is given. Blood and urine sample should be obtained for transfusion reaction workup. The remaining blood with bag & tube is sent back to blood bank, monitoring the patient for clinical status, vital signs, renal status, coagulation status and for signs of hemolysis. Patient may require hemodialysis.

A blood transfusion should never be ordered unless it is worth the risk. Blood transfusion is life saving but can lead to life threatening complications. Single unit transfusion has no significant therapeutic benefit. Blood should be used only in those conditions when equally effective alternatives cannot be used. Moreover, the collected blood should be separated into its components and used in conditions with specific requirements for optimal utilization. The aim is to reduce unnecessary blood transfusions, promoting proper use of blood and its components and to minimise it's complications. We should ensure the rational use of blood components meaning that the right patient is getting right product in the right amount at the right rate at the right time. All the efforts of obstetric management should be done to stop and control haemorrhage as well as to prevent recurrence of it.

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5. His book on Principles of critical care in Obstetric is available in more than 3000 world renowned medical libraries, published by an international publisher Springer and translated in Chinese and Spanish language.
6. He is instrumental for establishment of many Obstetric HUD/ ICU in India
7. Received best society, best RCH activities and best publication award from FOGSI.
8. Recently RCOG has conferred with Hon. FRCOG.
9. Organized all different types of FOGSI Conferences - YUVA FOGSI Conference, Satellite Conference and AICOG.
10. He was the Convener of one of the most successful AICOG 2017.

Diet and Nutrition In Pregnancy


Dr Milind Shah


Dr Pratik Tambe


Dr. Archna Tiwari

- **It would be ideal if a woman planning pregnancy would first reach the ideal BMI for her height with a view to decreasing the incidence of complications during pregnancy. This also impacts the fetal growth and development. Hence, an ideal BMI of 20-23 is recommended during the period when a woman is trying to conceive.**
- **Vitamin D deficiency is common in both non-pregnant and pregnant populations in India, in spite of there being good sun exposure with a significant number of sunny days throughout the year.**
- **While the NICE guideline recommends 10 mcg/day of vitamin D supplementation, WHO guidelines do not currently recommend additional vitamin D supplementation to improve maternal and fetal outcomes.**
- **With the advent of assisted reproduction, twin pregnancies are now far more common than previously encountered. In twins, the maternal metabolic rate is approximately 10% greater than in singletons.**
- **In multiple gestation one recommendation for macronutrient composition is 20% protein, 40% fat, and 40% carbohydrates. Caloric requirements are 40% higher in a twin pregnancy. Incidence of iron deficiency anaemia is 2.4-4 times higher in twins than in singletons. Anaemia due to folate deficiency is 8 times more common in twins compared to singletons. Hence, a 1 mg folic acid daily supplement has been recommended.**

1. INTRODUCTION

India is a country of great disparity in terms of health care accessibility, affordability and delivery. While the majority of urban population has access to health care, it may often be in the private sector; access is limited in small towns and villages and is mainly through government-run primary health centres, district hospitals and healthcare workers like ANMs and midwives.

It is beyond dispute that the keystone of a healthy, uncomplicated pregnancy with low risks of maternal, fetal and postpartum complications remains the foundation of good preconception counselling, a healthy diet and nutrition during pregnancy, regular antenatal visits and early identification of high risk status leading to consultant led care at the appropriate juncture. While there is a shortfall on many of these fronts, a consistently identifiable factor is the quality of diet and maternal nutrition during pregnancy and lactation

We always keep proud of our four square diet but with civilization and modernization, it is not well observed in many families and we find many antenatal patient with anaemia and deficient of vitamins.

2. BACKGROUND

Healthcare providers should be updated regarding the modern guidelines and approaches regarding nutrition during pregnancy, as these are different when compared to nonpregnant populations. Most policy documents and guidelines from healthcare bodies also recommend an individualised approach to diet and nutrition which considers a woman's access to food, socioeconomic status, ethnicity, cultural food choices and body mass index (BMI). While most guidelines focus on uncomplicated, planned pregnancies, these recommendations need to be made suitably modified when pregnancy complications such as gestational diabetes occur.

While it is of paramount importance to have a dietitian available for consultation, access to one who offers quality advice is rare beyond large metros in India. In the sections that follow, we discuss the current guidelines and recommendations which should be followed during pregnancy and lactation. We also give examples of specific foods and diet charts which can be recommended in the Indian population. There are specific recommendations for complicated pregnancies eg. multiple gestations, obesity, gestational diabetes and these are covered in brief.

Additional requirements during pregnancy

It would be ideal if a woman planning a pregnancy would first reach the ideal BMI for her height with a view to decreasing the incidence of complications during pregnancy. This also impacts the fetal growth and development. Hence, an ideal BMI of 20-23 is recommended during the period when a woman is trying to conceive. However, a large proportion of pregnancies are likely to be unplanned and hence, this is a far from ideal situation.

The basic increased requirement is 300 kcal/day over and above the routine requirement of an average built, moderately nourished woman.[1] By and large, energy requirements are not significantly increased in the first trimester when hyperemesis is a frequent issue. During the second trimester, the requirement increases by about 340 kcal/day and in the third by 452 kcal/day approximately.[2] As noted above, caloric intake requirements need to be individualised based on the lifestyle, work patterns, age, BMI and socioeconomic status of a woman.

3. PHYSIOLOGICAL CHANGES

Pregnancy is a time of subtle alterations to the body of a woman which are often unnoticed and ignored even by the attendant healthcare professionals. Reference ranges for several biochemical parameters are known to change significantly.

While haemoglobin and haematocrit values in nonpregnant women are 12-15 g/dL and 37-48% respectively, these are altered in pregnancy such that values <10.5 g/dL and <32% are considered abnormal. Owing to the increased plasma volume and dilution, serum albumin and total protein values fall by as much as 30%. While the volume of binding proteins increases in absolute terms, the free levels of hormones such as thyroid, sex steroids and vitamin D fall when compared to nonpregnant reference ranges.

Macro and Micronutrients

The ideal recommended protein intake during pregnancy is 60 g/day. Carbohydrates should comprise 45-64% of daily calories, including approximately 6-9 servings of whole grain daily. Total fat intake should comprise 20-35% of daily calories.[2]

Folic Acid - Folic acid supplements reduce the risk to the fetus of NTDs such as anencephaly and spina bifida. The NICE guidelines recommend that women who could become pregnant or who are already pregnant take them daily (400 micrograms [µg]) before conception and throughout the first 12 weeks of pregnancy. Higher doses (5 mg daily) are recommended for those who have had a previous NTD pregnancy or who have a family history of NTD. Higher doses are also recommended for women who have (or whose partner may have) an NTD and those who have diabetes.[3]

Health professionals and others working with women of childbearing age need further training so that they can explain the importance of folic acid and folate. They also need to stress that eating folic acid and folate-rich foods is important, but is not enough to reduce the risk of NTDs. Foods fortified with folic acid include: breakfast cereals and yeast extract. Those rich in folate include: peas, beans, lentils and orange juice.

Iron - Iron supplements is a mainstay during pregnancy because iron needs nearly double. Vitamin C supplements can assist with iron absorption, whereas milk and tea can inhibit iron supplementation. Women with iron deficiency can increase their haemoglobin by 2 g/dL over four weeks with daily consumption of 60-120 mg of elemental iron. Common side effects of iron such as abdominal pain, constipation, nausea and vomiting are reasons for poor compliance.

Vitamin D - Vitamin D deficiency is common in both non-pregnant and pregnant populations in India, in spite of there being good sun exposure with a significant number of sunny days throughout the year. The increasing amounts of environmental pollution and smog are among the reasons identified as responsible for this unique situation. Maternal skin exposure may hence not be adequate to achieve optimal vitamin D levels during pregnancy. This is also applicable to affluent women as well due to inadequate exposure to sunlight.

While the NICE guideline recommends 10 mcg/day of vitamin D supplementation, WHO guidelines do not currently recommend additional vitamin D supplementation to improve maternal and fetal outcomes.

Vitamin A - Vitamin A is essential for cell differentiation and proliferation as well as the development of the spine, heart, eyes, and ears. Excessive doses of Vitamin A (>10,000 IU/day) have been associated with craniofacial (face, palate, ears) and cardiac birth defects. The maximal supplement in pregnancy is 8000 IU/day. It should be noted that it is the retinol form of Vitamin A that is associated with teratogenic effects, not the carotenoid version found in food sources such as carrots.

Recommended Dietary Allowances

Nutrient	Non-Pregnant	Pregnant	Lactation
Vitamin A (µg/d)	700	770	1300
Vitamin D (µg/d)	5	15	15
Vitamin E (mg/d)	15	15	19
Vitamin K (µg/d)	90	90	90
Folate (µg/d)	400	600	500

Niacin (mg/d)	14	18	17
Riboflavin (mg/d)	1.1	1.4	1.6
Thiamin (mg/d)	1.1	1.4	1.4
Vitamin B_6 (mg/d)	1.3	1.9	2
Vitamin B_{12} (µg/d)	2.4	2.6	2.8
Vitamin C (mg/d)	75	85	120
Calcium (mg/d)	1,000	1,000	1,000
Iron (mg/d)	18	27	9
Phosphorus (mg/d)	700	700	700
Selenium (µg/d)	55	60	70
Zinc (mg/d)	8	11	12

WEIGHT GAIN

The average weight gain during pregnancy is approximately 8 kg including the fetus, the placenta, amniotic fluid volume and physiological maternal changes. Metabolic changes in women who fast or loose weight include ketonemia, increased urinary nitrogen excretion, decreased gluconeogenesis and amino acid production hence, fasting is not recommended in pregnancy.[5] Maternal ketonemia or ketonuria may subsequently be associated with abnormal fetal growth or later neurocognitive development.

Pre-pregnancy BMI	Total weight gain at term	Rate of weight gain in the 2nd and 3rd trimester; Mean (range)
Underweight(<18.5 kg/m^2)	12.5-18 kg	0.51 (0.44-0.58) kg/week
Normal weight(18.5-24.9 kg/m^2)	11.5-16 kg	0.42 (0.35-0.50) kg/week
Overweight (25.0-29.9 kg/m^2)	7-11.5 kg	0.28 (0.23-0.33) kg/week
Obesity (⩾ 30.0 kg/m^2)	5-9 kg	0.22 (0.17-0.27) kg/week

Table 2 Recommended Weight gain during pregnancy[4] as per the pre-pregnancy BMI

Women with a pre-pregnancy BMI ⩾ 30kg/m2 should gain 5-9 kg during pregnancy.[6] Women who are overweight or have obesity have lower ranges for recommended total gestational weight gain compared to normal-weight women and a significant proportion of all women commonly exceed the gestational weight gain recommendations. It is well known that women who gain weight in the appropriate range for their BMI during pregnancy have fewer adverse perinatal outcomes than those exceeding these guidelines.

Recommended diet for a pregnant woman - We need to observe following pyramid of diet during pregnancy.

Food group	Food stuff	Vegetarian	Total energy calories	Total protein mg/dL	Non-vegetarian	Total calories (kcal)	Total protein (mg/dL)
I	Rice, wheat and millets	300 gm (raw)	1035	20.4	300	1035	20.4
	Oils,ghee and butter	30 gm	279	0	30	279	0
	Jaggery and sugar	20 grams	7.96	0.02	20	7.96	0.02
II	Milk, curd, etc	500 gm	290	29.5	500	290	29.5
	Pulses, dried beans	60 gm (raw)	208.8	14.7	40	139.2	9.8
	Fish, eggs and meat	nil	nil	nil	20	23.6	4.8
III	Fruits	200 gm	169.5	1.65	200	169.5	1.65
	Vegetables	350 gm	121	3	350	121	3
	Green leafy vegetables	150 gm	48	3.65	150	48	3.65
	Other vegetables	120 gm	22.2	1.08	120	22.2	1.08
	Roots and tubers	100 gm	32	0.6	100	32	0.6
Total			2213.46	74.6	Total	2167.46	74.5

Table 3 Recommended diet during pregnancy[7]

Food group	Quantity/serving	Servings/day	Total intake per day
Cereals & Grains	100 gm	3	300 gm raw
Pulses	30 gm	2	60gm raw
Milk and milk products	250 mL	2	500 mL
Green leafy vegetables, other vegetables, roots and tubers	100 to 150 gm	4	400 gm
Fruits	100 gm	2	200 gm
Oil	30 mL		30 mL

Table 4 Meal plan for a 50 kg pregnant woman doing sedentary work[7]

While these are generalised guidelines, these can be modified by expert nutritionists or dieticians and individualised for each woman depending on her socioeconomic status, BMI, sociocultural beliefs and lifestyle.

WHO RECOMMENDATIONS

In 2016, the World Health Organisation (WHO) published a comprehensive guideline on antenatal care for pregnant women. Among others, it covers health promotion, screening and diagnosis and disease prevention. Implementing such timely and appropriate evidence-based practices has been clearly shown to save lives in the context of reproductive health care.[8]

Dietary interventions
A.1.1: Counselling about healthy eating and keeping physically active during pregnancy is recommended for pregnant women to stay healthy and to prevent excessive weight gain during pregnancy.
A.1.2: In undernourished populations, nutrition education on increasing daily energy and protein intake is recommended for pregnant women to reduce the risk of low-birth-weight neonates.
A.1.3: In undernourished populations, balanced energy and protein dietary supplementation is recommended for pregnant women to reduce the risk of stillbirths and small-for-gestational-age neonates.
A.1.4: In undernourished populations, high-protein supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.
Iron and folic acid supplements A.2.1: Daily oral iron and folic acid supplementation with 30 mg to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid is recommended for pregnant women to prevent maternal anaemia, puerperal sepsis, low birth weight, and preterm birth. A.2.2: Intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2800 µg (2.8 mg) of folic acid once weekly is recommended for pregnant women to improve maternal and neonatal outcomes if daily iron is not acceptable due to side-effects, and in populations with an anaemia prevalence among pregnant women of less than 20%.

Calcium supplements A.3: In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of pre-eclampsia.
Vitamin A A.4: Vitamin A supplementation is only recommended for pregnant women in areas where vitamin A deficiency is a severe public health problem,to prevent night blindness
Zinc supplements A.5: Zinc supplementation for pregnant women is only recommended in the context of rigorous research.
Multiple micronutrient supplements A.6: Multiple micronutrient supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.
Vitamin B6 supplements A.7: Vitamin B6 (pyridoxine) supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.
Vitamin C and E supplements A.8: Vitamin E and C supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.
Vitamin D supplements A.9: Vitamin D supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.
Caffeine intake A.10: For pregnant women with high daily caffeine intake (more than300 mg per day), lowering daily caffeine intake during pregnancy is recommended to reduce the risk of pregnancy loss and low-birthweightneonates.

Table 5 Nutrition recommendations for pregnant women[8]

MULTIPLE GESTATION

With the advent of assisted reproduction, twin pregnancies are now far more common than previously encountered. In twins, the maternal metabolic rate is approximately 10% greater than in singletons. As expected, the physiological changes in a singleton pregnancy are exacerbated in multiple gestations. These include an increase in plasma volume, consequent further decreases in haemoglobin, albumin and water soluble vitamins.

There are no standardised nutritional guidelines for multiple gestations. One recommendation for macronutrient composition is 20% protein, 40% fat, and 40% carbohydrates.Caloric requirements are 40% higher in a twin pregnancy. Incidence of iron deficiency anaemia is 2.4-4 times higher in twins than in singletons. Anaemia due to folate deficiency is 8 times more common in twins compared to singletons. Hence, a 1 mg folic acid daily supplement has been recommended. Some experts recommend 1000IU of vitamin D and 2000 – 2500mg/day of calcium daily for twins.[9,10] Multiple gestations have a higher risk of complications such as premature birth and low birth

weight. Evidence for nutritional management of higher order multiples (triplets, quadruplets) is lacking, but they can be managed similarly to twin gestations.

PREGNANCY AFTER BARIATRIC SURGERY

As assisted reproduction becomes more accessible to populations with the concurrent rise of obesity, pregnancy after bariatric surgery is not uncommon. Since this group of patients present some unique nutritional and dietary challenges, we discuss in brief the issues that they present.

Bariatric procedures create deficiencies of both micro- and macronutrients and a pregnancy occurring after a bariatric surgery procedure requires particular attention to the maternal nutritional status. Since the requirements for calories, vitamins, and minerals increase during any pregnancy, the nutritional deficiencies in the patient who has undergone bariatric surgery patient can only be exacerbated during pregnancy. The most common deficiencies that occur after bariatric surgery are Vitamin B12, folate and iron.

Not all bariatric surgeries are equivalent in terms of the physiological changes they cause. Malabsorptive procedures such as Roux-en-Y gastric bypass and biliopancreatic diversion have a higher risk for nutritional deficiencies than a simple banding or sleeve gastrectomy.Close surveillance in pregnancies that occur after these types of surgeries is appropriate.

However, derangements in nutrients can also occur after restrictive-type procedures such as laparoscopic adjustable gastric banding, so it may be reasonable to screen all women who are pregnant post-bariatric surgery for nutritional deficiencies.Guidelines for screening and management of nutritional deficiencies during pregnancy are adapted from those designed for non-pregnant states and include laboratory testing once a trimester or every 3 months if the levels are normal. Iron deficiency anaemia is frequently a long-term complication of bariatric surgery, occurring in 6% to 50% of patients.[11]

In pregnancies after bariatric surgery, iron deficiency anaemia can be diagnosed in the usual manner with a low mean corpuscular volume, and abnormal iron studies (eg, low serum iron, high total iron-binding capacity, and a low serum ferritin). Treatment of vitamin and mineral deficiencies during pregnancy is similar to that of non-pregnant states.[12]

OBESITY

The World Health Organization and the National Institutes of Health define normal weight as a BMI of 18.5–24.9 kg/m2, overweight as a BMI of 25–29.9 kg/m2, and obesity as a BMI of 30 kg/m2 or greater. Obesity is further categorized by BMI into Class I (30–34.9 kg/m2), Class II (35–39.9 kg/m2), and Class III or extreme obesity ($\geqslant$ 40 kg/m2).

Obesity has assumed epidemic proportions in western countries and in soon, urban populations in India will follow suit. Trends in adult weight over the past couple of decades highlight the escalating role that obesity plays in women's health: 31.8% of reproductive age women had clinical obesity in 2012.[13] Women with a higher pre-pregnancy BMI have a greater risk for adverse perinatal outcomes.These include both maternal complications such as gestational diabetes, pregnancy-related hypertension, and caesarean deliveries along with adverse fetal effects such as birth defects, stillbirth, and fetal growth restriction and macrosomia. Weight loss prior to pregnancy is strongly recommended in order to reduce the risk of these complications.14

Interventions to promote optimal gestational weight gain have emphasised lifestyle modification

and combinations of dietary counselling, weight monitoring and exercise programs. When the results of multiple studies are examined in meta-analyses, the interventions for women who are overweight or obese have been shown to have moderate or no influence at all on gestational weight gain or other perinatal outcomes.[15,16]

Further research is required to determine how to promote adherence to gestational weight gain guidelines with health behaviour interventions. Since maternal obesity has a direct linkage to childhood weight, resulting in a propagation of the cycle of obesity, it is possible that environmental, epigenetic influences and genetic mechanisms have a complex interplay and role in the obesity epidemic.

The Barker hypothesis suggests that in utero nutrition may impact chronic diseases such as diabetes, hypertension and other chronic metabolic diseases later in life in the offspring. Hence, clinicians should bear in mind that maternal nutrition during pregnancy may have life-long consequences for the offspring.[17]

CONCLUSION

Through the preceding sections, we have tried to address the complex issues that are encompassed in the field of diet and nutrition in pregnancy. While there is a plethora of guidelines on the subject, implementation is difficult owing to the vast differences in the healthcare provider practices, the health characteristics of women themselves, sociocultural aspects, food taboos, misconceptions and lack of awareness among caregivers.

We have attempted to unite the important guidance from WHO, NICE and ACOG in an effort to provide a concise at a glance list of recommendations regarding specific issues related to dietary interventions, biochemical testing and macro-, protein, vitamin and trace element supplementation. We have also provided general guidelines and diet charts relevant to the Indian population.

The sections on obesity, gestational diabetes and bariatric surgery are aimed at urban populations facing similar issues as in Western countries. While we await further meta-analyses and randomised trials in these subgroups, it is of paramount importance to bear in mind the role diet and nutrition plays on the incidence of maternal and fetal complications in pregnancy and during postnatal life.

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Social and Spiritual Aspects of Women Empowerment

Dr. Mala Arora **Dr. Richa Gupta**

- **Violence against women continues from womb to tomb.**
- **Awareness among women about their capabilities, their value and their rights. They should know that Indian Constitution has provision of 6 basic human rights for them.**
  - **Right to equality**
  - **Right to freedom**
  - **Right against exploitation**
  - **Freedom to practice any religion**
  - **Cultural and educational rights**
  - **Right to constitutional remedies.**
- **It's time to make equality between men and women a norm. It's time that women revive their lost glory. It's time that insecurities and ego driven patriarchal society melts away and reshapes itself to a new social structure.**

MEN ARE FROM MARS AND WOMEN ARE FROM VENUS

God created the diversity of two sexes in His creation of the entire animal kingdom. Each sex has a clearly defined role in reproduction, rearing of the young and procuring food for them that varies among different species. However the two sexes exist in harmony in all other species except the highest evolved of them – homo-sapiens.

Men are physically stronger but women are blessed with the unique ability of child bearing and nurturing. Due to this power of procreation, women are considered Second Creators next to God. All religions have paid tribute to the mother. Hindu Literature has pedestalled women as **"Janani"** for the pivotal role that women play in bearing children, rearing them and contributing to their character building. So much so that Hindu literature quotes **"Yatra Naari Poojyante, Tatraramte Devta"** ie "where women are respected , there spiritually elevated spirits choose their abode". Guru Granth Sahib says **"So Kyon Mandaa Akhiye, Jit Jamme In Rajan"** ie Woman who gives birth to kings cannot be referred to as inferior.

Quoting the Bible Proverb 31:25 **"She is clothed with strength and dignity; and laughs without fear of the future"** and again in Psalms 45:5 **"God is with her, She will not fall."** Regarding childbirth it says "The pain that you have been feeling can not compare to the joy that is coming. (Romans 8:18)

Islam says that **"Stick to her [his mother] for indeed Jannat lies beneath her feet.'**

فَالْزَمْهافانَّالجنّةَتَحْتَرِجْلَيْها

(SunanNasai, Hadith: 3104, Musnad Ahmad, vol.3 pg. 429)

Then again in the Quran Surat No 46 : Ayat No 15 وَوَصَّيْنَا الْاِنْسَانَبِوَالِدَيْهِ۔ اِحْسٰنًا ؕ حَمَلَتْهُ۔ اُمُّهٗ۔ كُرْهًاوَّوَضَعَتْهُ۔ كُرْهًا ؕوَحَمْلُهٗ۔ وَفِصٰلُهٗ۔ ثَلٰثُوْنَشَهْرًا ؕحَتّٰۤى اِذَابَلَغَ۔ اَشُدَّهٗ۔ وَبَلَغَ۔ اَرْبَعِيْنَسَنَةً ۙقَالَ۔ رَبِّاَوْزِعْنِىْۤ۔ اَنْ۔ اَشْكُرَ۔ نِعْمَتَكَالَّتِىْۤ اَنْعَمْتَعَلَىَّ

وَعَلٰىوَالِدَىَّ وَاَنْ اَعْمَلَصَالِحًاتَّرْضٰىهُوَاَصْلِحْ لِىْ فِىْذُرِّيَّتِىْ ۚ ؕ اِنِّىْ تُبْتُ اِلَيْكَوَاِنِّىْمِنَالْمُسْلِمِيْنَ(۱۵)

and we have enjoined upon man, to his parents, good treatment. His mother carried him with hardship and gave birth to him with hardship, and his gestation and weaning [period] is thirty months. [He grows] until, when he reaches maturity and reaches [the age of] forty years, he says, "My Lord, enable me to be grateful for Your favor which You have bestowed upon me and upon my parents and to work righteousness of which You will approve and make righteous for me my offspring. Indeed, I have repented to You, and indeed, I am of the Muslims."

Just by virtue of playing a key role of Child bearing, Nurturing & Home making women should be empowered and respected. After all these are most important aspects of social structuring. But paradoxically and sadly we don't see this translating in real life in current time and age.

Our Patriarchal Society has laid down societal norms like dowry to tie women down. Our social structure, instead of rewarding women is letting her down on many fronts. Being physically vulnerable, women have often been subjugated to abusive behavior and domestic violence. In the lower socioeconomic groups, she faces under nutrition during childhood, discontinuation of education, and responsibility of house hold chores from a young age. As an adult and after marriage she shoulders the responsibility of house hold chores and child rearing single handedly, inspite of pursuing a career. This results in loss of her personal time, and in many cases complete end of her career and loss of financial independence. Society doesn't ends here with violence against women. Abuses are rampant among the uneducated women end those not financially independent. However these crimes abound even among the educated and affluent class of working women.

VIOLENCE AGAINST WOMEN CONTINUES FROM WOMB TO TOMB :-

- In the womb in the form of selective female feticide, which though illegal is still not totally non-existent. It has skewed the sex ratio in our country
- As a neonate there are instances of female infanticide and inadequate medical treatment in

times of serious illness.

- As a child un-equal opportunity to pursue education & passion.
- As an adolescent - molestations, eve teasing, rapes, acid attacks and honour killing. As a repercussion she undergoes moral policing from puberty onwards.
- As an adult, after marriage dowry demands, emotional violence, subjugation and intimidation, physical violence, and it culminates with dowry deaths and rage murders.
- Harassment at work place, and unequal work opportunities and pay scales.
- Financial violence like surrendering of her income to the husband and/or family.
- Unequal inheritance of family assets.
- More recently Cyber Crime and lewd remarks and violation on social media.

Abuse for women is panoramic, as is illustrated by the points mentioned. As the child of the family she is entitled to equal inheritance, but most often her right is translated to dowry which is spend on whims and fancies of her in-laws, her choice and control over her own money is dissolved subtly and devoured ruthlessly even before she realizes what has happened. If some mishap happens with her marriage, she finds herself devoid of funds and unsupported (as parents feel that their responsibility ends with her marriage. It's a fantastic abuse cycle that society plays against women, very subtly torturing her, morally policing her, psychologically training her that her likeability equates with sacrifice and being dependent, pruning her feathers of financial independence, career and support system of family and friends and then finally when she is tattered - blaming and outcasting her as "unsuccessful, unlikable, incapable… there must be something wrong with her".To avoid these outcome women bear everything in silence to feel accepted.

This abuse cycle has to break and hence there is **NEED OF WOMEN EMPOWERMENT AND LEADERSHIP.** Education system has repeatedly shown equal or greater capabilities of women. Yet as life unfolds society norms and misconceptions subjugates women. Women most often are not seen rising the ladder of success compared to their male counterparts. Sometimes it is childbearing, sometimes it is child rearing, and many a times she struggles in complex family situations to save her marital status because she doesn't want to be seen as personal and public failure on the cost of professional success. As Society has already tagged woman's success on the basis of personal accomplishment, her professional success is not important and happens with little encouragement and sometimes in a hostile setting. So, she struggles to save her boat of success from drowning accepting all the crap that comes her way and in this process sacrificing her rights, her career and her financial independence. Most importantly, she sacrifices her freedom to make choices without fear of judgment and consequences.

This ugly situation can only change by Women Empowerment. Women have to come together and battle the social evil that has taken strong roots in our society.

TOOLS OF WOMEN EMPOWERMENT

Some tools of women empowerment which should be implemented are:

1. Awareness among women about their capabilities, their values and their rights. They should know that the Indian Constitution has provision of 6 basic human rights for them.
   a. Right to equality
   b. Right to freedom
   c. Right against exploitation
   d. Freedom to practice any religion
   e. Cultural and educational rights
   f. Right to constitutional remedies.

CERTAIN BASIC RIGHTS

1. Certain Basic Rights in a relationship and life -

- The right to good will from her spouse and their family.
- The right to emotional support.
- The right to be heard by the other and to be responded to with courtesy.
- The right to have your own viewpoint, even if your partner has a different view.
- The right to have your feelings and experiences acknowledged as real.
- The right to receive a sincere apology for any comments & jokes you may find offensive.
- The right to clear and informative answers to questions that concern what is legitimately your business.
- The right to live free from accusation and blame.
- The right to live free from criticism and judgment.
- The right to have your work and your interests spoken of with respect.
- The right to encouragement.
- The right to live free from emotional and physical threat.
- The right to live free from angry outbursts and rage.
- The right to be called by no name that devalues you.
- The right to be respectfully asked rather than ordered.

2. Parents giving Equal Inheritance to Male & Female children - Women accepting their inheritance as their right rather than shying off to increase their likeability in society.

3. End of Dowry System and Simple Marriages - dowry system is the root cause of all problems for women. Translation of inheritance to dowry to suit the convenience of in-laws

should end. Women should receive their rightful inheritance and should have control over the money/property/etc. to suit herself and her needs.

4. **Equal opportunities for Woman's Employment and Financial Independence** should be welcomed and encouraged.
5. When both partners are working, each has to perform their share of duties at the home front.The tagline should be "Partner a real Partner.' i.e. **Making Men and Women Equal Partners-participating in Domestic Chores and Child Upbringing.**
6. Women should be **Partners in Decision Making** in family matters both financial and otherwise. They should come forward and claim their right. They should actively sit on the Table and be the decision makers.
7. **Free Knowledge and availability of Contraceptive Methods :** Women of all status should know and implement the contraceptive methods to time, space and limit the number of pregnancies. This is part of her sexual and reproductive right to reproduce only if she chooses to.
8. **Right to terminate an unwanted pregnancy** within the legal boundaries. There is provision for this in our constitution under the "Medical Termination of Pregnancy (MTP) Act".
9. **Filling Women Leadership Gap-** Career progression of an individual often depends on taking risks and advocating for themselves-traits that girls are discouraged from honing and exhibiting. This explains why girls' academic gains have not translated into significantly higher number of women in top jobs. Society subtly psyches woman towards success based on personal achievements and men towards professional and leadership achievements. Ambitious and Aggressive woman violate unwritten rules about acceptable social conduct. While men are applauded for being ambitious, powerful, successful, and self-confident, however women with same traits often pay social penalty. Not surprisingly women are capable of both successful professional life and personal fulfillment at the same time. Women have to break barriers to unleash their potential and reach to the top in their fields. The more women we have on top, more comfortable working women will become and more balanced our society will be. Its time women fill the roles of leadership, visionaries, and entrepreneurs and are willing to take risks.
10. **Appreciating a new brand VERSION of Man -** over the period of time woman has continually upgraded herself to newer versions. She has excelled in education and profession, she has adapted and worked hard to attain the skill set of a man. It's time that men don't lag behind and upgrade themselves to their new Versions by learning and participating in domestic chores and child rearing, while welcoming equal status for their spouses. This way both men and women will feel less burdened and will enjoy each other without controlling and manipulative behavior.

Society has to evolve as a whole for the benefit of Men, Women, Children and Nature. It's time to

make equality between men and women a norm. It's time that women revive their lost glory. It's time that insecurities and ego driven patriarchal society melts away and reshapes itself to a new social structure, a balanced one based on mutual respect and love, providing each other with their rightful space and resources to flourish.

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Scientific Benefits of Lifestyle Modification Techniques Suggested to Antenatal Women during Garbha Sanskar

Dr. Pranav Pandya

- **Upbringing of children starts before their birth – right in the womb. Scientific studies and analyses on the gradual stages of child's growth in the fetus have shown that the baby enjoys, tastes, hears, remembers, learns, understands, feels, and also expresses joy, pain, tension, etc. Research on hormones and psychology has revealed significant impact of the mother's health, as well as her mental and emotional condition on the child. For this, it is essential to nurture the biological and inner growth of the baby right since the embryonic state. To a great extent, the physical, mental and spiritual development of the child could be shaped in the desired direction inside the mother's womb itself.**
- **The ancient sages realized that the baby to be born is the image of the Creator and the gift of God. Therefore, they devised the Garbha Sanskar, which is the formal welcome ceremony of the baby, done along with the invocation of the family deity. The present article highlights the importance of the Garbha Sanskar, as well as describes various lifestyle modification techniques like Jap, Dhyan, Pranayam, Yog, Music and Swadhyay that are advised to antenatal women during Garbha Sanskar; the scientific benefits of these techniques are also discussed. These techniques can play a vital role in ascertaining the physical and mental well being of the antenatal woman, as well as the fetus.**

Keywords: Pregnancy, Jap, Dhyan, Pranayam, Yog, Music, Swadhyay, Garbha Sanskar

1. INTRODUCTION

Every parent heartily desires to have a healthy, good-looking, intelligent and cultured child. For this, it is essential to nurture the biological and inner growth of the baby right since the embryonic state.[1] To a great extent, the physical, mental and spiritual development of the child could be shaped in the desired direction inside the mother's womb itself.

Upbringing of children starts before their birth – right in the womb. Scientific studies and analyses on the gradual stages of child's growth in the fetus have shown that the baby enjoys, tastes, hears, remembers, learns, understands, feels, and also expresses joy, pain, tension, etc. [2-13] Research on hormones and psychology has revealed significant impact of the mother's health, as well as her mental and emotional condition on the child.[3,11,13] Physical health of the mother, at the time of pregnancy, largely influences the health of her child; similarly, her thoughts, emotions and internal feelings also influence the child.[3,11,13] For example, the babies born to the mothers suffering from malnutrition, or having negative thinking, tension, anger, etc., during pregnancy, are most likely to be weak, as well as prone to various psychosomatic ailments and disorders. On the contrary, the babies born to contented, healthy, kind-hearted, happy mothers, who have positive and joyous outlook, who have been taking balanced, pure, honestly-earned and adequately nourishing diet, and, who are doing proper exercises during pregnancy, are most likely to be physically and mentally healthy.

The fetus also undergoes a subtle process of development that cannot be seen or recorded externally. As specific patterns of sound-waves are engraved or digitally stored on a magnetic tape or audio device, similarly, all emotional and mental perceptions, and experiences of the mother in the state of pregnancy get inscribed in the memory line of the baby. Consciousness-force of the child's soul remains active (in the subtle body), even though it is not fully manifested in a physical form (in a new body). So the child's sub-conscious mind continuously keeps recording/ assimilating all those feelings/ experiences even in this pre-birth state. Thoughts, emotional reflections, desires, mental perceptions, conduct, etc. of the mother greatly influence these sub-conscious impressions and conditioning of her baby's mind.[1,3,11,13,14]

It is well-known that healthy diet and climate for the pregnant woman are necessary for adequate nourishment of her baby's growth (biological and physical). It is equally essential to support the baby's mental and emotional development by making sure that the mother lives in a serene, pious, and positive ambience, and her mood remains calm and happy. What she eats, drinks, listens, smells, touches, sees, thinks, all experiences of her physical and mental faculties, should be compatible with the expected virtuous development of her baby.[1,14] Findings of recent scientific investigations on overall development of a baby also support the need for adequate conditioning of mother's psychology;[1,3,11,13,14] in this regard, the present article highlights the importance of the welcome ceremony for the baby (called Garbha Sanskar, Punsavan, Baby Shower, etc.), during which various lifestyle modification techniques like Jap, Dhyan, Pranayam, Yog, Music and Swadhyay are advised to antenatal women;[1,14] the scientific benefits of these techniques are also discussed.

2. GARBHA SANSKAR

The ancient sages realized that the baby to be born is the image of the Creator and the gift of God, who, in future, is going to be the medium of pleasure and prosperity, fame and glory to the family. Therefore, they devised the Garbha Sanskar (also known as Punsavan, Baby Shower, etc.), which is the formal welcome ceremony of the baby, done along with the invocation of the family deity. [1,14] It is done soon after conception or in the third month or in the seventh month of pregnancy.[1,14] In Garbha

Sanskar, in the presence of invoked deities, mother, father and other family members pray for the bright future of the coming baby and resolve to do their best to make the baby a righteous person.

3. LIFESTYLE MODIFICATION TECHNIQUES ADVISED DURING GARBHA SANSKAR

1) **Jap (Chanting) and Dhyan (Meditation)** The inner practice of spirituality consists essentially of two components, namely (1) Jap or repeated chanting of some scriptural text, divine name or Mantra and (2) Dhyan or meditation.[45]

Meditation is the process of collecting disarrayed currents of thoughts and concentrating them on a particular target. Practice of meditation frees the mind from purposeless wanderings and channelizes its energy in a focused way on inner exploration of Self.[45] Scientific studies have shown that meditation has a significant positive impact on the physiological and psychological well being of human beings.[15-20] Thus, it should be practiced regularly by the expecting mother.

One of the most suitable way for meditation is to take 'Savita' (the cosmic energy in Sun) as the representative of God.[45] The omnipresent cosmic energy is received all over this planet through the Sun and it is the sustainer of all biological systems on Earth. Hence, it is quite logical to consider the Sun as the universally visible symbol of God for meditation. If the Sun is taken as the deity for meditation, each of the three constituents of human existence namely physical, mental and emotional can integrally interact with Savita.[45] Physically, the solar radiations purify and invigorate the body. In the rays of the Sun, one finds a parallelism with the aspirations expressed in Gayatri Mantra for self- evolution, as righteousness in thoughts and actions. Emotionally the Sun, being the causative entity and sustainer of life, is comparable to mother, whose love for the infant knows no bounds. In this way, while meditating on the Sun one can interact with totality of physical-mental-emotional components of one's existence and invigorate all of them.[45]

Jap is a repetitive process to make the light of divine wisdom reach the deepest levels of human psyche, for achieving the state of recognition of relationship of man with God. [45] Human mind is generally not easily impressionable. Presented with logic, the mind may accept a concept temporarily but in order to make it acceptable to the human psyche without any reservations, it is required to be impressed again and again by repetition.[45]

In the realm of Indian spiritual literature, one of the most effective Mantra for Jap is the Gayatri Mantra. The Jap of Gayatri Mantra is extremely efficacious in refining the inner-self. [45]

Scientific studies have shown that the chanting of Gayatri Mantra is useful in the management of various physical and mental ailments like stress, anxiety, depression, obsessive compulsive disorder, etc.[18,20,28-37] Thus, it should be practiced regularly by the expecting mother.

2) **Yog and Pranayama -** Upon completion of routine cleansing activities, the expecting mother must practice yogasanas and pranayamas. Yogic postures have been shown to have significant positive impact on various physical and mental ailments.[16,21-27]

Some specific yogic postures advised to the expecting mother include: Setubandh Asana (Bridge Posture), Tadasana, Utkatasana (it provides strength to muscles of the thighs, knees, ankles and the uterus) and Shavasana (it provides peace and serenity to the mind).1 Pelvic-floor exercises / Mulabandh are also advised. Exercises of pelvic-floor and reproductive organs are important from the point of view of keeping the body ready for easy delivery and speedy recovery thereafter.[1]

The respiratory system should work efficiently during pregnancy. The baby in the womb gets oxygen through mother only; this requires additional oxygen. This need can be fulfilled through pranayama.1 Proper and regular pranayama provides physical benefits, as well as it relieves stress and other mental ailments.[17] Some practices advised to the expecting mother include deep breathing, Anulom-Vilom Pranayama, Pranakarsan Pranayama and Bhramari Pranayama.[1]

3) **Swadhyaya -** Swadhyaya is the study of spiritual books and self analysis in context of these books, which includes the philosophical works, teachings of illuminated sages and stories of saints.[38] Swadhyaya elevates the mind to high spiritual altitude and clears doubts. It brings us towards knowing ourselves by analyzing the positive and negative aspects of our personality in context of these books. Swadhyaya relieves all difficulties and misunderstandings of the mind, and gives the ability to cope up with all difficult and stressful situations.

The subconscious mind is most receptive in the morning time. So, reading and contemplation on noble thoughts and pious feelings should be practiced in the morning. This will help in the ideal nourishment of the expecting mother and the fetus. Holy religious texts, such as the Ramayana, Bhagvadgita, Guru Granth Sahib, Bible, or Quran, etc., according to one's faith, must be read. Inspiring texts pertaining to valor, courage, divine values and virtues must be read. Several studies have shown that Swadhyaya help in relieving various physical and mental ailments.[38-40]

Swadhyaya literally means study of the Self. The pregnant woman should always be alert in this direction. Whatever she reads and thinks is going to affect the baby in the womb. Therefore, in order to give birth to a well-cultured child, mother must study good literature.[1] Reading biographies of great personalities, reflection on the valiant deeds of courageous people, literature providing inspirations and enthusiasm, and the progressive aspects of religious books fulfill this need. [1] Therefore, for inner refinement of the self and the bright future of the coming child, swadhyaya is a must.

Depression may also occur during pregnancy due to some hormonal changes. In such cases swadhyaya serves as a medicine.[1] Noble and inspiring books have the power to transform the life. Satsahitya (Noble literature) is so powerful that it can guide even in the most unfavorable circumstances.[1] It contains the solutions to our day-to-day problems. When the mind is disturbed, there is unbearable pain, or one is under heavy stress, then reading satsahitya makes the mind stress- free; it is able to find the ways and means of solving the riddles of life that looked formidable earlier. Indeed, satsahitya plays a very important role in finding the right direction in life.

4) **Music -** The pregnant woman must listen to soothing music for about four hours every day, as the enchanting feel of its melodious reverberations is good for the child in the womb. Bhajans are simple songs in soulful language expressing the emotions of complete submission or self-surrender to God through singing. Music (including Sankeertan, i.e. singing devotional songs) has been shown to relieve various mental ailments like depression, anxiety, etc.[41-44]

Thus, the lifestyle modification techniques like Jap, Dhyan, Pranayam, Yog, Music and Swadhyaya, that are advised to antenatal women during Garbha Sanskar, must be practiced regularly for attaining healthy body and mind, both for the self and the fetus.

4. RESOLVES OF THE EXPECTING MOTHER AT THE TIME OF GARBHA SANSKAR

In order to make the baby in the womb physically, mentally and emotionally healthy, it is essential to pay attention to certain things. Therefore, during Garbha Sanskar, following resolves should be taken by the expecting mother.[1]

1. I resolve to fully take care of my health; I would save myself from physical and mental laziness.
2. After getting up in the morning, I would drink 3-4 glasses of normal or lukewarm water.
3. Would perform physical and breathing exercises regularly.
4. Would meditate on the Sun or my favorite deity, chant hymns, worship and pray regularly.
5. Would study religious books like Ramayana, Gita, Bible, Quran Sharif, or Guru Granth Saheb, etc.
6. Would consume pure, honestly-earned and nutritious food and drinks.
7. Would perform Agnihotra or Balivaiswa Yagya with five pieces of first bread mixed with raw sugar and ghee; would take food as Prasad.
8. Would sing/listen sweet, soothing music, hymns, couplets, shabad kirtan, etc.
9. Would discuss/reflect on noble things – virtues, people, thoughts; would remain happy and content; would remember better days of life.
10. Would keep home clean, beautiful, natural, healthy and positive.
11. Would keep pure feelings towards others; avoid jealousy, hatred, anger, stubbornness, retaliation, negative thoughts, etc.
12. Would strive to augment goodwill, love and affection with others; would help create an atmosphere of service, cooperation and help in the home.
13. Without wasting time and energy in complaining, would patiently try to provide good impressions to the child.
14. Would constantly establish communication of positive thoughts with the baby in the womb; would prefer reading good books and keeping the company of good people.
15. Would read literature pertaining to positive thoughts and life histories of great personalities; would avoid watching horror movies or serials.

5. RESOLVES OF THE FATHER AND OTHER FAMILY MEMBERS DURING GARBHA SANSKAR

It is an earnest duty of the 'would-be' father and other family members to take due care of the 'would- be' mother's well-being, and create a pleasant, peaceful, healthy, and spiritual atmosphere for her. In this regard, the following resolves must be taken by them.[1]

1. Considering the baby in the womb as the representative of God, coming through would-be mother, we will create a happy, healthy and spiritual atmosphere to welcome the child.
2. Womb is adorable; therefore, avoiding any enmity in behavior, we would create a serene ambience at home.
3. Would strive to avoid impressions of lack of things, intoxication, and evil culture; would establish an atmosphere suitable for swadhyay and satsang.
4. Would avoid an atmosphere of anger, tension, shouting, mutual abusing, strife, and so on.
5. Would suitably arrange appropriate food and drinks; would behave nicely and provide conveniences and resources for would-be mother.
6. Would fulfill appropriate desires of the pregnant woman regarding food, drinks and other things.

6. CONCLUSION

Upbringing of children starts before their birth – right in the womb. Scientific studies have shown that the baby enjoys, tastes, hears, remembers, learns, understands, feels, and also expresses joy, pain, tension, etc. Therefore, The ancient sages devised the Garbha Sanskar, which is the formal welcome ceremony of the baby, done along with the invocation of the family deity. V arious lifestyle modification techniques like Jap, Dhyan, Pranayam, Yog, Music and Swadhyay that are advised to antenatal women during Garbha Sanskar, can be beneficial for physical and mental well-being of the antenatal women, as well as the fetus.

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Preventing STI

Dr. Bhaskar Pal **Dr. Sebanti Goswami**

The major points to be taken into consideration for strengthening our armamentarium in preventing STI would be:

- **Knowing and limiting the number of partners**
- **Use of male condom correctly and consistently**
- **Increase availability and acceptability of female condom**
- **Vaccination**
- **Pre exposure prophylaxis in HIV**
- **Counselling and behavioural modification of intravenous drug users**

INTRODUCTION

Sexually transmitted infections (STIs) are infections that are spread predominantly by sexual contact. STIs have plagued humans for decades and can result in chronic disease, pregnancy complications, infertility, and even death. Recent technological advances have led to a better understanding of the causative agents for these infections as well as aspects of their pathogenesis that might represent novel therapeutic targets.

With the discovery of antibiotics, the development of vaccines and effective disease control programs, and the availability of condoms, why are sexually transmitted infections (STIs) still thriving amongst the human race? Certainly sex is necessary for survival of species and is a basic drive, but why should STIs still be present as a possible result of the activity? This is because of the unsolved puzzles in the network of STIs. Many STIs, often have no signs or symptoms. The infected person usually is not aware of the fact that he or she has been infected and can unknowingly pass the infection to others. Therefore the role of preventive strategies supersedes that of the therapeutic modalities available in the spectrum of STI. A range of preventive interventions is needed to reduce the risks of acquiring STI, including HIV infection, among sexually active people, and a flexible approach targeted to specific populations should integrate combinations of biomedical, behavioral, and structural interventions. [1]

THE LANDSCAPE OF INTERVENTIONS TO PREVENT TRANSMISSION OF SEXUALLY TRANSMITTED INFECTIONS (STIs)

The landscape of interventions to prevent transmission of sexually transmitted infections (STIs), including human immunodeficiency virus (HIV) infection, has changed considerably since the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (STD) Treatment Guidelines were last updated in 2006[2]. Major interval developments include -

(1) Licensure and uptake of immunization against genital Human Papilloma Virus (HPV)

(2) Validation of male circumcision as a potent prevention tool against acquisition of HIV and some STIs

(3) Failure of a promising HIV vaccine candidate to afford protection against HIV acquisition

(4) Encouragement about the use of antiretroviral agents as both early treatment for HIV-positive persons and preexposure prophylaxis for HIV-negative persons to reduce the risk of HIV and herpes simplex virus (HSV) acquisition

(5) Enhanced emphasis on expedited partner management and rescreening for persons infected with Chlamydia trachomatis or Neisseria gonorrhoeae

(6) Recognition that behavioral interventions will be needed to address a new trend of sexually transmitted hepatitis C among men who have sex with men (MSM)

(7) The availability of a modified female condom.

THE MAJOR POINTS TO BE TAKEN INTO CONSIDERATION FOR STRENGTHENING OUR ARMAMENTARIUM IN PREVENTING STI

Would be -

- Knowing and limiting the number of partners
- Use of male condom correctly and consistently
- Increase availability and acceptability of female condom
- Vaccination
- Pre exposure prophylaxis in HIV
- Counselling and behavioural modification of intravenous drug users

Knowing and limiting the number of partners - Knowing the sexual partners and limiting their number is a primary step towards prevention. The partner's sexual history is a very important component. Multiple sexual partners place an individual at high risk of acquiring infection.

Avoiding risky sex practices—Sexual acts that tear or break the skin carry a higher risk of STIs. Even small cuts that do not bleed let germs pass back and forth. Anal sex poses a high risk because tissues in the rectum tear easily. Body fluids also can carry STIs. Having any unprotected sexual contact with an infected person poses a high risk of getting an STI.

Male Condoms - The 2006 STD Treatment Guidelines noted that, when used consistently and correctly, male latex condoms are effective in preventing sexual transmission of HIV and other STDs, including chlamydia, gonorrhea, syphilis, genital HPV, and trichomoniasis. By limiting lower genital tract infections, male condoms might also reduce the risk of pelvic inflammatory disease in women[3]. In heterosexual serodiscordant relationships in which condoms were consistently used, HIV-negative partners were 80% less likely to become HIV infected than persons in similar relationships in which condoms were not used[4].Condom use might also reduce the risk for transmission of HSV-2, although data for this effect are more limited [5,6]. Finally, condom use reduces the risk of HPV infection[7,8] and HPV-associated diseases (eg, genital warts and cervical cancer) [9]. Use of condoms has been associated with regression of cervical intraepithelial neoplasia[10] and clearance of HPV infection in women, and with regression of HPV-associated penile lesions in men[11].

Since 2006, available data on male condom efficacy have emerged in several areas:

(1) Protection against infection with genital HPV, HIV, HSV-2, and C. trachomatis.

(2) The methodology of self-reporting on consistent and correct condom use.

(3) Interventions to reduce adolescents' sexual risk behavior

(4) Absence of condom use during first sex on adolescents' subsequent sexual risk behavior.

Estimating true condom efficacy requires that measures of consistent and correct use must be developed, understood, and used. Multiple problems with condoms occurred among 1152 participants who completed a supplemental questionnaire as part of Project RESPECT, a counselling intervention trial conducted at 5 publicly funded STD clinics in the 1990s [12]. Nearly half (41%) of respondents reporting condom use indicated that condoms broke, slipped off, leaked, or were not used throughout intercourse in the previous 3 months. Nearly 9% of acts in which condoms were used resulted in potential STI exposure because of delayed application of condoms, breakage, early removal, slippage, or leakage. Critically, use problems were significantly associated with reporting inconsistent condom use, multiple partners, and other condom problems.

Female Condoms - Laboratory studies indicated that the original version of the female condom (Reality) is an effective mechanical barrier to viruses and semen. If used consistently and correctly, the female condom might substantially reduce the risk for STI. Female condoms are safe to use repeatedly if proper care procedures are followed. Since the last guideline review, relatively few studies have been completed to evaluate the efficacy of female condoms in providing protection from STIs, including HIV infection. The new evidence uses post use markers of semen to measure more precisely the mechanical barrier provided by this method. Other in vitro data assess a new formulation of the female condom.

Two systematic reviews supported the potential effectiveness of female condoms. The first reviewed 137 articles and abstracts on various aspects of the female condom and 5 randomized controlled trials on its effectiveness[13]. The review concluded that although the evidence is limited, "the female condom is effective in increasing protected sex and decreasing STI incidence among

women." A second systematic review concluded that "randomised controlled trials provide evidence that female condoms confer as much protection from STIs as male condoms"[14].

Vaccination - Preexposure vaccination is one of the most effective methods for preventing transmission of 2 main STDs: HPV infection and Hepatitis B The best protection against the hepatitis B virus is a vaccine. The vaccine triggers the body's immune system to fight off the virus when one is exposed to it. It is usually given in three doses over a 6-month period.

Although the primary target of HPV vaccine is prevention of cervical cancer, but incidentally or additionally it prevents infection with certain types of HPV which is a sexually contacted infection. Qaudrivalent, bivalent vaccines are available and now even nonavalent vaccine is on the way. The ideal time to vaccinate a girl is between 11 to 12 years but she can be vaccinated anytime between 9 to 26 years. If she is less than 14 years she is to receive two doses and if she is more than 14 years she receives three doses. The quadrivalent vaccine confers protection against HPV types 6/11 (responsible for 90% of genital warts) and 16/18 (responsible for 70% of cervical cancers). In published clinical trials, the quadrivalent HPV vaccine has demonstrated efficacy for prevention of vaccine HPV type-related cervical, vaginal, and vulvar cancer precursor and dysplastic lesions, and external genital warts [15].

Pre exposure prophylaxis in HIV - Pre-exposure prophylaxis (PrEP) is a course of HIV drugs taken by HIV-negative people to reduce their risk of HIV infection. Since the last review, the field of preexposure prophylaxis (PrEP) has been galvanized by the results from clinical trials of antiretroviral therapy (ART) to reduce transmission and acquisition of HIV. In HIV-infected persons, ART reduces viral load and presumably reduces infectiousness, a concept illustrated by its efficacy in breast-feeding[16]. In HIV-uninfected persons, ART reduces susceptibility to infection, a concept initially supported by animal studies and by a study of safety and acceptability in West African women. The first trials to provide proof of concept for both topical and oral PrEP were the CAPRISA 004 and the iPrEX studies[17,18,19]. CAPRISA 004 randomized 889 women in South Africa to coitally dependent use of 1% tenofovir gel inserted vaginally (up to 12 hours before and within 2 hour after intercourse, not to exceed 2 administrations in 1 day) or to corresponding placebo gel, for a median of 30 months. Women randomized to the tenofovir gel group had a significantly reduced rate of HIV acquisition: 5.6/100 woman-years, compared with 9.1/100 woman-years (incidence rate ratio, 0.61; 95% CI, .40–.94). The risk of HSV-2 acquisition was also reduced in the tenofovir group (by 51%; P = .003).

If used consistently and correctly, PrEP can virtually eliminate the risk of becoming infected with HIV. A number of large, high profile trials undertaken across the world have continued to prove PrEP's effectiveness. PrEP will protect from HIV, but it doesn't give any protection against other sexually transmitted infections (STIs). Using a condom is the best way to prevent other STIs such as gonorrhoea, chlamydia and hepatitis C. Truvada is currently the only drug approved for use as PrEP. Truvada is a single pill that is a combination of two anti-HIV drugs, tenofovir and emtricitabine.

Counselling and behavioural modification of intravenous drug users - Although HIV, Hepatitis B, Hepatitis C are sexually transmitted, they all can be transmitted by intravenous route. The main aim would be counselling and trying to make behavioural changes which would help in stopping i.v. drug usage failing which at least sharing of needles should be stopped. Data continue to support the use of individual client-centered counseling to reduce recipients' risk of acquiring HIV infection or other STDs.

CONCLUSION

A range of preventive interventions is needed to reduce the risks of acquiring STIs , including HIV infection, among sexually active persons. A flexible approach targeted to specific populations should be available. These would ideally involve an array of prevention contexts, including -

(1) Communications and practices among sexual partners.

(2) Transactions between individual clients and their healthcare providers.

(3) Comprehensive population-level strategies for prioritizing prevention research, ensuring accurate outcome assessment, and formulating health policy.

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Obesity – A Serious Health Issue for Midlife Women

Dr. Anshu Jindal

- **As women age, their adiposity shifts from the being pear shape (gynoid pattern), which means more weight on the hips, thighs and lower abdomen, to the central obesity or android pattern i.e. apple shape. This increase in central obesity which translates into excess visceral fat leads to various metabolic derangements such as hyperinsulinemia, impaired glucose tolerance, diabetes mellitus, increased androgens and decreased levels of sex hormone binding globulin leading to increased risk of cardiovascular disease & non insulin dependent diabetes in the obese women.**
- **The obesity guidelines from the American College of Cardiology recommends a daily caloric deficit of 500-750 Kcal which translates to a calorie intake of 1200-1500 Kcal/day for most women and is expected to result in an average weight loss of 0.5kg – 0.75kg/week.**
- **Increased physical activity alone, in the absence of caloric restriction, is unlikely to lead to substantial weight loss initially. Conversely, dietary restriction alone is unlikely to provide sustained results in the absence of a regular exercise program or increase in Physical Activity. Sustained caloric deprivation leads to a decrease in the basal metabolic rate and energy expenditure, thereby negating the effect of reduced caloric intake. Resistance exercises are particularly beneficial because they improve lean body mass, thereby increasing the basal metabolic rate and energy expenditure.**

INTRODUCTION

Obesity has become a serious health issue all over the world. The World Health Organization (WHO) declared Global Obesity as an epidemic in 2014. According to the National Family Health Survey (NFHS 2015-2016), there are over 30 million obese people in India. Out of which over 20.8 million are women & 9.2 million are men. Women have surpassed men in obesity in India posing a serious health hazard especially in their midlife.

Weight gain is common among aging women especially during menopausal transition. This is because of increased central body fat particularly visceral fat. On an average, a women gains 0.5kg per year during midlife (fifth and sixth decade of life). This weight gain has serious metabolic consequences such as increased risk of cardiovascular disease which is a leading cause of death in post menopausal women.[1]

Obesity also predisposes to increased risk of diabetes, musculo skeletal disorders, sleep apnoea and gall bladder disease. It also impacts the women's menstrual cycle, reproduction and menopause itself. Obesity is a risk factor for cancers such as endometrial and breast cancer and it also increases the risk of depression, partly due to poor body image[2.]

Apart from aging, midlife women are exposed to several unique and potentially interrelated influences that promote weight gain such as estrogen deprivation, mood disorders and sleep disturbances. Hence this factor needs to be addressed along with lifestyle recommendations for optimal weight management in midlife women.

DEFINITION OF OBESITY :

Obesity is defined as an excess of body weight (20% more than the ideal weight). It is different from being overweight which is weight in excess of some standard or ideal weight. (15-20% more than the ideal weight).

Obesity is essentially an increase in fat deposition. Obesity is measured as a function of an individual's weight and height or the Body mass index. BMI = Kilograms/meter2

Overweight BMI = 25-29.9

Obesity BMI = 30 or higher

Table 1 shows the WHO definition of normal overweight and obese BMI

TABLE 1 BMI CLASSIFICATION

Category	BMI (kg/m2)
Underweight	<18.5
Normal	18.5–25.0
Overweight	25.0–30.0
Obese Class 1 (moderately obese)	30.0–35.0
Obese Class 2 (severely obese)	35.0–40.0
Obese Class 3 (very severely obese)	>40.0

BMI: body mass index

Obesity can also measured by determining the upper body adiposity by means of various indices

	Optimal cut off
• Waist circumference (WC)	80cm
• Waist to hip ratio (WHR)	0.87
• Waist height ratio (WHtR)	0.50

According to well established cutoff value BMI was found to be a more sensitive indicator of hypertension in both men and women while WC and WHR, WHtR were found to be better indicators of diabetes & dyslipidemia.

For most people affected by obesity, the cause of their condition are complex involving age, ethnicity, environmental factors, behavioural factors, childhood obesity rather than just genetics.

It is well documented that women have a greater prevalence of obesity compared with men. According to the National Family Health Survey 2015-2016, out of the 30 million obese population in India, 20.8 million are women compared to 9.2 million men. This could be due to the fact that women have a lower basal metabolic rate than men, even when adjusted for body composition and level of activity. Secondly, women gain more weight than men as they age.

FROM THE PEAR TO THE APPLE SHAPE

As women age, their adiposity shifts from the being pear shape (gynoid pattern), which means more weight on the hips, thighs and lower abdomen, to the central obesity or android pattern i.e. apple shape.[3] This increase in central obesity which translates into excess visceral fat leads to various metabolic derangements such as hyperinsulinemia, impaired glucose tolerance, diabetes mellitus, increased androgens and decreased levels of sex hormone binding globulin leading to increased risk of cardiovascular disease & non insulin dependent diabetes in the obese women.

Toth et al[4] utilized energy X-ray absorptiometry and computed tomography to show that early post menopausal women have increased intra abdominal fat and total fat mass compared to these who are premenopausal.

Asian Indian women tend to have more visceral adipose tissues despite having a lean BMI as compared to their Caucasian counterparts. Thus putting them more to the risk of developing diabetes and cardiovascular disease as compared to their western counterparts.

MEDICAL COMPLICATIONS OF OBESITY

Obese postmenopausal women have a higher overall mortality risk, with as much as a 4-fold increase in cardiovascular deaths in women with a BMI greater than 29 kg/m2[5]. Obesity, particularly in the presence of increased visceral fat, raises the risk of several adverse metabolic health consequences, including dysglycemia or frank type 2 diabetes mellitus, dyslipidemia, and hypertension[6]. Obesity also increases the risk of certain cancers including breast and uterine cancers.[7,8]

From a psychosocial standpoint, weight gain at midlife can adversely affect emotional health, self-image, and intimate-partner relationships. Any of these factors alone or in combination can contribute to sexual dysfunction[9].

EFFECT OF OBESITY ON MENOPAUSE

The main cause for the symptoms associated with menopause is the decline in estrogen production. While a raised BMI is associated with early onset of menarche, there is also evidence suggesting that the onset of menopause occurs at a later age in obese women and that the higher the BMI the later the age of natural menopause (ANM). An epidemiological study by Akahoshi et al[10] confirmed that raised BMI is associated with a delayed onset of menopause. It has been suggested that this phenomenon is reflective of increased levels of circulating estrogen, secondary to peripheral aromatisation of androstenedione secreted by the adrenal glands and ovary in obese patients. However, this relationship is complex because of the importance of other environmental factors such as smoking and genetic factors. Thus ANM is lower in South Asian women than their Caucasian counterparts despite having similar BMI.

Adults, both male and female, put on weight steadily as they age, gaining about 0.5 kg annually after midlife[11]. Both longitudinal and cross-sectional studies have failed to identify an impact of menopause itself and note the importance of both lifestyle and ethnicity.

Estrogen deficiency associated with menopause causes reduced bone density. There is evidence to show that obesity may be protective against osteoporosis[12] as a result of the mechanical stress of excess weight on the musculoskeletal system, increased androgen levels, as well as increased estrogen levels associated with increased adiposity. However, more recent data [13] have suggested that obesity, specifically fat mass, may be detrimental to bone health. The Global Longitudinal Study of Osteoporosis in Women suggested that age of menopause was more important than BMI in determining fracture risk.

It is no surprise that obese women have lower health related quality of life than non-obese women, particularly in regard to physical functioning and energy. Metabolic syndrome, which is known to be associated with obesity, has also been identified to be associated with poorer sexual functioning. Esposito et al[14] studied sexual function among premenopausal women who have metabolic syndrome using the Female Sexual Functioning Index (FSFI). The study showed that women with metabolic syndrome had a significantly lower FSFI score, compared with the control group.

MULTIDISCIPLINARY APPROACH TO MANAGEMENT

Clinicians caring for perimenopausal and postmenopausal women should routinely screen for obesity and offer appropriate weight management counseling to all women with an increased BMI, even when not specifically sought by the patient. An ideal weight management program is a multi component behavioral intervention that includes changes in eating habits, physical activity (PA), and psychological support to enable implementation of these behavioral changes. Weight loss interventions are hence best executed with a team-based approach involving medical practitioners, behavioral psychologists, dietitians, exercise specialists, and lifestyle coaches.

Weight loss medications, bariatric surgery, and endoscopic bariatric therapies may also be discussed in appropriate situations. Physicians should assess for medical obstacles to implementation of lifestyle changes, such as joint pain, unrecognized obstructive sleep apnea, or medications that affect weight.

Weight loss can be achieved by various diets such as the low carbohydrate or low fat diets. The Mediterranean diet consisting of primarily plant based foods such as fruits and vegetables, whole grains, legumes and nuts, replacing butter with olive oil, using herbs and spices instead of salt and limiting red meat to no more than few times a month is very popular diet for weight loss.

Weight loss - Weight loss is perhaps the most important management option as its benefits are manifold. A reduction in adiposity has been shown to be effective in reducing the severity of symptoms of PCOS. Weight loss can also lead to a reduction in menopausal symptoms as indicated in studies on hot flushes[15]. A weight reducing diet and increased exercise also have a beneficial effect on health-related quality of life. A study by Rippe et al[16] found that weight loss improved quality of life and psychological wellbeing in premenopausal and perimenopausal women.

Weight loss is also associated with improved metabolic profile and insulin sensitivity. Ryan et al[17] studied postmenopausal women who were underweight and obese, and have shown that insulin sensitivity and inflammatory markers (CRP) improved with weight loss. There are various diets available that can be implemented to aid weight loss but the bottom line is that the weight loss will be sustained only if there is sufficient caloric deficit. Otherwise, one tends to regain the lost weight.

The obesity guidelines from the American College of Cardiology recommends a daily caloric deficit of 500-750 Kcal which translates to a calorie intake of 1200-1500 Kcal/day for most women and is expected to result in an average weight loss of 0.5kg – 0.75kg/week.

Physical activity (PA) - Women who enter midlife with a greater level of PA and maintain it, or those who increase their PA after menopause, have a lower tendency to gain weight than do their less-active peers. [18] The obesity guidelines from the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Obesity Society[19] recommend 150 to 175 minutes of PA (brisk walking or similar aerobic exercise) per week for weight loss. However, the patients should be counselled that increased physical activity alone, in the absence of caloric restriction, is unlikely to lead to substantial weight loss initially. Conversely, dietary restriction alone is unlikely to provide sustained results in the absence of a regular exercise program or increase in PA. Sustained caloric deprivation leads to a decrease in the basal metabolic rate and energy expenditure, thereby negating the effect of reduced caloric intake. Resistance exercises are particularly beneficial because they improve lean body mass, thereby increasing the basal metabolic rate and energy expenditure. [20]

Moreover, regular physical activity in general helps ameliorate weight-related problems even in the absence of actual weight loss. For example, regular exercise improves insulin sensitivity and glycemic control, lowers cholesterol levels and blood pressure, and decreases cardiovascular and all-cause death.

Behavioral Support - Weight management is about changing behaviors, with the goal of a lifelong commitment to healthy lifestyle habits. Therefore, psychological support geared toward identifying barriers to change, monitoring behaviors, problem solving, strategizing, and reinforcement is an important component of weight loss programs. Such counseling can be pursued in individual or group sessions on the basis of the patient's needs, preferences, and available resources.

It is also important to manage psychological issues including depression and anxiety, which can compromise a patient's adherence to a healthy lifestyle. Along these same lines, women should be screened for sleep disturbances and stress, and appropriate treatment strategies should be offered to manage these issues.

Hormone Replacement Therapy (HRT) - Most, but not all, randomised trials show a decrease in central adiposity with hormone replacement therapy (HRT). A subset of women from the Women's Health Initiative indicated that HRT maintained lean body mass and also, resulted in a small shift away from android obesity. [21]

Menopausal HRT does not lead to weight gain or increased visceral adiposity and may even lead to a reduction in both. A meta-analysis by Salpeter et al [22] looked at the effects of HRT on the metabolic profile of postmenopausal women. This study showed a statistically significant improvement in insulin resistance, lipid profile and procoagulation factors (fibrinogen and PAI-1 antigen) in postmenopausal women using HRT. This meta-analysis also compared the effects of oral versus transdermal HRT agents and found that oral agents, in general, have a better effect on metabolic profile among these women. Oral HRT also leads to a reduction in the onset of diabetes and improved glucose control as exemplified by HbA1c levels.

Weight Loss Medications - Weight loss medications can be offered to women with a BMI greater than 30 kg/m2 or with a BMI greater than 27 kg/m2 in the presence of at least one weight-related comorbid condition.[23-24] Their use should be considered as an adjunct to lifestyle changes and not intended to replace them.

Some herbal medications for weight loss are available. But the effect of these medications has not been validated by studies & hence cannot recommend for weight loss.

Several US Food and Drug Administration approved medications are available (Table 1.2) to choose from, with some recent additions.

TABLE 1.2 US FOOD AND DRUG ADMINISTRATION-APPROVED MEDICATIONS FOR WEIGHT LOSS

Drug	Mechanism of action	Common adverse effects	Dosage
Orlistat	Lipase inhibitor	Changes in bowel habits, fatty stools, intestinal gas with discharge	Orally 60mg over weight 120mg obese

Liraglutide	GLP-1 receptor agonist; delayed gastric emptying and decreased appetite, resulting in reduced calorie intake	Nausea, vomiting, constipation, diarrhea, fatigue, headache	Initial: 0.6 mg SC once daily; increase weekly in increments of 0.6 mg/d until maintenance dosage of 3 mg once daily is reached
Lorcaserin	Selective serotonin 2C receptor agonist; promotes satiety and decreases food intake by activating hypothalamic neurons	Nausea, fatigue, headache, dizziness	20 mg/d orally, given as single dose or twice- daily dosing
Naltrexone/ bupropion SR	Regulates food intake by unclear mechanisms	Nausea, vomiting, constipation, diarrhea, headache, insomnia, dizziness, anxiety	Naltrexone 8 mg/ bupropion 90 mg (1 tablet) orally once daily, gradually increased to maintenance dose of 2 tablets twice daily
Phentermine	Appetite suppressant	Insomnia, central nervous system stimulation	15-37.5 mg/d given as single dose or twice-daily dosing
Phentermine/ topiramate ER	Phentermine: appetite suppressant Topiramate: suppresses appetite and increases satiety	Nausea, constipation, altered taste, xerostomia, paresthesia, dizziness, insomnia	Low-dose: 7.5 mg/46 mg once daily (starting dose: 3.75 mg/23 mg once daily) High-dose: 15 mg/92 mg once daily (starting dose: 11.25 mg/69 mg once daily

However, it is important to recognize the challenges of pharmacotherapy, including modest efficacy (about 5%-10% weight loss), expense, potential adverse effects, and possibility of weight plateau and regain despite continued use. Therefore, medication use should be considered to maximize weight loss for women who are motivated to pursue lifestyle changes but may be unable to achieve the amount of weight loss desired despite their best attempts at lifestyle interventions.

Bariatric Surgery - Bariatric surgery is indicated for patients with a BMI greater than 40 kg/m2 or with a BMI greater than 35 kg/m2 in the presence of weight-related complications. Candidacy for bariatric surgery is complex and is assessed by a team of experts including a medical practitioner (usually an endocrinologist), psychologist, and bariatric surgeon. Endoscopic bariatric therapies are an emerging line of treatment for obesity. These treatments include intragastric balloons, endoscopic gastroplasty, and the recently approved percutaneous endoscopic gastrostomy tube for aspiration of gastric contents (AspireAssist; Aspire Bariatrics).[25] These techniques are less invasive than bariatric surgery and offer greater efficacy than pharmacotherapy (about 20%-25% weight loss).

CONCLUSION

Obesity is undoubtedly a major healthcare challenge with its associated comorbidities and impact on female reproductive health. Weight gain and increased visceral fat are common problems in midlife women. These changes considerably affect the physical, emotional & psychosocial health of women. We recommend that medical practitioners should actively screen for obesity in midlife women and offer education, treatment and support. This includes management issues unique to midlife women including vasomotor symptoms, mood disorders and sleep disturbances that interfere with adoption of healthy lifestyle measures.

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Vaccination in Women

Dr. Rachna Dubey

- **Antibody testing is not necessary before vaccination.**
  - **Single dose rubella vaccine or MMR vaccine should be given**
  - **Pregnancy should be avoided within three months of vaccination.**

  However if pregnancy occurs within 4 weeks of vaccination there is a small chance of the fetus being born with CRS and usually close monitoring with USG is advised instead of MTP.
- **Since live vaccine poses a theoretical risk to a developing fetus, all live vaccines should be avoided during pregnancy.**
- **As rabies is nearly 100% fatal , there is no contraindication to post exposure vaccination . Pregnancy, lactation, infancy, old age & concurrent illness are no contraindications for rabies PEP in the event of an exposure. PEP against rabies takes preference over any other consideration as it is a lifesaving treatment. Moreover, rabies vaccine does not have any adverse effect on pregnant woman, course of pregnancy, fetus or lactating mother. Hence, complete PEP should be given depending on the category of the exposure.**

Vaccination before, during and after pregnancy helps protect women from serious infections . It can also help in improving the women's health in general. It is an important preventable measure which should be adopted rationally.

According to CDC (Centre for Disease Control & Prevention), women should receive annual assessment of infection, risks due to health, age, occupation, travel, lifestyle, and vaccinations. This article is for the age group of 11years onwards and takes into account the IAP recommendations of immunization for age group upto 12 years.[1]

These are not mandatory guidelines but serve as a base upon which one can build good practice with adequate leeway for specific situations, patients and providers.

1. ADOLESCENT AGE GROUP

Vaccination is generally considered the purview of the pediatricians in the childhood and physicians in the adult context .There are many vaccinations such as the rubella which need to be extended to the adolescent age group and hepatitis and HPV need to be considered in this age group.

Human papillomavirus (HPV) - Infection is associated with anogenital cancer (including cervical, vaginal, vulvar, penile, and anal), oropharyngeal cancer, and genital warts. The HPV vaccination significantly reduces the incidence of anogenital cancer and genital warts.

Cervical cancer is caused by HPV by strains which are 'oncogenic' or 'high risk types' .These are 15 in number. Globally, HPV 16,18,31,33 and 45 are the common oncogenic HPV types, of which 16 and 18 account for 70% of cervical cancer and HPV 31, 33 and 45 account for 12%. Phylogenetically, HPV 16 is closely related to 31 and HPV18 to 45. Together they are responsible for 82% of squamous cell carcinoma and 93.2% of adenocarcinoma of cervix.[2]

Types available in india -

Cervarix -

Bivalent vaccine protection against HPV16 & 18 with extra protection against HPV31 & 45.

Gardasil -

Quadrivalent vaccine protection against HPV16 & 18, 6 & 11 so protect against genital warts, vulval & vaginal cancers due to HPV.

Administration - It is given as IM injections in deltoid region. It can be given with other vaccines but at different sites.

- The Centers for Disease Control and Prevention (CDC) and the ACOG recommend routine HPV vaccination for females and males aged 9–26 years.
- The target age for HPV vaccination is 11–12 years for girls and boys, but the HPV vaccine can be given to both genders through 26 years of age.
- For girls and boys who receive their first dose of HPV vaccine before 15 years of age, only two doses are needed. The timing of the two doses is 0 (baseline) and 6–12 months. If the interval between the two doses is less than 5 months, a third dose is recommended.
- If females or males receive their first dose after 15 years, three doses are needed and given at 0 (baseline), 1–2 months after the first dose, and 6 months after the first dose.
- Testing for HPV DNA is not recommended before vaccination. Vaccination is recommended even if the patient is tested for HPV DNA and the results are positive.
- Even if a patient previously has had an abnormal Pap test or history of genital warts, vaccination is still recommended.[3]

Rubella Vaccine - If an unvaccinated pregnant woman gets infected with rubella virus she can have a miscarriage and the incidence of Congenital Rubella Syndrome (CRS) through vertical transmission is quite high. Serious birth defects are more common if a woman is infected early in her

pregnancy, especially in the first trimester. In fact, women infected with rubella early in pregnancy have a 1 in 5 chance of having problems with the pregnancy. Congenital birth defects includes heart problems, loss of hearing and eyesight, intellectual disability and liver / spleen damage.

Antibody testing is not necessary before vaccination.

- ❖ Single dose rubella vaccine or MMR vaccine should be given
- ❖ Pregnancy should be avoided within three months of vaccination.

However if pregnancy occurs within 4 weeks of vaccination there is a small chance of the fetus being born with CRS and usually close monitoring with USG is advised instead of MTP. [5]

Vaccination schedule - Children get 2 doses of MMR vaccine:

- The first dose at 12 through 15 months of age and
- The second dose at 4 through 6 years of age, before entering school.
- If the adolescent misses MMR then even single dose rubella vaccination can be given later

To decrease the disease burden Health Ministry has launched single vaccine shot for dual protection against measles and rubella (MR) vaccine as part of Universal Immunization Programme to be given to all children in the age group of 9 months to 15 years. Government of India has launched rubella campaign in 2017 for even those children, who have already been vaccinated for measles & rubella under immunization program, to take additional shot of MR vaccine during the campaign.[5]

Varicella - The varicella (chickenpox) vaccine is recommended for children in a two dose series with the first dose occurring at 12-15 months and second dose at 4-6 years. Adults & adolescents aged 7 years & older who do not have evidence of varicella immunity should receive two doses in order to achieve a maximal immune response.

For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

This vaccine is a live-attenuated viral vaccine. It should not be administered to pregnant women or women who desire to become pregnant within 1 month.

Women of childbearing age who are not pregnant, and who are not immune to varicella (chickenpox) should be vaccinated against varicella.

Do not get vaccinated for varicella if you have had an allergic reaction to the varicella vaccine, Neomycin, or gelatin.

In addition, Hep B, Hep A, Hemophillus influenza B (Hib), tetanus, diphtheria, varicella VAR[(2)] catch up vaccination is recommended from 11 years onwards in those who have missed in childhood. Typhoid and cholera vaccination can be given seasonally. Previous adverse effects of immunization especially allergies should be noted.[6]

Hepatitis A Vaccination - Children should receive a 2-dose Hepatitis A vaccine series starting at 12

through 23 months; separate the 2 doses by 6 to 18 months. Children who have received 1 dose of Hepatitis A vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.

For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of Hepatitis A vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired. [7]

1E. Hepatitis B Vaccination - The Hepatitis B vaccine is administered in a series of 3 shots. The Advisory Committee on Immunization Practices and ACOG recommend Hepatitis B vaccination for all infants at birth. Infants should receive a birth dose of Hepatitis B vaccine before leaving the hospital. The second dose should be administered at 1-2 months, and the third dose at 6-18 months.

The hepatitis B vaccine is also recommended for all individuals through 18 years of age and all adults who want the vaccine or who are at risk for hepatitis B virus (HBV). [8]

TABLE 1 -Indian Academy of Pediatrics schedule for adolescents and pre-pregnancy[8]

Vaccine	Recommended age of vaccination
Tdap/Td	Tdap is always preferred over Td at the age of 10 y followed by repeat Td every 10 y only when an adolescent immunized earlier with 3 doses of DPT below 1 y and booster at the age of 11/2 years and at 5 y
MMR	1 dose at 12–13 y of age, if not received earlier
Rubella	1 dose to girls at 12–13 y of age, if MMR or rubella is not given earlier
Hepatitis B	3 doses at 0, 1 and 6 months, if not received earlier
Hepatitis A	2 doses at 0 and 6 months,
Typhoid	Single dose intramuscular Vi polysaccharide or 3 doses of oral typhoid vaccine on alternate day empty stomach. Booster is given every 3 yr.
Varicella	1 dose up to 2–12 y and 2 doses after 12 y of age
HPV	Only for girls at the age of 10–12 y with 3 doses schedule either 0, 1, 2 or 0, 1, 6 months depending upon the vaccine used

2. VACCINATION IN PREGNANCY

Immunization of a pregnant woman enables a number of important health benefits for both mother and baby. Vaccine-preventable diseases have been shown to cause significant morbidity and mortality among maternal, neonatal, and young infant. Some of these infections can be serious enough to waste pregnancy or affect the infant post delivery.

Vaccination of the pregnant women has been shown to strengthen her immune systems to fight serious infectious diseases. It helps in protecting the mother from infections and this immunity passes to her infant during pregnancy, keeping the child safe during the first few months of life. The fear that fetus can be at risk after vaccination of the mother during pregnancy has no scientific bases. There have been no study to show if there is risk for fetus after maternal vaccination with inactivated

vaccines or bacterial vaccines or toxoids. Since live vaccine poses a theoretical risk to a developing fetus, all live vaccines should be avoided during pregnancy.[10]

Influenza vaccination - Flu is more likely to cause severe illness in pregnant women than in healthy women who are not pregnant. Changes in the immune system, heart, and lungs during pregnancy make pregnant women more prone to severe illness resulting in hospitalization. In addition, studies have shown that vaccinating a pregnant woman also can protect a baby for several months after birth from flu.

CDC recommends that pregnant women get a flu shot(inactivated influenza vaccine) during any trimester of their pregnancy to protect themselves and their newborn babies from flu. There is a lot of evidence that flu vaccines can be given safely during pregnancy .The nasal spray (live vaccine) is not recommended for use in pregnant women.[11]

Limitations of the Influenza Vaccination - Influenza vaccination is most effective when circulating viruses are well - matched with vaccine viruses. Even with appropriate matching, efficacy of vaccine may be about 70% to 80%. In case the locally circulating virus is different from vaccine virus recommended by WHO, it may be partially effective or not be effective at all. Hence, vaccine should not give a false sense of security. Considering the risk perspective, the modalities of infection ,prevention and control practices like personal hygiene, frequent washing of hands, respiratory etiquettes and airborne precautions (in hospital settings or domiciliary care settings) should be strictly adhered to. The effectivity is for one year.

The available vaccine takes about 2-3 weeks for development of immunity. Hence in an environment with likelihood of exposure to Influenza virus, vaccine should be administered at least one month prior to the commencement of the season.

Tetnus Toxoid / T-dap - In contrast to developed nations where tetanus is rare ,it remains endemic in the developing world. The incidence often increases following natural disasters such as earthquakes and tsunamis. In 2012 there were 2404 cases of tetanus reported to the WHO from India[4].

Two doses of tetanus toxoid injection at least 4weeks apart are given to all pregnant mothers commencing from second trimester. Some suggests that the second dose should be given 4 weeks prior to delivery .If the subsequent pregnancy occurs within 5 years only one booster is given.

Tetanus, diphtheria, acellular pertussis (T-dap) vaccination can be considered instead of the second dose of tetanus toxoid to offer protection against diphtheria & pertussis in addition to tetanus. The regular pertussis vaccine is contraindicated in pregnancy. (Tdvac) tetanus &diptheria vaccination can be an alternative if T-dap is not available. IAP suggests immunization of pregnant women with single dose of Tdap during the third trimester (preferred 27-36 weeks gestation) regardless of the interval between previous Td or Tdap vaccination. Tdap has to be repeated in every pregnancy irrespective of the status of previous immunization (with Tdap).[12]

Rabies - As rabies is nearly 100% fatal , there is no contraindication to post exposure vaccination . Pregnancy, lactation, infancy, old age & concurrent illness are no contraindications for rabies PEP

in the event of an exposure. PEP against rabies takes preference over any other consideration as it is a lifesaving treatment. Moreover, rabies vaccine does not have any adverse effect on pregnant woman, course of pregnancy, fetus or lactating mother. Hence, complete PEP should be given depending on the category of the exposure.

Post-exposure prophylaxis is a three-pronged approach. All three carry equal importance and should be done simultaneously as per the category of exposure

- Management of animal bite wound(s)
- Passive immunization with Rabies Immunoglobulin (RIG)
- Active immunization with Anti-Rabies Vaccines (ARV)

Rabies immunoglobulin for passive immunization is administered only once, preferably within 24 hours after the exposure (on day 0 along with the first dose of anti-rabies vaccine).

Rabies Immunoglobulin should never be administered in the same syringe or at the same anatomical site as vaccine.

Active immunization (Essen regimen) Post-exposure prophylaxis consists of intramuscular administration of five injections, one dose each given on days 0, 3, 7, 14 and 28. Day 0 indicates date of administration of first dose of vaccine.[13]

Recommendations for vaccinating a pregnant woman[14]

Routine	Hepatitis A	Base decision on risk vs. benefit.
	Hepatitis B	Recommended in some circumstances.
	Human Papillomavirus (HPV)	Not recommended.
	Influenza (Inactivated)	Recommended.
	Influenza (LAIV)	**Contraindicated.**
	MMR	**Contraindicated.**
	Meningococcal (ACWY)	May be used if otherwise indicated.
	Meningococcal (B)	Base decision on risk vs. benefit.
	PCV13	No recommendation.
	PPSV23	Inadequate data for specific recommendation.
	Polio	May be used if needed.
	Td	Should be used if otherwise indicated (Tdap preferred).
	Tdap	Recommended.
	Varicella	**Contraindicated.**
	Zoster	**Contraindicated.**

Travel & Other	Anthrax	Low risk of exposure — **not recommended.** High risk of exposure — may be used.
	BCG	**Contraindicated.**
	Japanese Encephalitis	Inadequate data for specific recommendation.
	Rabies	May be used if otherwise indicated.
	Typhoid	Inadequate data. Give Vi polysaccharide if needed.
	Smallpox	**Pre-exposure — contraindicated.** Post-exposure — recommended.
	Yellow Fever	May be used if benefit outweighs risk.

3. POST-NATAL VACCINATION

Postnatal period is a good window of opportunity which should not be missed to protect the mother and her future progeny.Influenza vaccination of the pregnant and parturient woman reduces the risk of respiratory illness including laboratory-confirmed influenza in their infants up to 6 months of age as a result of both tranplacental maternal antibodies, and increased anti-influenza antibodies in breast milk. Vaccines such as rubella can be safely administered in concurrence with postnatal contraception.

Cocooning: Adolescents and adults (parents, siblings, grandparents, child-care providers, and health-care personnel) who have or anticipate having close contact with an infant aged <12 months should receive a single dose of Tdap to protect against pertussis if they have not previously received Tdap.

FOGSI recommends postnatal rubella, hepatitis B, varicella, Influenza, tetanus and HPV vaccinations to all non immunized postnatal mothers.[15]

4. VACCINATION IN ADULT WOMEN

Almost 1 out of every 3 persons in the United States will develop shingles in their lifetime. Your risk of shingles increases as you grow older. Additionally, over 60 percent of seasonal flu-related hospitalizations occur in people 65 years and older.

As we get older, our immune systems tend to weaken over time, putting us at higher risk for certain diseases. This is why, in addition to seasonal flu (influenza) vaccine and Td or Tdap vaccine (tetanus, diphtheria, and pertussis), you should also get:

Shingles vaccine, which protects against shingles and the complications from the disease (recommended for healthy adults 50 years and older).

Pneumococcal vaccines, which protect against pneumococcal disease, including infections in the lungs and bloodstream (recommended for all adults over 65 years old, and for adults younger than 65 years who have certain chronic health conditions)

Recommended Adult Immunization Schedule-

Note: These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses.

VACCINE AGE GROUP	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	⩾65 years
Influenza	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)	Substitute Tdap for Td once, then Td booster every 10 yrs					
Varicella	2 doses					
Human papillomavirus (HPV) Female	3 doses					
Zoster[6]					1 dose	
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication					
Pneumococcal 13-valent conjugate (PCV13)*	1 dose					
Pneumococcal 23-valent polysaccharide (PPSV23)8	1 or 2 doses depending on indication					1 dose
Hepatitis A	2 or 3 doses depending on vaccine					
Hepatitis B	3 doses					
Meningococcal 4-valent conjugate (MenACWY) or polysaccharide (MPSV4)	1 or more doses depending on indication					
Meningococcal B (MenB)	2 or 3 doses depending on vaccine					
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication					

Recommended for all persons who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection; zoster vaccine is recommended regardless of past episode of zoster.

Recommended for persons with a risk factor (medical, occupational, lifestyle, or other indication).

No recommendation

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Maternal Health and NCDs : A new initiative by FIGO

Dr. Hema Divakar

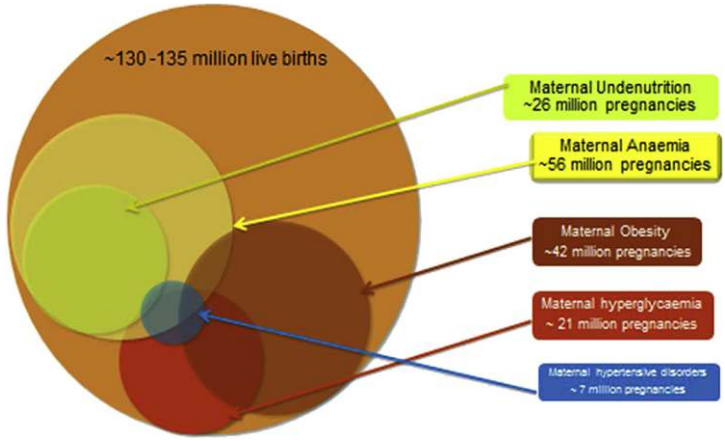
- **Undernutrition, overweight and obesity, hypertension, hyperglycaemia etc., are commonly associated with pregnancy and cause considerable maternal morbidity and mortality, poor pregnancy outcomes as well as fetal programming.**
- **The parents' health, particularly the mother's body composition, nutritional, metabolic and psychological status during pregnancy, determines the fetal environment and impacts the risk of later NCDs. Ensuring a healthy pregnancy and a disease-free early childhood may be the most effective means of attaining best future health and preventing NCDs. The fetal environment represented by the mother's peri-conceptional and gestational health determines whether one starts life with a health 'advantage' or 'handicap', and it is on this 'foundation' that NCD risk factors play out in later life. People starting life with a 'health handicap' may be less able to withstand lifestyle risks and may be vulnerable to developing disease early compared to those starting with a 'health advantage'**
- **Increasing knowledge and understanding in young women and adolescents of the behavioural and environmental risk factors for NCDs and their transmission across generations is empowering them to plan and prepare for pregnancy and parenthood.**

THE BACKGROUND

The global community is beginning to understand the enormity of the health and economic challenge that non-communicable diseases (NCDs) present. By 2030, NCDs are projected to claim 52 million lives annually. Almost 80% of these deaths will occur prematurely in low- or low/middle-income countries.Worldwide obesity has nearly doubled since 1980. In 2008, 35% adults aged >20 years (>1.4 billion) were overweight; of these,11%were obese (200 million men and nearly 300 million women). Over a billion people live with high blood pressure. In 2008, the global prevalence of high blood pressure in adults aged >25 years was around 40%. Over 700 million people have dysglycaemia (diabetes mellitus (DM) and impaired glucose tolerance (IGT)).

NCDS IMPACT MATERNAL HEALTH

Adaptation of the Millennium Development Goals (MDGs) resulted in justifiable attention on maternal and child health (MCH) programs, especially in the developing world. MCH programs focused on factors that directly impacted maternal, neonatal and infant mortality, resulting in improved access to maternity services and survival of 'at-risk' mothers and their offspring in many low and middle-income countries. Unfortunately, this narrow short-term focus failed to address the root causes and the social determinants of health, and the very individuals saved continue to be vulnerable and are at the highest risk of NCDs later in life. Undernutrition, overweight and obesity; hypertension; hyperglycaemia etc., are commonly associated with pregnancy and cause considerable maternal morbidity and mortality, poor pregnancy outcomes as well as fetal programming (Fig. 1).



To improve both the short term MCH outcomes and long-term population health, NCDs must be addressed simultaneously alongside MCH.

Almost 870 million people worldwide suffer from chronic undernourishment; 60% of these are girls or women. In most developing countries, maternal undernutrition is endemic contributing significantly to maternal morbidity, mortality, and poor birth outcomes including low birth weight (LBW), prematurity, still births, neonatal mortality, and subsequent childhood malnutrition. Thirteen million children are born annually with intrauterine growth retardation (IUGR), 112 million are underweight and 178 million children $\leqslant$ 5 years suffer from stunting. Stunting, severe wasting and IUGR-LBW together are responsible for 2.1 million deaths and 91.0 million disability-adjusted life years.

Anemia in pregnancy, defined as hemoglobin concentration (Hb) <110 g/L, affects >56 million pregnant women globally, two-thirds from Asia. Nutritional iron deficiency anemia (IDA) is most common and is associated with increased maternal and perinatal morbidity and mortality, and long-term adverse effects in the newborn. Studies show a significantly higher risk of LBW, preterm and still birth with anemia in the first or second trimester. Women with severe anemia have a higher risk of gestational hypertension and pre-eclampsia.

Vitamin D Deficiency - Studies from around the world show high rates of vitamin D deficiency among women of reproductive age or during pregnancy. Insufficiency is associated with an increased risk of gestational diabetes mellitus (GDM), pre-eclampsia and small for gestational age (SGA) and LBW infants.

High levels of overweight and obesity in the adult population including among women in the reproductive age is an important issue. The high prevalence of maternal obesity drives childhood

obesity and creates at a transgenerational cycle. In 2014, already 41 million children under the age of 5 were overweight or obese and more than half of the world's adult population was overweight (39%) or obese (13%).The number of reproductive-aged women who are overweight now exceeds the number of underweight women. Complications of overweight and obesity during pregnancy include hypertensive disorders, pre–eclampsia, coagulopathies, GDM, respiratory problems and fetal complications such as large-for-gestational-age (LGA) babies, congenital malformations, stillbirth, induction of labor, instrumental delivery, caesarean section (C-section), shoulder dystocia, post-partum hemorrhage, intensive care admission, maternal infection, and prolonged hospital stay. Maternal overweight and obesity is the most important modifiable risk factor for stillbirths in high-income countries, contributing to around 8000 stillbirths (>22 weeks of gestation) annually. In developing countries, it is associated with a two- to threefold increased risk of macrosomia, requiring institutional and assisted delivery, the lack of which results in a significantly increased maternal morbidity and mortality.

Hyperglycaemia - Worldwide, one in six pregnancies may be associated with **hyperglycaemia, 84% of which involve GDM.** In 2013, 16.8% live births (21.4 million) were associated with hyperglycaemia in pregnancy (HIP) and 16% of these were due to overt diabetes in pregnancy. This does not account for pregnancies ending in spontaneous abortions, stillbirths or intrauterine deaths that may have been associated with hyperglycaemia proven or otherwise. **High blood pressure and high blood glucose** are two leading risk factors for death from chronic conditions in women >20 years of age. Maternal mortality and morbidity attributable to diabetes in women may actually be higher than current estimates because most women are not tested for hyperglycemia. HIP significantly increases the risk of maternal and perinatal morbidity and mortality and pregnancy complications such as hypertension and pre-eclampsia, obstructed labor, postpartum hemorrhage, infections, still births, premature delivery, both LGA and SGA babies, congenital anomalies, newborn deaths due to respiratory problems, hypoglycemia and birth injuries. Apart from pregnancy complications and poor outcomes, HIP increases the vulnerability and is the most reliable marker of future type 2 diabetes and cardio metabolic disorders in women. Offsprings of mothers with HIP are at a heightened risk of early onset overweight, obesity, insulin resistance pre diabetes, type 2 diabetes and cardio-metabolic disorders as a consequence of intrauterine developmental programming. This makes female offsprings of mothers with HIP highly vulnerable to hyperglycemia during pregnancy as well as PCOs.

Worldwide, **high blood pressure with or without proteinuria** is a major cause of maternal morbidity and mortality and **hypertensive pregnancy disorders (HPD)** account for 10% and 15% of maternal deaths in low-/middle-income countries, as well as to increased perinatal morbidity and mortality as a consequence of prematurity and poor fetal growth. Although the incidence varies in different parts of the world, overall nearly 10% of normotensive women experience abnormally elevated blood pressure at some point during pregnancy. Preeclampsia/eclampsia have the highest impact on mortality and morbidity, including renal or liver failure, clotting disorders, stroke, preterm delivery, stillbirth or neonatal death and C-section, especially emergency C-section.Women with previous HPD manifest higher glucose, insulin, triglycerides and total

cholesterol levels after pregnancy. Women with HPD are at an increased risk of cardiovascular and metabolic disorders, including a twofold increased risk of hypertension, a threefold increased risk of type 2 diabetes mellitus (T2DM) and increased risk of dyslipidemia. Offspring of mothers with pre-eclampsia have higher blood pressure during childhood and young adulthood.

Thyroid diseases affect up to 4% of all pregnancies with primary hypothyroidism being the most prevalent disease. Thyroid disease during pregnancy is associated with an increase in maternal and fetal risk for a number of adverse effects such as miscarriage, placental abruption, anemia, gestational hypertension/preeclampsia, GDM, cardiac dysfunction, preterm births, low birth weight, fetal anomaly, fetal death, postpartum hemorrhage etc. Hypothyroidism during the first trimester may impair fetal brain development.

Chronic exposure to **ambient air pollution** is now becoming an important risk factor for underlying adverse pregnancy outcomes. The developing fetus is thought to be particularly susceptible to environmental pollutants. Various epidemiological studies have suggested associations between environmental exposures such as air pollution, environmental tobacco smoke, smoke use of firewood and coal for household cooking and heating, pesticides, solvents, metals, radiation, water contaminants (disinfection by-products, arsenic, and nitrates) and chemicals (persistent organic pollutants (POPs), Bisphenol A, phthalates, and perfluorinated compounds and pregnancy outcomes such as miscarriage, stillbirth, fetal growth retardation, preterm birth and congenital anomalies. There is now also mounting evidence that stress can interact with chemical exposures to exacerbate the toxic effect and the physiological response to a greater extent than either insult (stress or chemical) acting alone.

Intimate partner **violence during pregnancy** is a common but often under reported cause for pregnancy complications including miscarriages, preterm births, LBW, SGA and perinatal death. Psychological stress may exacerbate preexisting conditions such as hypertension and gestational diabetes, or may lead to pregnancy complications including preeclampsia or preterm labor. Women with significant psychosocial stressors, including the experience of IPV, are more likely to engage in risky health behaviors such as smoking, alcohol use, and substance use and are less like to seek health care. Similarly, research supports an association between high levels of depressive symptoms and preterm birth or LBW.

Exposure to environmental pollution, IPV and psycho social stress, malnutrition may often occur simultaneously as a consequence of low education, social standing, poverty and gender inequality and the very same factors also limit access to access to information and care. The consequences of these for maternal health and pregnancy outcomes are disastrous. Therein lays the making of future population health.

MATERNAL HEALTH IMPACTS FUTURE BURDEN OF NCDS

Prenatal and early-life development through epigenetic changes influences the risks of NCD in later life, and this might be especially relevant to low-resource countries. The parents' health, particularly the mother's body composition, nutritional, metabolic and psychological status during pregnancy, determines the fetal environment and impacts the risk of later NCDs. Ensuring a healthy pregnancy

and a disease-free early childhood may be the most effective means of attaining best future health and preventing NCDs. The fetal environment represented by the mother's peri-conceptional and gestational health determines whether one starts life with a health 'advantage' or 'handicap', and it is on this 'foundation' that NCD risk factors play out in later life. People starting life with a 'health handicap' may be less able to withstand lifestyle risks and may be vulnerable to developing disease early compared to those starting with a 'health advantage'. Similarly, lifestyle interventions in adult life to prevent diseases may have variable effects based on early life programming. The impact of living conditions - the social determinants of health - is high on the global development agenda, and it is relevant to consider that these social determinants may get hardwired into the next generation's genome through epigenetic changes.

Developmental effects operate through a gamut of subtle influences which provide the fetus the cues (via the intrauterine environment) to predict the external environment it will be born into, as well as the flexibility to adjust its growth trajectory to match that environment. Cues such as under nutrition to excess maternal nutrition (pregnancy weight gain), maternal obesity or GDM or other maternal health issues like stress or infections create multi generational cycles of disease through epigenetic changes. The mismatch between the predicted environment for survival programming and the actual environment in adult life may be a critical factor driving the type2 diabetes and obesity epidemic. In young women, themselves born small, the physiological effects of pregnancy-induced weight gain, insulin resistance and increased insulin demand may be exaggerated by the pre-existing insulin resistance and the lower ability to produce insulin as a consequence of their early-life programming, resulting in higher rates of gestational diabetes and/or pregnancy-induced hypertension. The concept of fetal programming and its consequences is paradigm changing. It highlights that pregnancy offers a window of opportunity to provide maternal care services, not only to reduce the traditionally known maternal and perinatal morbidity and mortality indicators but also for inter generational prevention of several chronic diseases.

The focus of the UN Sustainable Development Goals on several issues which are important social determinants of health such as poverty, hunger, education, gender equality, water and sanitation, clean energy and pollution as well as an integrated action on health to address maternal and child health, non-communicable diseases and common infectious diseases, provides a unique platform to address the links between maternal and child health and NCD prevention and care.

FIGO'S FOCUS ON NCDS

Since 1954FIGO is the only global organization representing national societies of obstetricians and gynecologists and has Member Societies in 130 countries or territories. **FIGO's vision is that women of the world achieve the highest possible standards of physical, mental, reproductive and sexual health and well being throughout their lives.** FIGO's work is dedicated to the improvement of women's health and rights and to the reduction of disparities in healthcare available to women and newborns, as well as to advancing the science and practice of obstetrics and gynecology.

Realizing the increasing relevance of non-communicable diseases in maternal and offspring health FIGO set up two expert groups one on Hyperglycemia in Pregnancy (HIP) and the other on

Adolescent, Pre-conception and Maternal Nutrition(APMN) which resulted in the release of Recommendations on Adolescent, Preconception, and Maternal Nutrition: "Think Nutrition First" and the FIGO Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care at the FIGO World Congress in Vancouver in 2015.Subsequently working groups on HIP and APMN were created to address these issues.

In 2017 FIGO decided to merge the two working groups into the FIGO committee on maternal and offspring health and prevention of non-communicable diseases to **emphasize on the centrality of the health, nutrition and behavior of girls, adolescents and young women of reproductive age (and, where appropriate, their partners) not only to improve pregnancy outcomes but also as the most effective and sustainable way to address the prevention of NCDs and build the foundation for better population health in the next generation.**

It is in this context that the FIGO committee on maternal and offspring health and prevention of non-communicable diseases will base its work.

The key focus areas of the committee will be on **Prediction and Prevention of Pregnancy Complications as a consequence of common NCDs and the Life Course Approach to NCD Prevention.**

Pregnancy, in particular the first trimester, will receive substantial attention but with other crucial points of intervention – e.g. pre-conception and postpartum also getting their fair share of attention. **Non communicable maternal conditions with the greatest potential for causing pregnancy complications and fetal origins of NCDs such as malnutrition, anemia, overweight and obesity, hyperglycemia, hypertension, thyroid disorders, environmental pollution and smoke (household, environmental and tobacco smoking) and gender violence and mental health will form the basis for action for this committee.**

While all areas will require a public health, awareness and advocacy approach, in some areas a more focussed clinical or basic science approach will be required including developing guidelines and practice recommendations. When possible and feasible interaction with programs related to maternal communicable diseases such as HIV, malaria or TB with significant impact on pregnancy outcome and fetal development will be considered but will not be a focus of this committee.

Thus, **Pregnancy** will be in the center with specific endpoints for intervention at:

- **Pre – pregnancy** (already with NCD)
- **Pregnancy** – as early as possible but focusing on the **1st Trimester** and throughout gestation.
- **Post–Pregnancy** for mother and offspring with links to major health organizations: Neonatologists, Pediatricians, Family Physicians and others related to morbidities (Diabetes, Cardiovascular, other) leading towards prevention of NCD for mother and offspring.

Executive summary and action points outlined by Moshe Hod – Chair of FIGO NCD committee / Dr Hema Divakar – Vice Chair /Dr Anil Kapoor – Executive member

- Non communicable diseases (NCDs) are now the leading cause of mortality worldwide, accounting for 70% of death sannually[1]. 80% of these deaths now occur in low and middle-

income countries (LMICs), necessitating urgent action[2].The UN Sustainable Development Goals (SDGs) recognise NCDs as a major challenge that was not addressed in the Millennium Development Goals. The aim is to reduce by one third premature mortality from NCDs by 2030.

- There is increasing recognition that promoting women's health is especially important in addressing the challenge of NCDs[3]. FIGO offers a unique opportunity to do this by focusing on maternal health, especially maternal malnutrition (both under- and over nutrition), obesity and physical inactivity which are linked to the rising burden of NCDs globally; in addition, dysglycaemia in women of reproductive age impacts adversely on pregnancy outcomes and predisposes substantially both the mother and her offspring to future NCDs and therefor needs to be identified early and managed.
- NCDs are a leading cause of death in women, globally accounting for two in every three deaths annually. This issue has received insufficient recognition, especially for LMICs, because NCDs are sometimes thought primarily to affect males in high income countries.
- Studies of the developmental origins of health and disease (DOHaD) have shown consistently that NCD risk is passed across generations by processes which are not purely genetic[4]. Maternal under nutrition, including micro nutrient deficiencies, not only leads to adverse outcomes such as low birth weight (LBW), preterm labour, still birth, and neonatal and maternal mortality, but also passes increased risk of NCDs to the offspring, for example via an unhealthy body composition with low muscle mass but increased abdominal fat deposition[5]. Furthermore, maternal over nutrition, with diets often also deficient in some nutrients, diabetes and obesity can perpetuate the cycle of obesity and NCDs in the next generation.
- Maternal overweight and obesity increase the risk of pre-eclampsia, gestational diabetes, and are associated with type two diabetes and cardiovascular disease. Prevalence of maternal overweight and obesity is increasing even in LMICs, with prevalence up to 50.7% in African countries.[6]High maternal pre-pregnancy BMI and excessive weight gain during pregnancy are both linked to childhood obesity and adverse body fat distribution which tracks into adulthood. Intervening before pregnancy and in the inter-pregnancy period to achieve optimum weight and body composition is important[7].
- Adolescence is a crucial time for establishing behaviours that affect health and wellbeing in later life, particularly those affecting mental health and risk factors for NCDs such as smoking and unhealthy diets. Investment in this period of the life course will have long-term benefits[8]. The adolescent period provides a window of opportunity to improve nutritional status in women, prevent early pregnancy and decrease the risk of STDs.
- Teenage pregnancies are associated with greater risk of LBW, preterm labour and maternal death, especially in LMICs. As pregnancies in young women are often unplanned, and many women in LMICs do not receive health care until the end of the first trimester, if at all, risk factors influencing the early development of the embryo and fetus,such as folic acid intake, micronutrient status, alcohol use, healthy diet and BMI, may not be addressed in a timely manner to prevent NCDs in the woman and her child.

- Globally, general practitioners obstetricians and gynaecologists, midwives, social workers and other healthcare practitioners, who are part of antenatal care, play a crucial role in NCD risk reduction before, during and after pregnancy. However, globally only half of all pregnant women receive the WHO-recommended four antenatal visits during pregnancy, especially in rural areas.[9] Access to antenatal services is lower among hard-to-reach sections of the population such as women from lower socioeconomic or educational attainment groups.

THE UNIQUE OPPORTUNITY PROVIDED BY FIGO

- FIGO offers a unique opportunity for a new global initiative to focus on women's health and NCDs. To meet this goal FIGO has established an NCD Committee.
- Through its 130 regional or country organisations of Ob/Gyn specialists, serving populations across the spectrum of incomes and resources across the world, FIGO offers truly global reach.
- FIGO provides direct access to influential health care practitioners involved in women's health and pregnancy care, with linkages to other professional bodies such as the IPA, WHO, UN organisations and NGOs, and to government policy-makers. These health care practitioners are widely respected by other professional groups such as educators and social workers and the general population.
- By operating across legislative and political jurisdictions, FIGO can engage with global multinational corporations and private sector organisations.
- Potential areas for action by FIGO's NCD Committee include:

i. Promoting awareness among health care practitioners of the importance of women's health in addressing the challenge of NCDs.

ii. Robust monitoring of maternal risk factors for NCDs such as screening for glycaemic control in women with existing type I/II diabetes and increasing the uptake of screening for GDM in the first trimester.

iii. Empowering health care providers to monitor gestational weight gain and to provide appropriate interventions to reduce risk factors for GDM and obesity across the population with particular attention to high risk pregnancies.

iv. Collaborating with existing platforms aimed at optimising adolescents' and women's nutrition (tackling both under- and overnutrition), smoking cessation and achieving healthy BMI/ body composition before, during and after pregnancy.

v. Integrating NCD-related information with other data on the health of women, children and adolescents, in order to achieve greater traction and synergy with ongoing or planned health and social policies and interventions.

vi. Advocating for placing women, children and adolescents at the centre of all community based programmes.

vii. Increasing knowledge and understanding in young women and adolescents of the behavioural and environmental risk factors for NCDs and their transmission across generations and empowering them to plan and prepare for pregnancy and parenthood.

viii. Engaging in collaborative partnerships with organisations involved in NCD prevention in young people and women in all settings, including governments, NGOs, civil society organisations, philanthropists and the private sector.

ix. Conducting media and public awareness-raising activities to draw attention to the importance of women's health in addressing the challenge of NCDs.

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Osteoporosis

Dr. Ranjana Khanna **Dr. Parul Gupta**

- **WHO in 1994 came up with the definition which was based on T score of the Bone mineral density (BMD) and it said that a T score less than -2.5 can be considered as osteoporosis.**
- **Features of Postmenopausal Osteoporosis include -**
  - **Low Bone mass: measured by BMD**
  - **Fracture: Single most important manifestation of postmenopausal osteoporosis.**
- **US preventive task force recommends that HRT should be used as the last option only when there are contraindications for the use of other antiosteoporotic drugs. The risks and benefits should be well explained to the patient and HRT should be used for the shortest possible duration with the lowest effective dosage.**
- **In patients taking HRT it is essential to do routine mammogram, PAP smears and pelvic examinations to rule out the above mentioned complications.**
- **Concomitant use of anti-osteoporotic drugs was thought to reduce the fracture risk better than using a single drug. However, further studies have led to the non-recommendation of this practice. The sequential use of drugs, first the anabolic group followed by the anti-resorptive drugs has been found to be beneficial for patients.**

INTRODUCTION

Osteoporosis is a silent condition which has been on the rise in the recent times due to the increase in the life expectancy of the patients.[1] This affects the physical, mental as well as socioeconomic status of the patient.

DEFINITION

Osteoporosis has been defined by NIH consensus team as the skeletal disorder in which there is decreased bone strength leading to increased risk of fractures. The working group of WHO in 1994 came up with the definition which was based on T score of the Bone mineral density (BMD) and it

said that a T score less than -2.5 can be considered as osteoporosis.

EPIDEMIOLOGY

The number of patients with osteoporosis is on a rise and it is expected that the number will soon reach 43 million in India, out of which 80% are expected to be women. The incidence of osteoporosis increases exponentially with age and there is a sharp increase in cases following menopause in females. The incidence of osteoporosis is also associated with an increase in the incidence of fractures following the decrease in the bone mineral density.[2]

ETIOPATHOGENESIS OF OSTEOPOROSIS

1. **Age and sex specific changes in BMD :** The bone mineral density increases rapidly in the early years of life especially in children and adolescents. This is the phase of maximum growth of the bones. The phase of bone growth is more in males as compared to females. This leads to increased BMD in males and also increase in length and width of bones in males.[3] As the growth phase halts the peak bone mass is achieved. Once the length of the bone has maximally increased, the girth of the bone increases with periosteal apposition and decreases via bone loss from the trabecular area of the cancellous bone and endosteal surface of the cortical bone.[4] A balance of these processes determines the final BMD outcome. When it is in balance the BMD remains stable whereas when the bone loss exceeds the deposition then BMD decreases.

   In females during the fertile period of her life the BMD is more or less preserved due to the protective effect of the female sex hormones. However, after menopause there is marked reduction of the BMD due to loss of protective effect of the hormones. This loss may be up to 40% of the premenopausal BMD.[4]

   In males, contrary to the popular belief there is decrease in the BMD as soon as the peak bone mass is achieved. However, the bone loss is slow and only 20 – 25% of the peak bone mass is lost. Hence, due to the increased bone growth phase the peak BMD is higher than that of females and the bone loss is also less. That is the reason for the higher BMD in males as compared to females.

2. **Decrease in hormones :** This is the major factor responsible for the postmenopausal osteoporosis. In menopause there is rapid decrease in 17β-estradiol levels. This in turn leads to increase in the cytokines level which activates the osteoclasts along with RANKL, interleukin-1β, interleukin-6 and tumor necrosis factor α. This causes loss of bone and decrease in the BMD.

   Calcium and Vitamin D deficiency especially in elderly age group causes the increase in the parathyroid secretion which is in turn responsible for the increased calcium absorption from the bones especially cortical bones. This decrease in calcium and vitamin D is due to the decreased absorption from the gut and also decreased conversion of vitamin D due to less sunlight exposure.

3. Other risk factors - Some studies have mentioned the importance of hereditary factors. It is seen that if one twin has osteoporosis then the other one also has osteoporosis this is seen especially in monozygotic twins. Genetic component is thought to be there however, the exact genes responsible are not known. Lifestyle choices also affect the BMD. Factors which accelerate bone loss are included in table 1.

TABLE 1: FACTORS ACCELERATING BONE LOSS

Endocrine disorders	**Neuromuscular disorders**
Hyperthyroidism	Muscular dystrophy
Hypogonadism	Paraplegia
Cushing disease	Quadriplegia
Gastrointestinal disorders	**Medications**
Short bowel syndrome	Corticosteroids
Hematologic disorders	Antiepilepsy drugs
Multiple myeloma	Medroxyprogesterone acetate
Renal disorders	SSRI
Renal failure	Thiazolidinediones

TABLE 2: FACTORS INCREASING THE RISK OF FALLING

Neurologic disorders	**Medications**
Parkinson disease	Sedatives and hypnotics
Neuropathy	Antihypertensive agents
Stroke	**Environmental factors**
Dementia	Poor lighting
Impaired balance	Wet, icy, or uneven pavement
Orthostatic hypotension	Uneven roads
Impaired vision or hearing	Electric cords
Frailty	Rugs

FEATURES OF POSTMENOPAUSAL OSTEOPOROSIS

These include:

1. Low Bone mass: measured by BMD
2. Fracture: Single most important manifestation of postmenopausal osteoporosis.

LIFESTYLE AND NONPHARMACOLOGIC MEASURES FOR BONE HEALTH

Goals of this therapy include :

- Optimizing skeletal development to increase the peak bone mass
- Prevent secondary bone loss
- Preserve the skeletal structural integrity
- Prevent fractures

Following diets should be taken into consideration:

1. **Good Nutrition :** A balanced diet is necessary for the development of a good peak bone mass. The peak bone mass also depends upon the protein intake as well as the activity level of the patient.[7,8]
2. **Calcium :** The recommended dose of daily requirement of calcium in various situations is given in table 3. Some points to be taken into consideration are that calcium is absorbed better with food and calcium citrate gives the least amount of GI side effects as compared to other calcium compounds.

Table 3

Age	Daily Calcium Recommendation (mg/dl) for females[9]
9-18yrs	1300
19-50yrs	1000
51-70yrs	1200
70yrs+	1200

3. **Vitamin D :** It is important to assess serum Vitamin D in all individuals suffering from osteoporosis. Vitamin D is found in food stuff like fish oils, fortified milk, cereals and breads. National Osteoporosis foundation recommends a dose of 800-1000 IU for patients more than 50 years old. However, many experts feel that the dose should be between 1000-2000 IU (Safe upper limit being 4000IU/day)[9]. Currently the normal level of vitamin D level in body is 30-32 ng/ml(Upper limit being 60ng/ml)[10]. Even though daily doses are present still it has been seen that the intermittent dose was found to be 3 times more potent[11].
4. **Other dietary supplements :** Magnesium doesn't increase the calcium absorption but decreases the GI side effects.[12] Excessive Vitamin A was harmful for the bones in large doses (more than 100000 IU). Vitamin K (1mg/day) has been found to decrease the bone turnover and hence decrease the bone loss.[13] Natural estrogens (isoflavones) were thought to prevent bone loss but there has not been any scientific evidence for the same.
5. **Alcohol :** Excessive alcohol intake causes bone loss. Postmenopausal women should not take more than 7 drinks a week.
6. **Caffeine :** Postmenopausal osteoporotic women should limit their caffeine intake less than 1-2 servings/day as it decreases the intestinal absorption of calcium.[14]

7. **Smoking :** It is associated with osteoporotic fractures. Patients who give up smoking are at a lesser risk than those who are active smokers[15].
8. **Exercise :** Regular light exercises (30-40 mins) everyday increases the muscle strength and it has been seen that it also causes the bone strength to increase. However, patients with severe osteoporosis should avoid heavy exercises like lifting weights or excessive pushing or pulling.

PREVENTION OF RISK FACTORS FOR OSTEOPOROSIS

1. **Spine Imaging :** to rule out any fractures
2. **BMD :** measured either at the spine or the neck of femur. It can be used to assess the probability of fracture in the next 10 years in a patient using the FRAX tool. However, this modality is still expensive and the benefit to the society is still not confirmed. Lists of indications have been summarized in table 4.

TABLE 4, INDICATIONS FOR DOING BMD

Women > 65 years	Low body weight (BMI <20 kg/m2)
Postmenopausal women	Family H/o fragility fracture
H/o Fragility fractures after age 40 years	Early menopause
Osteopenia	Smoking
Long-term systemic glucocorticoid therapy	Alcohol

INVESTIGATIONS

1. Conventional X-Ray
2. DEXA (Dual Energy X-ray Absorptiometry)
3. Quantitative Computerized Tomography
4. High resolution peripheral quantitative computed tomography (HR-pQCT)
5. Quantitative Ultrasonography
6. Magnetic resonance imaging (MRI)
7. Bone turnover markers

Conventional X-Rays : This is calculated with the degree of bone loss by appearance of trabecular pattern. The Singh and Maini grading for osteoporosis studies the trabecular pattern of the proximal femur. These consist of primary and secondary compressive and tensile trabeculae pattern and the grading ranges from grade 0 to 6. This grading for osteoporosis is relatively

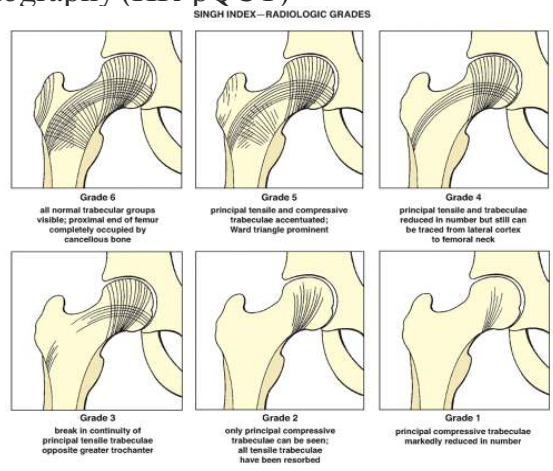

Figure 1: Singh and Maini Index for Osteoporosis[16]

insensitive, requires substantial amount of bone loss (>30%) to indicate osteoporosis. This grading system has been explained in Fig. 1.

DEXA (Dual Energy X-ray Absorptiometry) : DEXA is used to measure BMD at the lumbar spine, hip, distal forearm, calcaneum and whole body.The bone density is calculated with the help of Two Photoelectric peaks which are quantified and device is able to subtract the contribution of soft tissue. Hence, the name dual energy X-Ray absorptiometry. This value is then compared with the average value of a person with the same age, sex, ethnicity, race and geographical location to get the Z score and compared with the average value of a 25 years old person of the same sex, ethnicity, race and geographical location to get the T-score (Fig. 2). These values are used in the WHO definition of osteoporosis. This reading may be faulty due to various factors like Spinal Artifacts, Rotation of hip, vertebral marker and femoral neck marker.

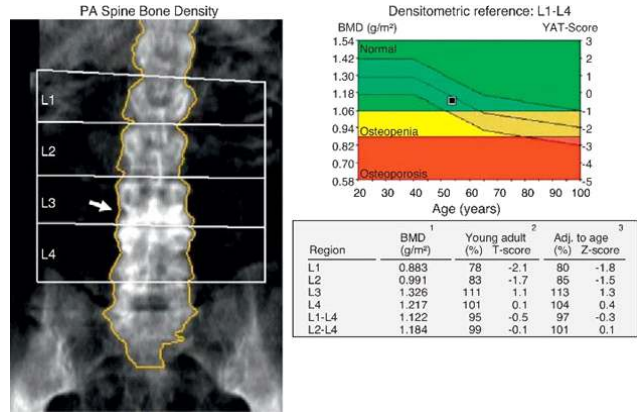

Figure 2 : T score in DEXA scan

Quantitative Computerized Tomography : This is the quantification of the spinal BMD using the 3-Dhydroxyapatite phantom using CT scan. This also helps in distinguishing between cancellous and cortical bones.[17, 18] It gives a 3-D volumetric analysis which is more specific than DEXA scan. However, it is not very widely used as it is expensive and exposure to radiation is high.

High resolution peripheral quantitative computed tomography (HR-pQCT) : It is capable of achieving good resolutions (up to 80 nm) with low radiations. It has the advantage that it can study the micro architecture of the bones and hence, is very useful to study the trabeculae structure of distal tibia and distal radius.[19-24] It gives precise measurements for bone density and micro architecture and hence is thought to be the most accurate. However, this is not yet available in India.

Quantitative Ultrasonography : It is one of the devices which may be used as a screening tool. It can be done with the help of a portable machine and hence, can be done in a small setup. It is a relatively inexpensive machine and also easy to operate. It uses the sound interference, speed of sound, broadband ultrasound interference and stiffness index to calculate the T-score which then can be used as the measure of osteoporosis. It can only be used at peripheral sites like calcaneum, phalanges of fingers, patella and tibia [25] which is not helpful as the fragility fractures rarely occur in calcaneum. Fig 3.

Figure 3: QUS Portable Machine

Magnetic resonance imaging (MRI) : Magnetic resonance imaging gives an insight into the micro architecture of the bone using non-ionizing radiation.[26-27] High resolution of the bone architecture may be seen with the help

of MRIs due to the vibration of the hydrogen atoms present in the bones leading to the formation of the bone microarchitecture.[27] This is currently being used for research purposes.

Bone turnover markers : It is a new modality of investigation for the diagnosis of osteoporosis. These include bone formation and bone resorption markers. The bone formation markers consist of proteins secreted by active osteoblasts (bone forming cells) whereas bone resorption markers are proteins secreted by active osteoclasts (bone resorpting cells) (Fig 4). The bone formation markers consist of osteocalcin, bone specific alkaline phosphatase (BAP), procollagen type I N-propeptide and C-propeptide[28]. Whereas, bone resorption markers consist of type I collagen measured in serum and urine: C-terminal and N-terminal cross linking telopeptides of type I collagen, deoxypyridinoline (cross linking molecule) and certain amino acids such as hydroxyproline or galactosylhydroxylysine. These markers have the advantage over the imaging modalities that they are very sensitive and show changes well before the imaging modalities show. They can also be used to monitor the effect of anti-osteoporotic drugs[29] as the bone resorptive markers decrease and the bone formation markers rise almost immediately after the administration of anti-osteoporotic drugs. Also they can be used to study the mechanism of action of various drugs and hence, determine the mechanism of action of various drugs.

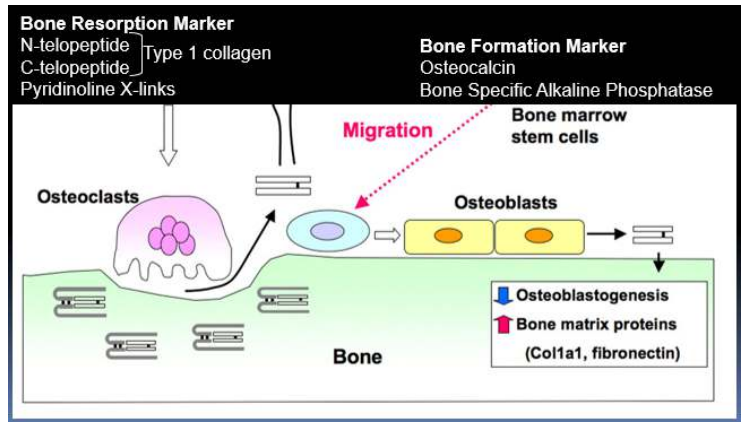

Figure 4: Bone turnover markers.

WHO FRACTURE RISK ASSESSMENT TOOL (FRAX®)

It is a new algorithm which requires special mention. This uses clinical risk factors which are independent of BMD to calculate the risk of fragility fractures in males and females over the age 40 years.[30] This is freely available online (http://www.shef.ac.uk/FRAX) and uses large cohort studies to calculate the risk of fragility based on few well-known clinical risk factors (Fig 5). These risk factors include age, weight, height, previous fragility fracture, parental hip fracture, current smoking, and regular intake of 3 or more units of alcohol daily, rheumatoid arthritis, oral glucocorticoids (current therapy or former exposure to

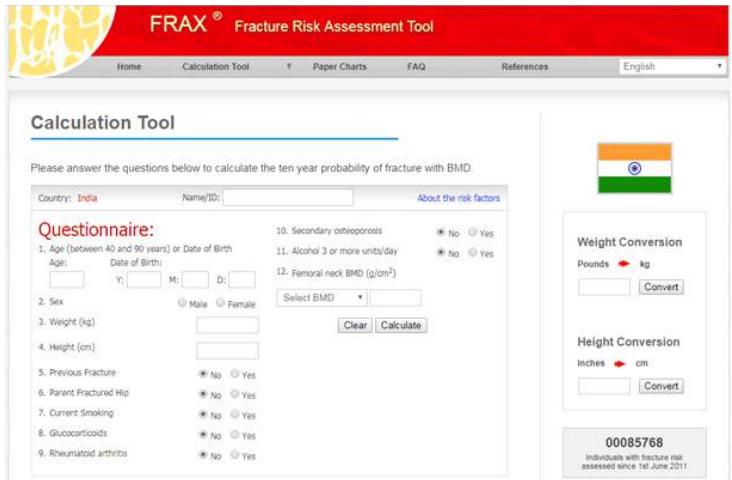

Figure 5: FRAX online

glucocorticoids) as well as, alternatively, causes of secondary osteoporosis or decreased femoral BMD. This gives an estimate to calculate the fragility fracture probability for the next 10 years. However, it is a limited response study and does not take into consideration the amount of alcohol or smoking intake. It also does not take into consideration the potential risk factors for fall and it also does not take into account the spine BMD and hence has a low sensitivity to predict fragility fractures of the spine.

TREATMENT OF OSTEOPOROSIS

Candidates requiring treatment for osteoporosis include:

1. Hip or spine fracture
2. T score <-2.5
3. T score between -1 to -2.5 with a probability of fracture as calculated by FRAX tool

DRUGS USED IN OSTEOPOROSIS

Several drugs are used for the successful management of osteoporosis. They decrease the incidence of spinal and non-spinal fragility fractures. These drugs can be broadly classified into antiresorptive and anabolic drugs. Drugs included in the groups are given in table 5.

TABLE 5: CLASSIFICATION OF ANTI-OSTEOPOROTIC DRUGS

Anti-resorptive	Anabolic
Estrogen	Parathyroid hormone (PTH1-84)
Selective estrogen receptor modulator	Teriparatide (PTH1-34)
Bisphosphonates	
Human monoclonal antibody to receptor activator of NFκB ligand (RANKL)	
Strontium ranelate	

Postmenopausal Osteoporosis

Drug	**Prevention**	**Treatment**
Estrogen	Multiple regimen	
Calcitonin		200 IU intranasal OD
Denosumab		60mg SC x 6 mthly
Raloxifene	60 mg OD	60 mg OD
Ibandronate	150 mg mthly	150 mg mthly
Alendronate	35 mg wkly	70 mg wkly
Risendronate	35 mg wkly	35 mg wkly
Zoledronic Acid	5 mg IV x 2 yrs.	5mg IV yrly
Teriparatide		20 µg SQ daily

TABLE 6: LIST OF DRUGS APPROVED FOR OSTEOPOROSIS

TAB Risk Reduction TION

Drug	Vertebral	Hip Fractures
Calcitonin	Yes	No
Denosumab	Yes	Yes
Raloxifene	Yes	No
Ibandronate	Yes	No
Alendronate	Yes	Yes
Risendronate	Yes	Yes
Zoledronic Acid	Yes	Yes
Teriparatide	Yes	No

Calcium and Vitamin D : There is no evidence to suggest the efficacy of calcium and vitamin D alone for the treatment of osteoporosis. Daily dosage of Vitamin D of 700-800 IU with 1-2 gms of Calcium is found to be adequate. Levels of 60nmol/L or more may be considered as adequate to prevent fragility fractures.[31] The effect was better seen when calcium and vitamin D were used as an adjunct to therapy. This should be kept in mind while making a drug regime for patients with osteoporosis.

Hormone Replacement Therapy: This consists of the use of estrogen, progestin or a combination of both. It has a good effect in postmenopausal osteoporosis. It decreases the fracture risk by 20-35%[32,33] by decreasing the bone turnover and thereby increasing the BMD. However, this protective effect is lost as soon as the HRT is stopped.

Despite the good antiosteoporotic effect these drugs also may increase the risk for cardiovascular events, endometrial and breast carcinoma[32, 33]. HRT may also lead to increased risk of MI, ovarian cancer and decreased cognition. Recent studies have also indicated the advantage of low dose HRT in management of postmenopausal osteoporosis; however, studies to assess the reduction of fracture risk have not been assessed.

US preventive task force recommends that HRT should be used as the last option only when there are contraindications for the use of other antiosteoporotic drugs. The risks and benefits should be well explained to the patient and HRT should be used for the shortest possible duration with the lowest effective dosage[34]. However, the Australian osteoporosis guideline states that for women less than 60 years of age short duration (up to 5 years) low dose oestrogen may be used after the other treatment modalities have been explored. This is because they are at a lower risk for developing complications associated with HRT. If the patient is over 60 years of age then it is advisable not to give HRT as the patients will already be at a high risk to develop complications from HRT drugs[35]. In patients taking HRT it is essential to do routine mammogram, PAP smears and pelvic examinations to rule out the above mentioned complications.

Soyaisoflavones (SI) : The modern applications of SI are based on their estrogenic activities. SI has demonstrated their viable potential in decreasing bone resorption and enhancing formation.

However, more studies are warranted to delineate the underlying mechanisms, efficacy, and safety of this compound, and especially, an investigation on the preventive effects of SI on typical human diet and potentials of dietary supplements is critically needed. Other meta-analysis revealed that soy isoflavone supplements significantly increased bone mineral density and decreased the bone resorption marker but showed no significant effect on bone formation marker.

Selective estrogen receptor modulators (SERM) : SERMs are synthetically produced molecules which bind with the estrogen receptors and act as agonists or antagonists depending on the target organ. This was first seen for tamoxifen which acted as antagonist for breast (used in breast cancer) and agonists for bones. Raloxifene is used (60 to 120 mg daily) for osteoporosis and has the same action on breast cancer as tamoxifen. It decreases the bone turnover and reduces the fragility fracture risk by 40-50%[36, 37]. Studies show that raloxifene did not have any effect on the cardiovascular events and in some studies it was shown to reduce the risk. However, it increases the risk of venous thromboembolism. Hence, patients should be counselled regarding the complication and kept under regular follow-up. Another drug Bazedoxifene is also coming up and it has shown that it has no complications. However, this drug is not yet approved for osteoporosis.

Bisphosphonates : These inhibit the activity of the osteoclasts. They reduce risk of vertebral fractures, hip fractures as well as increase the BMD. Out of the various options alendronate which was initially in vogue is not being used now.

Risendronate : Decreases risk of hip fracture by 40%[38]. Effective against osteoporosis following glucocorticoid therapy.

Ibandronate : It is the most commonly used bisphosphonate. Its action is fast and well sustained. It increases the BMD and reduces vertebral fracture risk by 50%. Out of the weekly and monthly dosage the monthly dosage is found to be more effective and gives a better response in osteoporosis.

Zoledronic Acid : It is an injectable bisphosphonate which gives protection for upto 1 year. Decreases bone turnover and increase BMD. Reduces fracture risk by 70% for vertebral fractures and 40% for hip fractures[39].

Side Effects :

- "Severely suppressed bone turnover" Long duration of bisphosphonate intake may lead to insufficiency fracture. To prevent this a drug holiday should be taken.

Patient's fracture risk	Suggested duration of treatment	Suggested duration of drug holiday[a]
Low	Treatment rarely indicated	NA
Mildly increased	Treat for approximately 5 yr	Stay off bisphosphonate until BMD decreases significantly or fracture occurs
Moderately increased	Treat for 5–10 yr	Stay off bisphosphonate for 2–3 yr (or less if BMD decreases or fracture occurs)
High	Treat for 10 yr	Stay off bisphosphonate for 1–2 yr (or less if BMD decreases or fracture occurs); alternate medication (*e.g.* raloxifene, teriparatide) may be given during the holiday from bisphosphonates

Duration is based largely on personal opinion.

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- Osteonecrosis of the jaw – For prevention of this complication the medication should be taken in standing position and patient should not lie down for another 30 mins.
- Atypical femoral shaft #s – Same as first point.
- Higher risk of atrial fibrillation – Injectable bisphosphonates should be given slowly over 45 mins and should not be given to high risk patients.

Calcitonin : This is available in the form of nasal spray. It mildly increases BMD by inhibiting the osteoclasts. It has a little painkiller effect in the initial phase. For the antiosteoporotic action to start the drug has to be taken for 3 years. Its nasal form may cause nasal irritation. Due to its limited benefit it cannot be used as the first line of management for osteoporosis.

Antibody to RANK Ligand : Denosumab: For the activation of osteoclasts the receptor activator of nuclear factor-κB ligand (RANKL) binds to receptor activator of nuclear factor-κB (RANK). Denosumab is the antibody to RANK ligand hence; it is a competitive antagonist of the RANK receptor and hence, binds with the RANKL ligand, thereby deactivating the osteoclasts and decreasing the bone resorption.

Parathyroid Hormone : Teriparatide is the drug used in this class for osteoporosis. It is the only anabolic drug that actively increases the bone deposition in osteoporosis whereas the other drugs decrease the bone resorption. They act by promptly increasing the bone formation followed by slow increase in the bone resorption and hence, change the bone turnover to the positive side (bone forming). They decrease the incidence of fragility fracture of spinal and non-spinal by 65% and 60% respectively[40].

Strontium Ranelate : Strontium Ranelate (2 g daily) slightly inhibits bone resorption, slightly stimulates bone formation and progressively dose-dependently increases BMD. Decreases the risk of spinal fractures by 35 % and hip fractures by 40%[41,42].

Concomitant use of anti-osteoporotic drugs was thought to reduce the fracture risk better than using a single drug[43]. However, further studies have led to the non-recommendation of this practice. The sequential use of drugs, first the anabolic group followed by the anti-resorptive drugs has been found to be beneficial for patients.

BMD in progression of the treatment : BMD may be used for the prognosis and the follow-up of the treatment of osteoporosis. The treatment is said to have failed if there is substantial fall in the BMD or any fracture occurrence.

OPERATIVE TREATMENT FOR OSTEOPOROSIS

Most commonly occurring fractures are the vertebral fractures and there has always been a difference of opinion regarding the management of the same. Vertebroplasty though decreases the pain instantly but does not increase the vertebral height to normal whereas, Kyphoplasty increases the vertebral height along with the reduction in the pain but is expensive[44-48]. The surgeon should be careful in the fixation of the other fractures by using locking plates and HA coated implants to provide a stable fixation.

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Mid Life Crisis

Dr. Maninder Ahuja

- **GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes in the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections. Women may present with some or all of the signs and symptoms.**
- **Various studies have shown that GSM has a negative effect on quality of life of women but very few women seek help and visit medical practitioners. May be they feel treatment is not available or are afraid that they wont pay heed to their problems.**
- **The FDA and the American College of Obstetricians and Gynecologists consider bioidentical hormones to be a marketing term and not an alternative treatment based on scientific evidence.**

INTRODUCTION:

Menopause is characterised by absence of menstruation for twelve months so it is a retrospective diagnosis. This occurs because of depletion of ovarian follicles as women are born with fixed number of eggs, about 7-10 million at 24 weeks of pregnancy which decreases to about 3-4 lacs when a girl is born. There is gradual depletion of eggs from puberty to menopause. When only about 500 eggs are remaining , then menopause occurs. Before menopause there is a period of perimenopause. This perhaps can be called as mid life when hormonal fluctuations start and women have irregular periods and hot flushes. It is after ovarian activity cessation occurs that the MID LIFE CRISIS starts.

Basic fact is that menopause is a hypoestrogenic state caused by depletion of ovarian follicles that affects many women by having adverse effects on many tissues of the body which can be either prevented or corrected by hormonal or non hormonal treatments and these women do need help.

Age of menopause is not constant all over world and in India it is 46.5 years[1] Problems of dwindling hormones are hot flushes, mood changes, sleep disturbances, depression, cognitive changes, irregular periods , heavy periods, weight gain specially redistribution of fat in the midrif, fatigue and decreased strength. Other late effects are metabolic syndrome, development of coronary artery disease, alzheimers and dementia.

Loss of libido , dsyparunia and vaginal sypmptoms are sequelae of hypoestrogenic state and are the crisis of mid life which are not discussed openly by patients, health care providers and public.

What we have not been talking about is atrophic changes in the vagina which was called VVA and now called Genital urological syndrome of menopause –GSM.

This is old wine in a new bottle as VVA is replaced by GSM

The terms vulvo vaginal atrophy (VVA) and atrophic vaginitis were the terms used previously but were considered by many to be inadequate and did not describe the range of menopausal symptoms associated with physical changes of the vulva, vagina, and lower urinary tract associated with estrogen deficiency.

HISTORY

The term VVA describes the appearance of the postmenopausal vulva and vagina without specifying the presence of associated symptoms. Atrophic vaginitis means a state of inflammation or infection, neither of which is a primary component of VVA.

In 2012, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of Trustees of The North American Menopause Society (NAMS) acknowledged the need to review current terminology associated with genitourinary tract symptoms related to menopause. Therefore they had a joint consensus conference in 2013 and came to the conclusion that the term genitourinary syndrome of menopause (GSM) is a medically more accurate, all encompassing, and publicly acceptable term than vulvo vaginal atrophy(VVA). GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes in the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections. Women may present with some or all of the signs and symptoms, which must be bothersome and should not be better accounted for by another diagnosis. The term was presented and discussed at the annual meeting of each society. The respective Boards of NAMS and ISSWSH formally endorsed the new terminology genitourinary syndrome of menopause (GSM) in 2014 (Other terminology offered was USM but it was preferred to have the word Genital rather than Urogenital)

- Specifically, VVA mentions the words vulva and vagina which cannot be used comfortably in general social discussion and in the media.
- The term atrophy has negative connotations for many women.

- Furthermore, the term VVA does not include the lower urinary tract and describes the appearance of vaginal structures, rather than what is clinically most important - vagina related genitourinary symptoms.
- Atrophic vaginitis carries similar limitations and implies that inflammation or infection is involved, neither of which is inherently a part of the condition.
- GSM will be acceptable for use by primary care providers, clinical specialists, researchers, educators, affected women, the media, and the public, and that it will serve to improve and increase communication, research, education, and treatment related to the genitourinary and sexual health of menopausal women.[2]

EPIDEMIOLOGY AND PREVALENCE

In India mean age of menopause is 46.4 years and 130 million Indian women are expected to live beyond menopause into old age by 2015 and 19% of women aged 40–41 years have already reached menopause, and the incidence of menopause increases rapidly after the age of 41 years. By the age of 48–49 years, two-thirds of women are in menopause. So the number of women in menopause is increasing with increase in life expectancy and so is the increase in reported problems. Therefore quality of life of this population becomes a major issue and understanding of menopause is very important issue for all the clinicians as most of the time it is a multidisciplinary approach to the problems of menopause.

GSM

- GSM is a **progressive disorder** unlike hot flushes which tend to get cured over a period of time. One study found the prevalence of GSM to be 4% during perimenopause, rising after menopause to 25% after 1 year and to 47% after 3 years[3]
- Menopause-related genitourinary symptoms can affect up to 50% of midlife and older women.[4]
- Another review of the impact of this condition by Nappi and Palacios estimated that, by the year 2025, there will be 1.1 billion women worldwide older than the age 50 with specific needs related to GSM[5]
- The Vaginal Health: Insights, Views, and Attitudes (VIVA) survey found that 80% of women with genital atrophy considered its impact on their lives to be negative, 75% reported negative consequences in their sexual life, 68% reported that it made them feel less sexual, 33% reported negative effects on their marriage or relationship, and 26% reported a negative impact on their self-esteem.[6]

  Various studies have shown that GSM has a negative effect on quality of life of women but very few women seek help and visit medical practitioners. May be they feel treatment is not available or afraid that medical practitioners wont pay heed to their problems.[7,8]

Age of Symptoms of GSM - Although distressing symptoms occur mostly after menopause, they may be seen in women of any age who experience a hypo-estrogenic state, even if it is transient.

Other causes of hypoestrogenic state are:

- Premature ovarian failure
- Hypothalamic amenorrhea
- Hyperprolactinemia.
- Use of Gonadotropin-releasing hormone agonists and aromatase inhibitors.
- Chemotherapy, radiation
- Surgical removal of ovaries
- **The abrupt onset of menopause that may occur with these treatments is often associated with significantly greater sexual dysfunction and negative impact on quality of life.**
- Cigarette smoking also leads to lower estrogen levels, which may contribute to GSM.

Effect of GSM on Male partners - Male partners of symptomatic women also note adverse emotional and physical effects.[9] In The CLOSER (Clarifying Vaginal Atrophy's Impact On Sex and Relationships) trial, an online survey of 4,100 men and 4,100 women aged 55 to 65, in 52% to 78% of men and 58% to 64% of women expressed the negative effects of vulvovaginal symptoms on intimacy, libido, and sexual pleasure.[10]

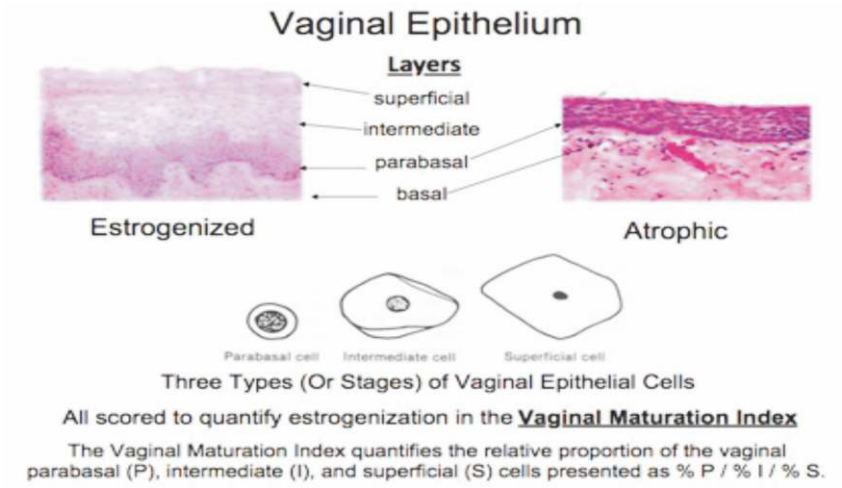
Pathophysiology of GSM - The genitourinary system has a common embryologic tissue urogenital sinus tissue, as are the vulvar vestibule and the upper vagina.[29] Androgen receptors are also widely distributed in the vestibule and within its glands, making urogenital tissues responsive not only to estrogen but to androgens as well and that is the basis for the functional and clinical connection Estrogen receptors are present in vagina, vulva, urethra, bladder trigone and estrogen acts through these receptors. Normal vaginal epithelium before menopause is stratified squamous epithelium which is rich in glycogen this is supported by fibromuscular layers. The epithelium is composed of superficial, intermediate, and parabasal cellular layers. In the presence of estrogen, the superficial and inter-mediate cellular levels predominate, with few parabasal cells.

Microbiome and Glycogen and Estrogens - Superficial cells of Stratified Squamous epithelium are rich in Glycogen. Glycogen has a great role to play as it acts as a substrate for lactobacilli, producing organic acids, primarily lactate, that help maintain an acidic pH of 2.8 to 4.0. The low pH helps protect against pathologic shifts in the microbiome. Estrogen also maintains the collagen content of the epithelium, maintains acid mucopolysaccharides and hyaluronic acid, and optimizes vaginal blood flow. These effects result in optimal epithelial thickness and elasticity, moisture, vaginal secretions, and lubrication.

How menopause effects tissues of Genital urinary System? Low levels of estrogen after menopause bring out anatomic, physiologic, and clinical changes. There is loss of collagen and adipose, leading to decreased elasticity and vaginal mucosal thinning. Physiologically vascular flow is decreased. The epithelial cytology transitions to a predominance of parabasal cells and a decrease in superficial and intermediate cells. (FIG_1.[2])

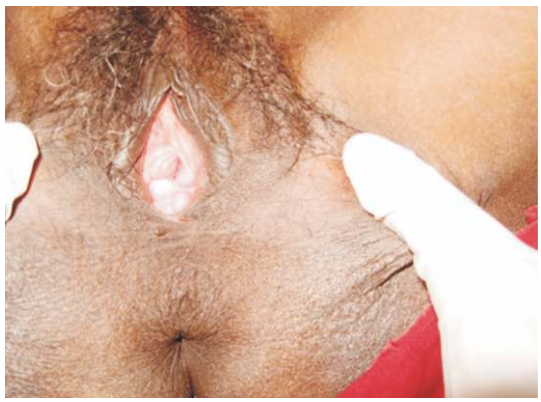
FIG-1: Premenopausal and Post Menopausal Vaginal Epithelium

FIG-2 VMI –Vaginal Maturation Index



Eccrine and apocrine glands become attenuated. These changes result in decreased vaginal secretions, diminished or delayed lubrication, effect on sexuality and friable vaginal walls and dryness.[10] FIG -3

FIG-3: Pale Vagina, Absence of Rugosities



Other Effects of Estrogen Loss - Anatomic effects of estrogen loss are not limited to the vagina.

- The epithelium, connective tissue, and smooth muscle of the vulva, vagina, urethra, and bladder trigone are also affected.
- The labia minora become thinner and regress,
- The introitus retracts, and narrowing and stricture of the vaginal canal and introitus may result.
- In some women, the urethral meatus becomes prominent relative to the introitus and more vulnerable to physical irritation, infection, and trauma.

It is important that patients define their symptoms and rate whether they are bothersome or not [12] Although this measure does not help diagnose GSM, it can be used effectively to follow response to treatment and this was approved by FDA in the Vaginal Symptom Questionnaire.[12] It can be useful for assessing symptoms. It is a validated 21-item questionnaire that measures the quality of life impact of genital, but not urinary, symptoms of menopause.

Healthcare providers should ask about GSM symptoms during routine clinical visits from women who are peri or postmeno- pausal or who have become hypoestrogenic from other causes, as many women are reluctant to initiate this discussion. Conversely, in women who present with sexual problems, such as difficulty with arousal or dyspareunia, GSM should be considered as a possible cause.

Women should be asked if they have any of the following symptoms :

- Vaginal itching, burning, discomfort, or irritation
- Malodorous or irritating vaginal discharge
- Urinary frequency, urgency, dysuria, urethral discomfort, or recurrent urinary tract infections
- Sexual symptoms of entry dyspareunia, vaginal pain, or irritation with sexual activity, which may be complicated by post coital bleeding, spotting, or fissuring.
- Vulvovaginal pain or irritation may be constant or may be present in the absence of sexual activity, such as with exercise, wearing tight clothing, or sitting for long periods

History should review current medical conditions, medication use, nongenital skin disorders (eg, eczema), and systemic menopausal symptoms, such as hot flashes.

Non hormonal causes of GSM should be evaluated(FIG:4)

Conditions	Associated symptoms
Medical problems	
Sexually transmitted infections Candidiasis Bacterial vaginosis Trichomoniasis	Vaginal discharge, odor, irritation
Lichen sclerosis	Hypopigmented, waxy, agglutination, loss of labial folds

Lichen planus	Red plaques, pain
Lichen simplex chonicus	Lichenified skin
Vulvar intraepithelial neoplasm	Raised or eroded lesions
Vulvar cancer	Ulcer with raised edges
Paget disease	Red, scaly plaque with sharp border
Vulvodynia	Dyspareunia
Vaginismus	Dyspareunia
Psoriasis, eczema	Multiple plaque-like lesions, nongenital lesions
Inflammatory bowel disease	Fissures

Skin irritants, Perfumes, Contact dermatitis, Powders, skin irritation, reactions, Deodorants Soaps, Spermicides, Lubricants, Hot tub and pool additives, Foreign bodies, Panty liners, Perineal pads, Tight-fitting or synthetic clothing, Retained foreign body.

Any isolated ulcer should be biopsied

DIAGNOSIS SYMPTOMS AND CLINICAL EXAMINATION:

Characteristic physical findings of GSM include :

Vulva :

- Scarce pubic hair,
- Thinning of the labia from loss of labial fat, resorption of the labia minora,
- Fusion of the labia minora and majora .[13]
- The vulvar skin is pale and thin.
- The clitoral hood may retract, exposing the glans (which may lead to increased pain with sexual stimulation), or clitoral hood fusion may occur.
- Presence of uretheral caruncle
- Prolapse may become more pronounced because of laxity of all fibromuscular and collagen tissues.

Vagina :

- The vagina is pale, dry, smooth, and shiny with loss of rugosities .
- Shortening or stricturing may be present.
- Vaginal elasticity decreases.
- Inflammation and petechiae (pinpoint, non raised, round purple-red spots) may be present.
- The cervix may be flushed with the vaginal fornices.

Because of prolonged atrophy and narrowing and stricture of vagina, sexual activity or insertion of speculum can lead to tearing of vagina.

Special precautions during Examination of these patients :

Counsel them that if they have pain during examination we would stop the examination -

- Hand held mirror may relax the patient
- In initial examination don't do speculum examination and postpone till second visit
- If vaginal swabs and cultures are indicated we may take them by gently inserting cotton buds without speculum examination or lubricant use
- Lubricants should be used for gentle insertion of speculum
- Topical lidocaine gel (diluted, as it may burn) may be placed against the perineum on a gauze pad for 3 to 5 minutes before insertion of the speculum.
- When an internal pelvic examination is necessary in a timely manner, such as with postmenopausal bleeding or a history of an abnormal Papanicolaou smear, but is too painful for the patient, the examination should be done under anesthesia.

LABORATORY TESTS

Lab tests not required. However, office-based objective evaluations such as vaginal pH testing and the maturation index can support the diagnosis.

Vaginal pH

- The pH of the estrogenized vagina ranges from 3.8 to 4.2, whereas in women with GSM, the pH may reach 5.5 or higher.
- The pH can be obtained by placing a pH-sensitive paper against the lateral vaginal wall,
- A vaginal pH of 5 or greater in the absence of blood, semen, or infection suggests vulvovaginal atrophy.[14]

Vaginal Maturation Index –VMI

- The vaginal maturation index is determined by a vaginal smear using Rakoff staining, in which 100 cells are counted and the number of parabasal, intermediate, and superficial cells is determined. In general, a well-estrogenized vagina has mostly superficial and intermediate cells, which shifts to a predominance of parabasal cells as estrogen levels decline. (15)

FOLLOW UP

A recent review of vaginal atrophy suggests that after a diagnosis of GSM, healthcare providers can consider the most bothersome symptom along with the vaginal pH to assess the response to treatment. [16] In general, schedule a follow-up appointment at 8 to 12 weeks to review treatment response. If treatment has not resulted in adequate symptom relief, consider a pelvic examination and further testing.

MEDICAL MANAGEMENT OF GSM :

We have now available with us a basket of therapies some of them are over the counter drugs and some are prescription drugs. Lasers are the new arrival on scene for Sexuality and initial prolapse Problems.

Non hormonal therapies available without a prescription provide sufficient relief to most women

with mild symptoms. When they don't provide relief then the first choice is vaginal estrogens in various forms.

Vaginal lubricants : Lubricants can only provide short term relief because of lubrication so are used for ease with sexual activity or penetrative activity like P/V or Per speculum examination There is no evidence of any impact on histologic changes of atrophy. They are meant to relieve friction. Lubricants may be water-based, oil-based, silicone-based, or a combination. Individual products have different effects on condom integrity. Perfumed, warming, or stimulating products may be irritating to some women and should be tried initially in small amounts, as they can also cause local allergies.

Vaginal moisturizers : These products are intended to treat GSM. They are applied regularly and not just with vaginal activity but usually once or twice a week. Some vaginal lubricants can maintain an acidic pH in the vagina and may reverse the histologic changes of atrophy. Symptomatic improvement over placebo or estrogen has been shown in clinical trials.[21,22]

Women should be advised that trial and error in choosing products may be necessary to establish a successful regimen. Products should be tried in succession, not simultaneously, with a "wash-out" period between, to be able to evaluate response.

When low dose estrogen is administered locally, a progestin is not indicated for women without a uterus and generally is not indicated for women with an intact uterus. that the choice of therapy for genitourinary syndrome of menopause (GSM) depends on the severity of symptoms, the efficacy and safety of therapy for the individual patient preference[16]

All forms of local estrogens are equally effective for symptoms of vaginal atrophy, stress incontinence, urge incontinence and recurrent UTI; this was Cochrane review and Society of Gynecological Surgeons Systematic Review Group [16,17]

However, endometrial safety has not been studied in clinical trials beyond 1 year. Data are insufficient to confirm the safety of local estrogen in women with breast cancer.If we want to use for more than one year then we can either do TVS for endometrial thickness or can do serum estradiol levels.

Locally applied estrogens can reverse the atrophic changes of estrogen deprivation,

They act by an

- Increase in blood flow,
- Increase in elasticity,
- Increase vaginal wall thickness. There is growth of superficial and Intermediate cells
- This therapy also can normalize pH levels
- With subsequent restoration of a healthy lactobacilli based flora.
- Locally applied estrogens also have been shown to decrease the frequency of recurrent urinary tract infection.[20]

Various Estrogen products : Estrogen-containing vaginal creams, rings, and a tablet are available,

and each has been shown to be effective for GSM. Locally applied estrogens at recommended dosages tend to have fewer adverse effects and risks as compared to systemic estrogens. Estradiol levels generally do not exceed levels found in the untreated menopausal population, although a dose- and duration-dependent increase in systemic levels may occur[22]

The conjugated-estrogen vaginal cream Premarin is the only locally applied estrogen approved by the FDA to treat dyspareunia. It is dosed at 0.5 g intravaginally for 21 days and is then either withdrawn for 7 days or, more commonly, administered at 0.5 g twice a week.

Initially we should use daily for 1 to 2 weeks and then change to twice weekly regimen. Women with vaginal fissures or tearing will benefit from externally applied creams in addition to internal applications. Response to therapy is usually seen within 4 to 6 weeks. Once symptom relief is obtained, treatment should continue indefinitely. Although long-term safety studies are lacking, risks are believed to be minimal. When used for more than one year patient should be reevaluated by TVS to see endometrial thickness.

FDA APPROVED DOSAGE

PRODUCT	PROPRIETARY NAME	DOSING
Vaginal Creams		
17-beta estradiol	Estrace vaginal cream 0.1 mg/g	Initial: 2–4 g/day for 1–2 weeks Maintenance: 1 g at 1–3 times a week[a]
Conjugated estrogens	Premarin vaginal creamb (0.625 mg/g)	Vulvovaginal atrophy: 0.5–2 g/d for 21 days, then off 7 days or twice a week[a] Dyspareunia: 0.5 g/day for 21 days, then off 7 days or twice a week[a]
Vaginal ring		
17-beta estradiol Estradiol acetate	Estring (7.5 µg/day) Femring (5 and 10 µg/day)	Inserted for 90-day intervals without interruption
Vaginal tablet inserts		
Estradiol hemihydrate	Vagifem, Yuvafemc (10 µg/day)	Initial: 1 tablet/day for 2 weeks Maintenance: 1 tablet twice a week
DHEA (prasterone)	Intrarosa (6.5 mg insert)	1 insert into vagina, once daily
Oral tablet		
Ospemifene	Osphena (60 mg)	1 tablet orally every day

a. Common clinical dosage is 0.5 g twice a week for maintenance.

b Premarin vaginal cream is the only locally applied preparation with FDA approval for dyspareunia due to GSM.

c Yuvafem is an FDA-approved generic equivalent to Vagifem.

DHEA = dehydroepiandrosterone; FDA = US Food and Drug Administration

Endometrial surveillance is not required in lower dosage and upto one year . After one year or when

we are using higher dosage TVS or Serum estradiol levels can be tested. Addition of Progesterone is not required unless patient is obese or there is some other risk factor for endometrial cancer.

DHEA(Dehydro epiandrosterone) - DHEA is an endogenous steroid that is converted by aromatase activity into testosterone and estradiol. 12 weeks of vaginal DHEA supplementation (0.25%, 0.5%, and 1% DHEA ovules) is more effective than placebo in improving vaginal dryness and dyspareunia in women with GSM.[29–31] Locally applied DHEA decreases parabasal cells, decreases vaginal pH, increases vaginal secretions, and improves epithelial surface thickness and integrity without any significant impact on serum levels of DHEA, DHEA-sulfate, estradiol, testosterone, or their metabolites. Importantly, transvaginal DHEA had negligible endometrial effect.Breast cancer risk is a warning and not an contraindication

Selective Estrogen Receptor Modulator-Ospemifene - Ospemifene, an estrogen agonist activity in the vagina, is taken daily as a 60-mg oral dose. Long-term safety studies suggested no adverse effects on the endometrium or breast for at least 52 weeks. It decreases dryness of vagina and dysparunia, improves VMI , decreases Parabasal cells and increases superficial cells. Warning is regarding risk of stroke,or endometial cancer. Hot flushes may increase in7% of patients.

ALTERNATIVE THERAPIES

Treatments for GSM not approved by the FDA include laser and radiofrequency therapies, testosterone, isoflavones, and bioidentical hormones.

Laser and radiofrequency therapies - Both of these therapies aim to promote tissue remodeling with increased collagen and elastin production and increased vascularity. This, in turn, increases muscle support and tone. Laser therapies act by ablating and coagulating vaginal tissues; radiofrequency therapies directly heat the tissue. Both treatments are office-based, require up to 3 initial treatments, and are followed by re-treatment at ap-proximately 1-year intervals.

Mechanism of Action :

- The supraphysiologic level of heat generated by the CO2 laser induces a rapid and transient heat-shock response that temporarily alters cellular metabolism and activates a small family of proteins referred to as the “heat shock proteins” (HSPs). HSP 70, which is overexpressed following laser treatment, stimulates transforming growth ¬factor beta, triggering an inflammatory response that stimulates fibroblasts, which produce new collagen and extracellular matrix.

  In a Study reported in climacteric (26) about effect of fractional Co2 laser was effective to improve VVA symptoms
- Three applications of laser over 12 weeks in 50 women (age 59.6 5.8 years)
- Dissatisfied with previous local estrogen therapy
- Fractional CO 2 laser treatment was effective to improve VVA symptoms
- Physical and mental scores of quality of life were significantly improved
- Satisfaction with the laser procedure was reported by 84% and a minimal discomfort was

experienced.

- No adverse events were recorded during the study period.

The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women - MFCO2-Laser therapy increased Lactobacillus ($p < 0.001$) and normal flora ($p < 0.001$) after the completion of the therapeutic protocol, which decreased vaginal pH from a mean of 5.5 ± 0.8 (initial value) to 4.7 ± 0.5 ($p < 0.001$). The prevalence of Lactobacillus changed from 30% initially to 79%[27]

Fractional microablative CO2 laser for vulvovaginal atrophy in women treated with chemotherapy and/or hormonal therapy for breast cancer: a retrospective study.

Fractional microablative CO2 laser treatment is associated with a significant improvement of VVA symptoms in women affected by hormone-driven breast cancer.[28] This procedure has the advantage of relieving iatrogenic/physiological VVA symptoms without resorting to contraindicated estrogen preparations, which have been the most effective therapy so far.

VAGINAL LAXITY – VAGINAL REJUVENATION

- Vaginal laxity, despite the absence of symptomatic prolapse, is a common complaint amongst parous women.
- Although reduced sexual sensation is the most common specific symptom, it is not clear whether laxity is directly related to sexual dysfunction.
- Other symptoms include pelvic discomfort, an inability to retain tampoons, vaginal wind and entrapment of bathwater.
- There is very limited evidence that surgical repair improves any of these symptoms of laxity.
- In the absence of objective prolapse, 'vaginal rejuvenation' procedures may include posterior colporrhaphy or perineorrhaphy, either of which may risk bowel symptoms and dyspareunia. Observational Studies have shown improvements with laser treatment.

Laser Rejuvenation - Studies have reported high patient satisfaction rates (91% to 100%), improved sexual functioning, and decreased GSM symptoms of vaginal dryness, burning, itching, and dyspareunia. Data, however, are from observational studies, not placebo-controlled trials.

Although laser and radiofrequency therapies are FDA-approved for several indications, laser treatment for symptoms of vulvovaginal atrophy is not currently an approved indication. Patients should be counselled for this.

The indications for which in India laser and RF treatments are being uses are following:

- Vaginal tightening
- SUI
- Vulvar rejuvenation
- Vulvodynia/Vestibulitis
- Vaginal infections
- Post delivery rehabilitation
- Vaginal dryness
- Scars
- Lichen sclerosis
- Bleaching

Testosterone - Locally applied testosterone was shown in a small study to improve dyspareunia and

vaginal dryness associated with aromatase inhibitor use in breast cancer patients. However, due to the lack of safety and efficacy data from larger, controlled trials, testosterone therapy is not currently recommended.

Isoflavones - Not much data is there on efficacy of Isoflavones but small study of 60 postmenoapausal women ,12-week, double-blind placebo-controlled study of vaginally applied 4% soy isoflavone gel, improvements in vaginal atrophy symptoms, maturation values, and vaginal pH were found.38 Additional data on efficacy and safety are needed before isoflavones should be considered as a treatment for GSM.

Bioidentical hormones - Bioidentical hormones are plant-derived hormones that are chemically similar or identical to those produced by the body. Although there are FDA-approved bioidentical hormones (eg, micronized progesterone, estradiol, DHEA), the term bioidentical usually refers to non-FDA-approved, commercially available hormones produced and compounded by specialty pharmacies.

Patients often view these substances as being better, safer, and more acceptable for use, and healthcare practitioners need to be prepared to address these beliefs. The FDA and the American College of Obstetricians and Gynecologists consider bioidentical hormones to be a marketing term and not an alternative treatment based on scientific evidence.39 Patients should be informed that bioidentical hormones have the same risks as any similar hormone preparation along with additional risks related to potential lack of purity and potency. Further, they have not been adequately studied in controlled clinical trials.

CONCLUSION AND FOLLOW-UP CARE

With millions of women suffering from GSM, it is duty of all HCP to proactively diagnose and treat these patients to improve their Quality of Life.

To date, estrogen therapy is the most effective treatment for moderate to severe GSM, although a direct comparison of estro-gen and ospemifene is lacking. Nonhormonal therapies available without a prescription provide sufficient relief for most women with mild symptoms. When low-dose estrogen is administered locally, a progestin is not indicated for women without a uterus—and generally is not indicated for women with an intact uterus. However, endometrial safety has not been studied in clinical trials beyond 1 year. Data are insufficient to confirm the safety of local estrogen in women with breast cancer.

Future research on the use of the fractional CO_2 laser, which seems to be a promising emerging therapy, may provide clinicians with another option to treat the common and distressing problem of GSM.

And once diagnosis of GSM is established and treatment is under way, practitioners can use symptom questionnaires and vaginal pH testing as easy and reliable means of measuring clinical response to therapy.

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Premenstrual Syndrome – Unravelling the Mystery


Dr. Kiran Pandey


Dr. Kalpana Dixit


Dr. Meera Agnihotri

- **Diagnosis of PMS**
  1. **Symptoms should be recorded prospectively for at least two cycles using symptom diary (no value of retrospectively recording of symptoms)**
  2. **Daily record of severity of problems: Symptom charts or diary should be made according to National Association of Premenstrual Syndrome and accordingly graded into Mild, Moderate and Severe PMS.**
  3. **Definitive diagnosis is established by administering GnRH analogues for 3 months, if 2 month prospective diary is inconclusive.**
- **It is important to keep in mind that a patient of PMS must never be dismissed as a 'functional' case, because of the non-specific nature of symptoms. Rather, she must be accorded the due medical, obstetric and psychological attention to help her cope with this disabling disease.**

DEFINITION

Premenstrual syndrome (PMS) is a condition which manifests with **distressing physical, behavioural and psychological symptoms** in the absence of organic or underlying psychiatric diseases, which **regularly recur during the luteal phase** of each menstrual cycle and disappears or significantly regress by the end of menstruation.[1]

Premenstrual Dysphoric Disorder (PMDD) is a **serious variant** of PMS that is characterised by more severe symptoms that **disrupt the day-to-day functioning of the woman.**

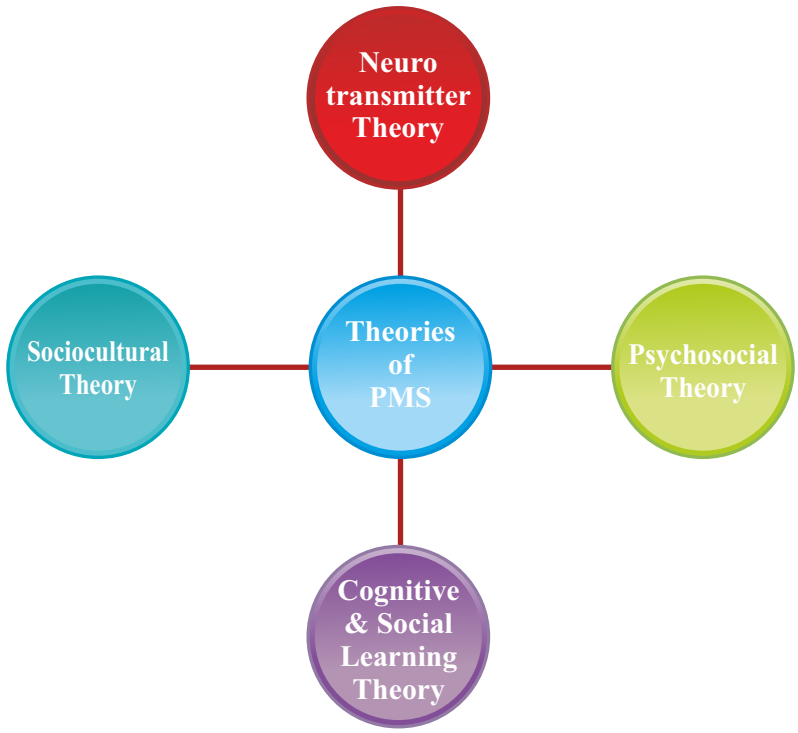
EPIDEMIOLOGY

The pooled prevalence of PMS is reported to be around 47.8%. Of all countries, France has the lowest prevalence (12%) and Iran has the highest prevalence (99%).[3] It has been found that the overall prevalence of PMS in females of reproductive age group is 30-40%; while the prevalence of PMS specifically in the pre-menopausal age group is 20-32%.[2],[3]

According to an Indian study done in Bhavnagar, Gujarat, the prevalence of PMS was estimated to be around 18.4%. [5]

ETIOPATHOGENESIS

There are several postulated theories explaining the pathogenesis of PMS. [6] They are explained as follows:



Neurotransmitter Theory - Ovarian hormones, estrogen and progesterone, have a direct bearing on the levels and action of serotonin and GABA, which are the chief hormones whose fluctuation leads to mood disturbances. It has been found that administration of GnRH agonists as well as supplementation with serotonin can help alleviate the mood disturbances seen in PMS. [7],[8],[9]

Psychosocial Theory - This theory suggests that PMS is more a psychological problem stemming from a woman's unconscious internal conflict regarding womanhood and motherhood. It has been hypothesised that the physical and emotional symptoms of PMS manifest as a reminder to the woman that she is not pregnant and thus has not fulfilled her traditional social role. This theory however has little scientific basis.

Cognitive and Social Learning Theory - This theory suggests that the emotional disturbances associated with PMS are actually a maladaptive coping mechanism in response to the phenomenon of menstrual bleeding which can be an excessively stressful event for some women.

Sociocultural Theory - According to this theory, the clinical manifestations of PMS are in essence, a woman's cultural response to a sense of dissatisfaction arising out of feeling confined in stereotyped gender norms and societal roles and a perception of social inequality. [10]

RISK FACTORS

- High caffeine intake
- Alcohol abuse
- Stress
- Anxiety
- History of depression
- Increasing age (worse in late 30s)
- Overweight
- Family history
- Dietary factors (certain vitamin and mineral deficiencies)

CLINICAL PRESENTATION

The clinical features usually begin a few days prior to menses, and subside with the onset of bleeding. The symptoms of PMS are generally non-specific – that is, they are not indicative of any one cause, but may stem from a variety of disorders. For example, fatigue is a common symptom between PMS and anaemia. But, a woman suffering from PMS will experience fatigue only in the luteal phase of the cycle; whereas an anaemic woman will experience fatigue throughout the month. **So, it is the timing of symptoms, rather than the symptoms themselves, that is critical in establishing the diagnosis of PMS.**

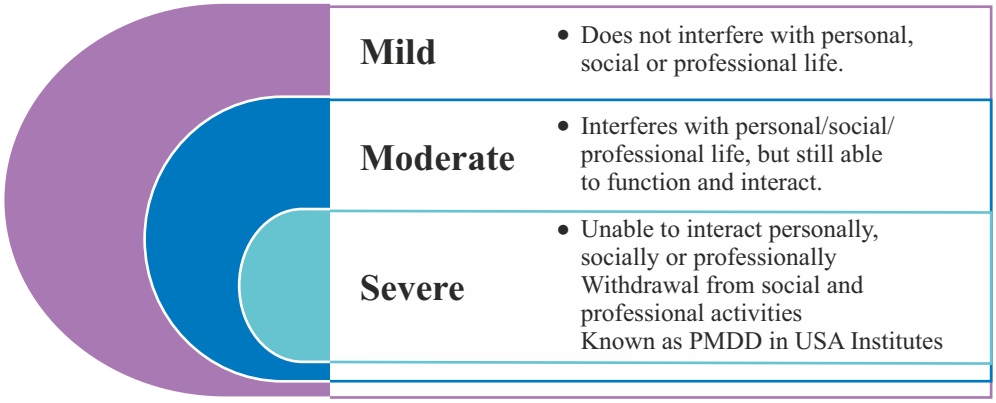
The usual symptoms of PMS are:

Psychological	Physical	Behavioural
Irritability	Breast tenderness	Aggression
Mood swings	Bloating	Decreased cognitive ability
Anxiety	Heaaches	Decreased concentration
Depression	Acne	Forgetfulness
	Changes in appetitie	Accidents
	Pelvic/joint pain	

CLASSIFICATION

PMS can be classified in two ways:

On the basis of severity



Classification as per ISPMD (International Society for Premenstrual Disorders) Consensus

I. Core Premenstrual Disorders

- Most common type
- Symptoms affect daily functioning
- Symptoms recur in ovulatory cycles, in luteal phase and abate as menstruation begins; follows a symptom free week
- Some individuals will have predominantly psychological, somatic or a mixture of symptoms.

II. Variant Premenstrual Disorders

- Do not meet the criteria for Core Premenstrual Disorders
- Premenstrual exacerbation of an underlying disorder such as, diabetes, depression, epilepsy, asthma and migraine.
- Experience symptoms relevant to their disorder throughout the menstrual cycle

III. Progesterone-induced Premenstrual Disorders

- Caused by exogenous progesterone present in HRT and COC
- Reintroduces symptoms to women sensitive to progesterone

IV. Premenstrual Disorders with absent menstruation

- Include women who still have a functioning ovarian cycle, but for reasons such as hysterectomy, endometrial ablation or LNG-IUS, they do not menstruate.

V. Premenstrual Dysphoric Disorder (PMDD)

DIAGNOSIS OF PMS

1. Symptoms should be recorded prospectively for at least two cycles using symptom diary (no value of retrospectively recording of symptoms)

2. Daily record of severity of problems: Symptom charts or diary should be made according to National Association of Premenstrual Syndrome and accordingly graded into Mild, Moderate and Severe PMS.
3. Definitive diagnosis is established by administering GnRH analogues for 3 months, if 2 month prospective diary is inconclusive.

   It is important to note that it is the timing, rather than the symptoms which is important.

A number of standardised methods have been developed to describe PMS. Some of these tools are designed to be a one-time measure of symptoms as indicated by abbreviations for single assessment like:

- COPE – Calendar of Premenstrual Experience
- PRISM – Prospective Rescend of Impact and Severity of Menstruation
- DSRP – Daily Recording of Severity of Problems
- DSR – Daily Symptom rating Scale
- MSSL – Menstrual Symptom Severity List
- PMSD – Pre Menstrual Symptom Diary
- PMST – Pre Menstrual Symptom Tracker
- PMP – Pre Menstrual Profile

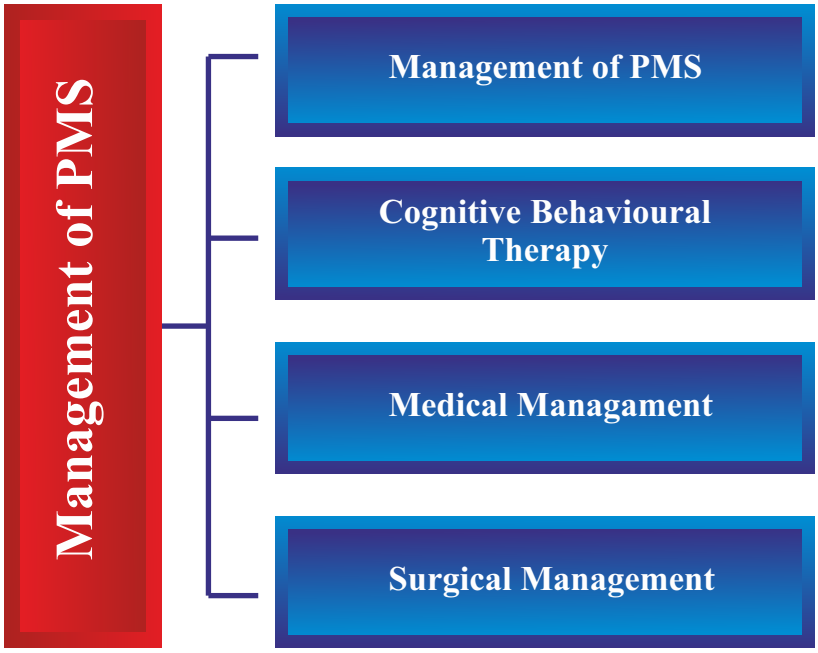
Diagnosis of PMDD - The American Psychiatric Association Consensus requires fulfilment of strict criteria for the diagnosis of PMDD.

- At least 5 of the following 11 symptoms must be present, out of which one symptom must be related with mood disturbances and one must be from among the first four symptoms listed:
  1) Marked depressed mood, feelings of hopelessness or self-deprecation
  2) Marked anxiety, tension or a feeling of 'being-on-edge'
  3) Marked emotional lability (suddenly feeling sad or tearful)
  4) Marked persistent anger, irritability and increased conflicts.
  5) Decreased interest in usual activities (school, friends, hobbies)
  6) Subjective sense of difficulty in concentration
  7) Lethargy, easy fatiguability, lack of energy
  8) Changes in appetite (overeating, binge eating or specific food cravings)
  9) Insomnia or hypersomnia
  10) Subjective sense of being overwhelmed or 'out of control'
  11) Physical symptoms

- ❖ Breast tenderness
- ❖ Swelling
- ❖ Sense of bloating
- ❖ Joint/muscle pain
- ❖ Headaches
- ❖ Weight gain

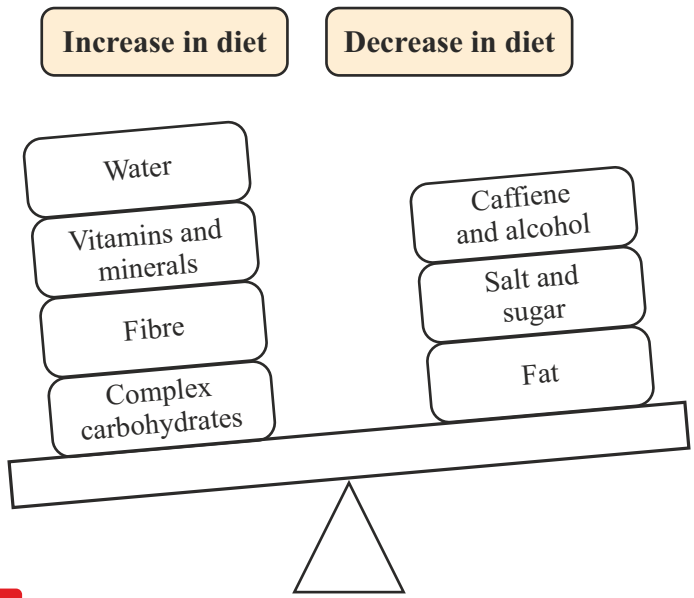
- The symptoms must be present strictly in the luteal phase and must be severe enough to disrupt daily functioning

MANAGEMENT



Complementary Therapy - These include self-help techniques such as dietary alteration, exercise, Yoga, meditation, massage, etc.

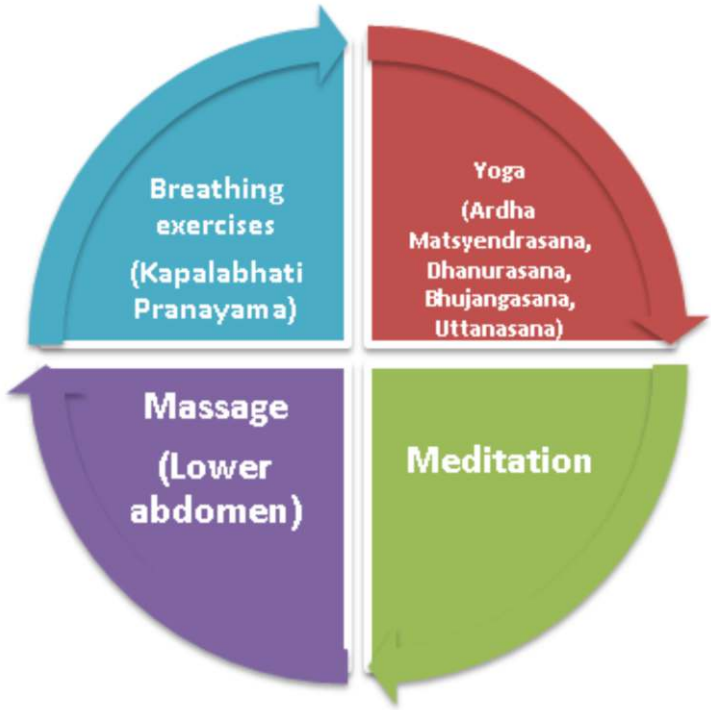
1) Modifications in diet



Dietary Supplements that can be added:

- Vitamin B6
- Vitamin E (400-600mg/day)
- Calcium (1200-1600 Mg)
- Magnesium - Most beneficial for Premenstrual Anxiety
- Evening Primrose Oil (1-2 Gm/day X 3 Months) – for Mastalgia
- Chasteberry Extracts (600 Mg TDS) – Decrease Estrogen, Increase Progesterone, Dopamine and Prolactin Levels
- Black Cohosh (40-80 Mg Bd) – Suppress LH
- St. John's Wort – Hypericum Perforatum is a herbal remedy shown to alleviate mild to moderate depression, by influencing the serotonergic system.
- Micronutrients

2) Stress-relieving methods



Cognitive Behavioural Therapy (CBT)

- Should be routinely considered as a treatment option for women with severe PMS, along with psychological counselling.
- Aim is to help the patient to achieve a harmonious balance between mind, mood, body and behaviour.

Medical Management

Hormonal	Non-Hormonal
• Combined Oral Contraceptives • Percutaneous Estradiol with progesterone • Ovulation suppression	• SSRIs • SNRIs

Hormonal Medical Treatment

Combined Oral Contraceptives

- Most evidence-based method of managing PMS
- Drosperinone (Dose: 2 mg) -containing COCs form the first line medical management of PMS
- COCs may be given continuously or in cyclic fashion, but continuous COC treatment is better than cyclical
- Treatment for 3 months reduces the symptoms
- Recommended dose of ethinyl estradiol: 30 mcg and 20 mcg

Percutaneous Estradiol with Progesterone

- Effective for physical and psychological symptoms
- Micronized progesterone is the best and first line treatment, which works by means of progesterone opposition, rather than as progestogens.
- Lowest effective dose is given for minimum period, to minimize adverse side effects.
- Dose: 100 mg/day from day 17 to day 28 of cycle
- Low dose LNG-IUS (52 mg) – to prevent endometrial hyperplasia

Ovulation Suppression

1. **DANAZOL**

- It is an effective drug for breast tenderness when given in luteal phase only. It has not been approved for the treatment of PMS as such.
- Side effects: Significant masculinisation
- Dose: 200 mg BD

2. **ESTROGEN**

- Well established and widely accepted means of treatment
- Estradiol patch: 100 mcg, twice weekly with a progestogen (cyclical basis)

3. **GnRH ANALOGUES (with/without add-back HRT)**

- Proven benefit for severe PMS, but not recommended for routine use.
- GnRH test is useful for those considering hysterectomy and bilateral salpingo-oophorectomy for severe symptoms
- Considered as a second or third line treatment
- Add-back hormone therapy can be used as

  Continuous combined HRT

  Tibolone
- Duration of treatment

  If used alone: 6 months

  If combined with continuous combined HRT: Perform annual Bone Densitometry (by DEXA scan). Stop treatment if BMD is low.

  Note: Progesterone therapy alone in the form of pessaries, suppositories, depot injections, has not been found to be beneficial. Its only role is to restrict the action of estrogen.

Non-hormonal medical treatment

SSRIs and SNRIs

- Considered as first line treatment in severe PMS
- Use in luteal phase is superior compared to continuous use
- There is no evidence to support its combined use with ovulation suppression.
- To be discontinued pre-conceptionally and during pregnancy, as PMS symptoms will abate.
- Mechanism of action of SNRIs and SSRIs:

  SSRIs (Selective Serotonin Reuptake Inhibitors) prevent the reuptake of serotonin in the synaptic cleft, thereby preventing the termination of its action and prolonging its effect.

  SNRIs (Serotonin Noradrenaline Reuptake Inhibitors) prevent the reuptake of serotonin and noradrenaline in the synaptic cleft, thereby preventing the termination of its action and prolonging their effect.
- SSRIs used are: Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram. Citalopram may be effective when other SSRIs fail.
- Possible side effects:

  Nausea, vomiting

  Insomnia

  Fatigue

  Decreased libido

  Risk of congenital deformity

  May cause severe depression or even lead to suicide.

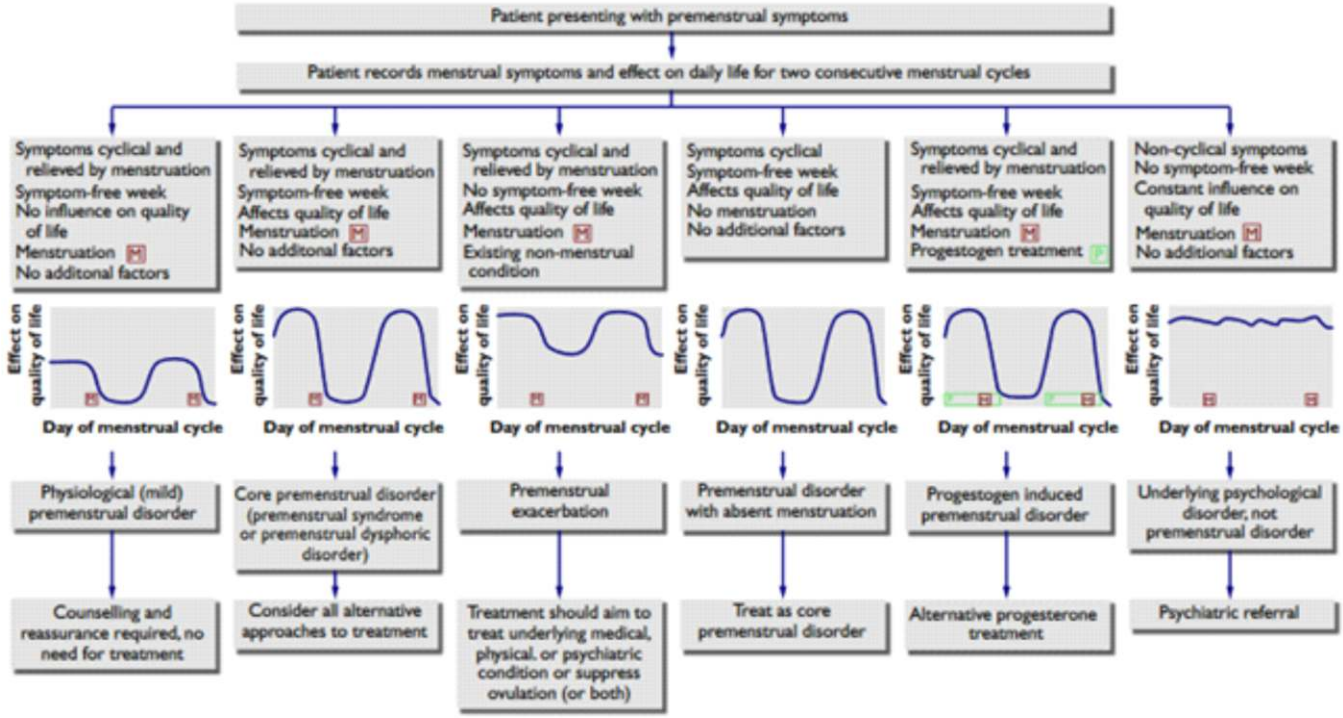
SURGICAL TREATMENT

Total Abdominal Hysterectomy + Bilateral Salpingo-oophorectomy

- Rarely done for the treatment of PMS
- Used as a last resort in very severe cases if medical treatment has failed
- GnRH agonists should be used preoperatively as a test of cure and HRT tolerance (to be done after surgery) should be ensured.

TREATMENT PROTOCOL

General, complementary therapy and cognitive behavioural therapy is to be instituted in all patients.



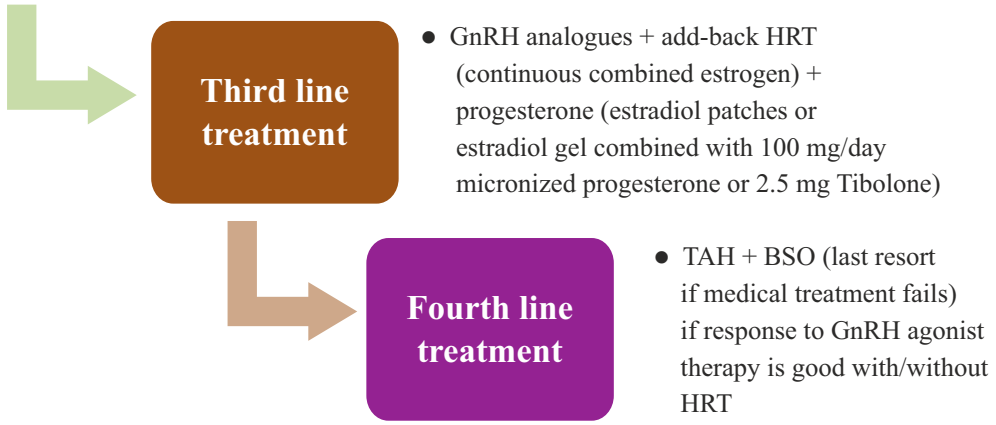
RCOG Green Top Guidelines for Management of PMS [1]

First line treatment

- Exercise, CBT, vitamin supplementation
- Drosperinone containing COCs
- Continuous/Luteal phase low dose SSRIs (10-20 mg)

Second line treatment

- Estradiol patches (100 mg) + Micronised Progesterone (100/200 mg/day, oral/vaginal) or LNG IUS 52 mg
- Higher dose SSRIs (20-40 mg) continuously or during luteal phase



CONCLUSION AND TAKE-HOME MESSAGE

- Revolutionary changes in definition, diagnosis and treatment of PMS and PMDD have occurred, according to ISPMD consensus and RCOG Green-top Guideline – 48, 2017
- Diagnosis:

  Symptoms recorded prospectively over 2 cycles. It is time, not severity of symptoms that is important.

  GnRH Agonist for 3 months is used in making the diagnosis, if symptom diary is inconclusive.
- Management:

  Holistic approach (Complementary treatment, Cognitive Behaviour Therapy, diet, Yoga, exercise) is advised in all cases.

  Medical management – hormonal and non-hormonal

  i. COCs have best evidence treatment – Drosperinone containing COCs form first line treatment. Continuous use is better than cyclical.

  ii. Percutaneous Estradiol combined with cyclical progesterone is best for alleviation of physical/psychological PMS. Micronized Progesterone is first line for progesterone opposition.

  iii. GnRH agonists – Highly effective in severe PMS, not recommended routinely. Treatment is for 6 months. Add-back hormone therapy is given as continuous, combined HRT or Tibolone. BMD must be done every year by DEXA – if BMD falls, stop treatment.

  iv. SSRIs and SNRIs are first line treatment in severe PMS. Luteal phase use is superior to continuous use.

  Surgical Management – Total Hysterectomy + Bilateral Salpingo-oopherectomy is advised as a last option if medical treatment fails. GnRH agonist test should be done pre-operatively.

It is important to keep in mind that a patient of PMS must never be dismissed as a 'functional' case, because of the non-specific nature of symptoms. Rather, she must be accorded the due medical, obstetric and psychological attention to help her cope with this disabling disease.

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Dilemma in Diagnosis and Management of Female Genital Tuberculosis

Dr. Vinita Das
& Dr. Smriti Agrawal

- **Menstrual symptoms are the commonest presentation of genital tuberculosis followed by infertility. Around 19% of infertile women are reported to have genital tuberculosis. The other common clinical presentations are abdominal pain, tubo-ovarian masses, ectopic pregnancy, PID refractory to treatment, cervical growth, ulcers, vulval lesions. Tubercular endometritis accounts for 1% of postmenopausal bleeding. Around 11% women are asymptomatic**
- **Role of TST (Tuberculin skin testing- Mantoux test) in diagnosis of GTB in suspected patients. A positive skin test supports a diagnosis, but a negative test does not necessarily exclude EPTB.**
- **Role of diagnostic laparoscopy and diagnostic criteria: GTB is detected by laparoscopy in 46.5% infertile patients. Laparoscopy is increasingly being used for the early detection of GTB because it offers the dual advantage of pelvic organ visualization and sample collection from inaccessible sites.**
- **The diagnosis of GTB is made if any of the laboratory tests on tissue specimens like Endometrium/ peritoneal fluid is positive (i.e. AFB smear, culture, histopathology), or if laparoscopy has positive findings. Endometrial / peritoneal fluid PCR alone does not confirm tuberculosis. There is no evidence of geneXpert in FGTB.**

1. BACKGROUND:

Clinical interest of gynaecologists aroused after the accidental finding of tuberculous lesions, by Sutherland in 1943, in specimens of endometrium, obtained during routine investigations for sterility and menstrual disorders. According to the World Health Organization Global Tuberculosis Report from 2013, there were 8.6 million incident tuberculosis (TB) cases globally and India alone contributed 26% to this global scenario. Female Genital TB is one of the forms of extrapulmonary TB (EPTB) and has been reported to contribute up to 9% cases of EPTB.[1] 5-13% of patients with pulmonary TB develop Genital TB.[2]

The exact incidence of Female Genital Tuberculosis (FGTB) is not known due to under-reporting as it frequently presents without symptoms, requiring high index of suspicion for diagnosis. Up to 11% patients lack symptoms.[3] FGTB produces devastating effects by causing irreversible damage to fallopian tubes which is difficult to cure both by medical and surgical methods.[4] FGTB poses a diagnostic dilemma because of its varied clinical presentations and lack of sensitive and specific diagnostic methods.

2. INCIDENCE/PREVALENCE/IMPORTANCE

The incidence of GTB varies and can be as low as 0.69% in Australia or as high as 19% in India. The fallopian tubes and endometrium are the prime sites of involvement in FGTB with following clinical presentation[5]. Menstrual symptoms are the commonest presentation of genital tuberculosis followed by infertility. Around 19% of infertile women are reported to have genital tuberculosis. The other common clinical presentations are abdominal pain, tubo-ovarian masses, ectopic pregnancy, PID refractory to treatment, cervical growth, ulcers, vulval lesions. Tubercular endometritis accounts for 1% of postmenopausal bleeding[10]. Around 11% women are asymptomatic or may present with varied symptomatology. Patients who need to be investigated for genital TB (presenting with Infertility, menstrual problems, TO mass) are considered as **Presumptive EPTB.** Confirmed TB cases are those presumptive cases with any of the laboratory tests positive (i.e. AFB smear, culture, histopathology, or if laparoscopy has positive findings, **Definitive Tuberculosis** - presence of tubercles, caseation, or beaded tubes) and will be treated with ATT..

It is very important that diagnostic work-up is done to diagnose active lesions of tuberculosis and rule out other important differential diagnoses in presumptive cases. It is also important to rule out concomitant pulmonary tuberculosis

3. DIAGNOSTIC TESTS FOR FGTB

In absence of gold standard, diagnosis of genital TB is a dilemma. If a patient has symptoms as defined in the disease morbidity or even asymptomatic infertile females should be investigated for FGTB.[11] For suspected FGTB, appropriate specimens from the suspected sites (endometrial aspirate, peritoneal wash or fluid) should be obtained for microscopy, culture, and histopathological examination in a quality-assured laboratory.

Criteria for a Definitive Diagnosis Includes -

1. Demonstration of Mycobacterium tuberculosis on microscopy. It is hardly ever met in paucibacillary FGTB[12], because AFB Microscopy requires $\geqslant$ 10000 bacilli/mL specimen and culture requires $\geqslant$ 100 bacilli/mL[13]
2. Culture (on solid and liquid media) is the most widely used gold standard for validating results in diagnosing EPTB specimens, although pick up rates are low.
3. Composite reference standard(CRS).Whenever practical, every effort should be made to obtain clinical samples for both myco-bacteriology (AFB smear and culture) and histopathologic tests.[14,15]
4. Laparoscopy offers the dual advantage of pelvic organ visualization and sample collection from inaccessible sites.

5. The inconsistency among various laboratory tests signifies the need for multi sampling for multiple tests which may increase the diagnostic yield.[16]

Comparison of definitive diagnostic tests and their yields

	HPE	AFB Smear	AFB culture	PCR	Laparoscopy
Ease of obtaining sample	Easy	Easy	Easy	Easy	Needs expertise
Sensitivity	2.6-18.5%	1.1-8.3%	2-18.3%	22.2-97.6%	17.1-85.7%
Specificity	high	high	High	Poor - Moderate	Moderate
Availability	Easy	Easy	Moderate	Easy	Moderate
Cost	low	low	Low	moderate	high
Specific advantage	confirmatory	confirmatory	confirmatory	?	Useful in diagnosing presumptive cases
Specific disadvantage	Poor sensitivity	Poor sensitivity	Long time to result, Low availability	High false positive	Expensive Expertise

Role of TST (Tuberculin skin testing- Mantoux test) in diagnosis of GTB in suspected patients: Mantoux test cannot distinguish between infection and disease. Reported sensitivity is 55%, specificity is 80%, with 45% false negativity in women with laparoscopically diagnosed tuberculosis.[17]A positive skin test supports a diagnosis, but a negative test does not necessarily exclude EPTB.[18]

Interferon gamma radio immunoassay (IGRA) is more specific than TST particularly in people who have received BCG, however like TST, it cannot distinguish between infection and disease. Currently there is no evidence to support the use of IGRA in routine practice.[19]

Role of Endometrial Aspirate(EA) for AFB microscopy, culture and histopathology in patients with suspected GTB: EA for AFB microscopy has a pickup rate of 1.1% to 8.3%. EA culture for AFB by LJ (solid) medium has a pickup rate of 2% to 18.3% and by Bactec (liquid medium) method, the pickup rate is 2% to 8.8%.EA histopathology pick-up rate is 3.4% to 18.5%[3,16,20-28].

Role of Endometrial Aspirate DNA PCR in patients with suspected GTB: The role of PCR is controversial because of the high rate of false positives. Most studies advocate the commencement of ATT in women with a positive PCR result only if there is evidence of GTB on clinical examination also or if the hysteroscopy or laparoscopy is suggestive of GTB.[21,29,30]

Role of newer molecular tests RT PCR in the diagnosis of GTB: There is 1 study related to

reverse transcriptase PCR. 4/143 women had RT PCR positive which correlated 100% with Bactec.[24] Study concluded that mRNA PCR was only positive if the culture was also positive- hence offered no extra benefit.

Role of newer gene Xpert in the diagnosis of GTB: Sensitivity of the Xpert assay with tissue specimens was 69.0% and 100% sensitivity found with the urine and stool specimens. The combined sensitivity and specificity of the Xpert assay were calculated to be 77.3% and 98.2%, respectively. There are no good studies on FGTB so far and very low- quality evidence available for GTB. Cost of gene Xpert and its availability may also be of concern.

Role of adenosine deaminase (ADA) testing on ascitic fluid in patients presenting with adnexal mass with ascites: This is a non-specific chemical marker, yet helpful in pelvic-peritoneal tuberculosis presenting as an adnexal mass and mimicking ovarian cancer. Ascitic fluid ADA activity has good accuracy but poor sensitivity and imperfect specificity. There is no consensus in exact cut off, however values between 21-40IU/L are considered as cut offs

Role of diagnostic laparoscopy and diagnostic criteria: GTB is detected by laparoscopy in 46.5% infertile patients. Laparoscopy is increasingly being used for the early detection of GTB because it offers the dual advantage of pelvic organ visualization and sample collection from inaccessible sites. The classification of laparoscopic findings indicative of FGTB varies; Variously classified as:

- **Laparoscopic findings include**
  - presence of tubercles, caseation, or beaded tubes
  - presence of straw-colored fluid in the Pouch of Douglas, extensive, dense pelvic and/or peri-tubal/periovarian adhesions, hydrosalpinx, tubo-ovarian mass, thick fibrosed tubes, mid-tubal block, perihepatic adhesions, hyperemic tubes/blue uterus on chromo-tubation also may point towards tuberculosis

Complications during laparoscopy are inability to see pelvis, peritonitis, trocar site discharge and need for laparotomy[21]. Fitz Hugh Curtis Syndrome in GTBmay be seen in upto 48% in mild disease, 30% in moderate disease, 35% in severe disease[32]

- **Hysteroscopy :** hysteroscopy may detect uterine adhesions.Complications encountered during hysteroscopy are inability to distend cavity, excessive bleeding, uterine perforation, flare-up of tuberculosis.[33]

The diagnosis of GTB is made if any of the laboratory tests on tissue specimens like Endometrium/ peritoneal fluid is positive(i.e. AFB smear, culture, histopathology), or if laparoscopy has positive findings. endometrium / peritoneal fluid PCR alone does not confirm tuberculosis. There is no evidence of geneXpert in FGTB.

SUMMARY OF ALL DIAGNOSTIC TESTS

Test	Which patients?	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray to look for evidence of previous or active pulmonary TB.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered VCT. (Voluntary Counselling and Treatment)
Pregnancy test	All	To rule out pregnancy as possible cause of symptoms, and to ensure further testing is safe and appropriate.
Pelvic ultrasound	All	Part of the initial assessment of most patients presenting with gynaecological symptoms.
Hysterosalpingogram	Selected	May be done as part of the investigation of infertility, but many women with FGTB will have a normal HSG.
CT pelvis or MRI pelvis	Selected	To further characterise lesions and plan surgical intervention in selected patients. Disadvantage of CT is exposure to ionising radiation, particularly a concern in women of childbearing age.
FDG-PET CT	Selected	Although not widely available, PET scans may give more information about the presence and activity of tubercular tubulo-ovarian mass lesions. Further evidence about the diagnostic accuracy of PET CT for detecting and monitoring the progression of FGTB is needed.
Endometrial aspirate	Selected	Where facilities exist, endometrial aspirate can be obtained and sent for a) staining and microscopy for AFBs; b) culture and drug susceptibility testing. Sensitivity is low, and negative results cannot rule out FGTB.
Laparoscopy	Selected	Laparoscopy with biopsy of lesions is required when - Other less invasive tests are inconclusive - Malignancy is also suspected Laparoscopy offers the dual advantage of pelvic organ visualization and specimen collection from otherwise inaccessible sites. Specimens should be subject to a) staining and microscopy for AFBs; b) culture and drug susceptibility testing; c) histopathology.

MANAGEMENT

Aim of treatment is to achieve tuberculosis cure in genital tract and to prevent the long term sequalae. If possible effort is made to restore normal anatomy of female genital tract.

All new patients should receive an internationally accepted first-line treatment regimen for new patients and the recommended regimen is using a daily dosing schedule which may include combination tablets. The initial phase should consist of two months of Isoniazid (H), Rifampicin I, Pyrazinamide (Z), and Ethambutol (E). The continuation phase consists of three drugs (Isoniazid, Rifampicin, Ethambutol) for four months

The patients should be given dosages of the drugs depending upon body weight in weight bands. Fixed dose combinations (FDCs) of four drugs (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol) and three drugs (Isoniazid, Rifampicin and ethambutol) are recommended.

TREATMENT PROTOCOLAS PER STANDARD TB CARE

Type of TB CASE	Treatment regimen in IP Initial Phase	Treatment regimen CP Continuation Phase
New	(2)HRZE	(4)HRE
Previously treated	(2)HRZES+(1)HRZE	(5)HRE

DRUG DOSAGE FOR ADULT TB- FIXED DOSE COMBINATIONS

Weight category	Number of tablets(FDC)		Inj. Streptomycin
	Intensive phase HRZE 75/150/400/275	Continuation phase HRE 75/100/275	Gm.
25-39 kg	2	2	0.5
40-54 kg	3	3	0.75
55-69 kg	4	4	1
⩾70 kg	5	5	1

Inj. Streptomycin to be added in IP phase for 2 months in the previously treated regimen of drug sensitive patients

DRUG DOSAGE FOR LOOSE DRUGS

S.No.	Drugs	16-25 kg	26-45 kg	46-70 kg	>70 kg
1	Rifampicin (mg)	300	450	600	600
2	Isoniazid (mg)	200	200	300	450
3	Ethambutol (mg)	400	800	1200	1600
4	Pyrazinamide (mg)	500	1250	1500	2000

Daily Vs Intermittent - It can be given as intermittent (DOTS strategy) under RNTCP where a box is booked per patient with quality assured drug and treatment. It is given under supervision with onus of treatment being on health provider with the aim of not missing any dose even for 1 day.However if the patient has to buy the medicine (patients are not under RNTCP programme), medication must be taken daily.

In Genitourinary disease, 6 months of treatment may be adequate. No difference in efficacy of 6 months vs 9 months ATT. There were equal number of treatment failures(2 in each group)after the end of treatment)[35]

Monitoring of Treatment is done as other EPTB - Follow up depends on initial presenting symptoms. In case of badly damaged tubes, In vitro fertilisation/surrogacy/adoption is to be offered. In case of persistent TO mass, PET CT to be done to determine the activity.

Surgery is not primary treatment in genital tuberculosis, it should be avoided, however it is needed for large, residual TO abscess[30]. Surgery in FGTB is associated with higher complication rates as there are a lot of adhesions as well as possibility of infection flare up. Tubal anatomy should be restored surgically as far as possible in infertile women.

Outcomes (Successful Treatment, Treatment Failure) - End point of treatment is considered as initially diagnosed with microbiology/ HPE, patients with negative respective tests at the end of ATT. If initially diagnosed with laparoscopic findings suggestive of active TB(tubercles, extravasation, fluid in POD), negative relook laparoscopy confirms cure or resolution of clinical symptoms.

Cured Cases -

- If initially diagnosed with microbiology/ HPE patients with negative respective tests at the end of ATT
- If initially diagnosed with laparoscopic findings suggestive of active TB(tubercles, extravasation, fluid in POD), negative relook laparoscopy
- Resolution of clinical symptoms

Confirmed Treatment Failure -

Persistent microbiology / HPE or persistent laparoscopic findings are suggestive of active TB (tubercles, extravasation, fluid in POD) at the end of ATT. Appropriate tissue sample should be obtained for drug sensitivity testing for MDR.

Management of Treatment Failure -

1. Appropriate tissue specimen to be subjected to DST (Drug Sensitivity Test)
2. CAT II treatment (SHRZE for 2 months, RHZE for 1 month, RHE for 5 months)
3. CAT IV treatment for MDR TB

TREATMENT IN SPECIAL GROUPS

- **In pregnancy -** Pregnant women with TB should start or continue ATT in the same way as other patients. These first-line drugs cross the placenta but do not appear to be teratogenic. Streptomycin can cause congenital deafness and prothionamide is teratogenic, so both should be avoided. Ethionamide causes birth defects at high doses in animals. Pyridoxine 10 mg/day is recommended for pregnant women taking isoniazid.
- **In lactating mothers -** Women who are breast-feeding should be given standard TB treatment regimens. Nursing mothers should continue breast feeding as its discontinuation poses a serious risk to the infant's health.
- **Contraception -** Since rifampicin reduces the effectiveness of oral contraceptives, for effective contraception, women should be advised to choose between one of two options for contraception :
- An oral contraceptive pill containing estrogen (50 µg) following consultation with a clinician,
- A non-hormonal method of contraception throughout rifampicin treatment and for at least one month subsequently.

Drug resistant EPTB should be managed by obtaining tissue specimen and subjecting to drug sensitivity testing and ATT should be started accordingly. The duration of the treatment is to be decided as per the guidelines

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Clinical Approach to the Management of Infertility in PCO Patients

Dr. Sonia Malik
& Dr. Neeti Chhabra

- **Obesity has a negative impact on the reproductive outcome in PCO women. It is associated with insulin resistance which in turn is associated with hyperandrogenism and hyperandrogenemia which is a vicious self propagating cycle.**
- **Lifestyle modifications not only help obese PCO women but also lean PCO.**
- **20-60 minutes of physical activity, 3-5 times a week for 6 months is recommended for patients with a BMI of 25Kg/m2. This improves insulin resistance and thus hyperandrogenism leading to improved hormonal profile and ovulation.**
- **Letrozole is used as a first line therapy for ovulation induction in anovulatory infertility. It forms an important modality of treatment in estrogen dependent Breast cancer in postmenopausal women. The recent surge of use of Minimal stimulation protocols in IVF especially for poor responders and PCO patients involves the use of ovulation induction drugs like letrozole and clomiphene citrate. Letrozole is also used as the drug for folliculogenesis in fertility preservation programs in patients with estrogen dependent tumors. It is also used as an ovulation induction drug in frozen thaw embryo transfer cycles.**

INTRODUCTION

Polycystic ovarian syndrome is the most common endocrinopathy affecting women of reproductive age group. It was first described by Stein and Levinthal in 1935 and is linked with anovulation[(1)].It is a heterogenous disorder affecting 5 -10 % of women in this age group. The prevalence of PCOS defined in various studies from India varies between 3.7% to 25.5 % [(2)]. It is the most common cause of anovulatory infertility and involves a triad of oligomenorrhoea ,hyperandrogenism and polycystic appearance of the ovaries on ultrasound. There is an association between PCOS,hyperandrogenism, obesity and insulin resistance. The first association between glucose intolerance and hyperandrogenism was demonstrated by Archard and Thiers in 1921[(3)]in a bearded diabetic woman .Since insulin resistance is high in the Indian scenario therefore the prevalence of PCOS is expected to be higher and India is probably the PCO capital of the world.

CLINICAL APPROACH TO THE MANAGEMENT OF INFERTILITY OF PCO PATIENT

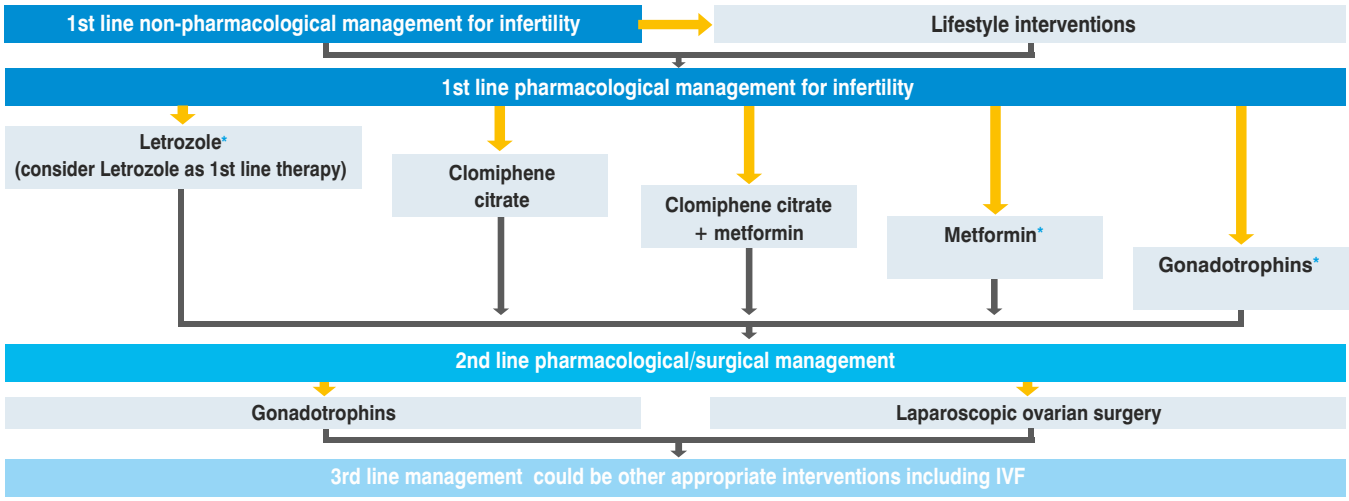

Fig-1 Algorithm for the Management of Infertility in PCO Patient (International PCOS Guidelines 2018) [4]

Women diagnosed with PCOS and desirous of pregnancy should seek treatment early in the course of their reproductive career. A detailed history and physical examination of the couple needs to be done to identify or exclude other associated factors contributing to infertility like endometriosis, thyroid dysfunction, hyperprolactinemia ,infections and male factors. For PCO women with normal semen analysis, the risks, benefit, cost and timing of tubal patency testing should be discussed on an individualized basis[4]. Also, women with PCO with suspected tubal factor infertility should undergo tubal testing prior to ovulation induction[4]. Pure anovulatory infertility is common .Factors like smoking ,alcohol intake, diet, exercise, sleep and mental faculties ,emotional and sexual health need to be optimized in women with PCOS so that the overall reproductive and obstetric outcome can be improved [4].Weight, BMI and blood glucose management has to be along the lines of managing deranged blood sugar-Impaired glucose tolerance and Diabetes Mellitus as insulin resistance is a common factor present in PCOS.

The following text broadly outlines the management of PCOS according to this new guidance.

First line Nonpharmacological -

Lifestyle modifications - Obesity has a negative impact on the reproductive outcome in PCO women. It is associated with insulin resistance which in turn is associated with hyperandrogenism and hyperandrogenemia which is a vicious self propagating cycle . Obesity reduces the chances of spontaneous ovulation in women, causes menstrual abnormalities ,increases rates of miscarriage, complications during pregnancy and adverse perinatal outcomes. Insulin resistance, metabolic syndrome and increased androgens are associated with deranged hormones like increased lutenizing hormone, reduced follicle stimulating hormone and causing menstrual abnormalities in them.

Lifestyle modifications not only help obese PCO women but also lean women with PCO. Those

who achieve weight loss are benefitted but even those who do not , diet and exercise do improve metabolic parameters[5]

A hypocaloric diet helps those with a BMI >25Kg/m2. The aim is to reduce at least 5-10 percent of the present body weight[6].This allows spontaneous ovulation thereby correcting the menstrual abnormalities and improve the chances of conception.

20-60 minutes of physical activity , 3-5 times a week for 6 months is recommended for patients with a BMI of 25Kg/m2 [7]. This improves insulin resistance and thus hyperandrogenism leading to improved hormonal profile and ovulation .

Polycystic ovarian syndrome is associated with sleep, mood and behavioral disorders. Early identification and correction of the same is warranted.

Bariatric Surgery - Bariatric surgery should be included as an important mode of adult weight management .It involves a multidisciplinary team approach which includes the surgeon, dietician, nurse, psychologist and physician. Indications are [8]-

- PCO patients with a BMI >40 Kg/m2
- PCO patients with BMI>35Kg/m2 with obesity related co morbidities (hypertension, diabetes, dyslipidemia, obstructive sleep apnoea and Gastro esophageal reflux disease)
- There is insufficient evidence of the benefit of the procedure in those with BMI<35 Kg/m2 These patients should have tried weight loss for at least 6 months by lifetstyle modifications but have failed to achieve it.

Laparoscopic banding and Biliopancreatic diversion with or without Roux en Y gastric bypass are the procedures offered[8] . Bariatric surgery improves the chances of spontaneous conception[8]. Cycles change from anovulatory to ovulatory by restoring the Hypothalamic pituitary ovarian axis. There is a reduction in hyperandrogenism and insulin resistance[9]. Bariatric surgery prevents and even reverses metabolic syndrome .Cardiovascular risk is greatly reduced[10]. Results of Assisted Reproductive techniques also improve.

The pregnancies thus resulting have a lower chance of gestational diabetes ,large for gestation babies and pre eclampsia on one side but chances of small for gestation babies ,shorter gestation and still births may be higher[11]. The risk of pre term births and babies with congenital malformations is reported to be the same with or without surgery.

It has to be noted that conception has to be planned 12 to 18 months after surgery as this is the period of maximal weight loss and nutritional deficiencies[10][12].

PHARMACO THERAPY -

If the patient compliance with lifestyle is limited, consider pharmacotherapy.

First line pharmacological management -

❖ **Letrozole -** Letrozole is an aromatase inhibitor used in cancer units for estrogen dependent cancers.Till now ,its use as an ovulation induction agent was not allowed due to the associated risk

of congenital malformations[13]. Recent publications have shown no such risk and the drug is back in the market for use in ovulation induction. International 2018 guidelines on PCO[4] have made it the first line drug for ovulation induction in this group of patients.

Letrozole is a competitive inhibitor of enzyme Aromatase (cytochrome P450 dependent enzyme). Starting dose 2.5 mg twice a day for 5 days to a maximum of 7.5mg twice a day for 5 days in successive cycles based on the response.

The drug binds to the heme of aromatase cytochrome P450 subunit in the ovarian follicle, muscle, fat, liver and brain [14]. It prevents the conversion of androgens to estrogen. Levels of estradiol, estrone and estrone sulphate reduce. By negative feedback , the gonadotrophins release from the ovary, allow follicular recruitment and growth. It does not affect adrenal corticosteroid synthesis ,aldosterone synthesis or synthesis of thyroid hormones[15]. The first aromatase inhibitor Aminoglutethemide 's use was discontinued due to the associated adrenal suppression. It's half life is shorter as compared to clomiphene citrate and the elimination time is 48 hours .Maximum suppression is achieved in 48-78 hours[15]. The drug is metabolized in the liver and excreted in bile (85%) and urine (11%).

AROMATASE INHIBITORS

	CLASS I-steroid analogues of androsteindione	CLASS II-non steroidal
FIRST GENERATION	None	Aminoglutethemide
SECOND GENERATION	Formestane	Fadrozole Rogletimide
THIRD GENERATION	Exemestrane	Anastrazole Letrozole

It is used as a first line therapy for ovulation induction in anovulatory infertility. It forms an important modality of treatment in estrogen dependent Breast cancer in postmenopausal women. The recent surge of use of Minimal stimulation protocols in IVF especially for poor responders and PCO patients involves the use of ovulation induction drugs like letrozole and clomiphene citrate. Letrozole is also used as the drug for folliculogenesis in fertility preservation programs in patients with estrogen dependent tumors. It is also used as an ovulation induction drug in frozen thaw embryo transfer cycles.

Letrozole has been proven to have an edge over clomiphene citrate .It does not have the anti estrogenic side effects that clomiphene has over the cervix and the endometrium.It allows monofollicular folliculognesis as compared to more than one in case of clomiphene citrate thus reducing the risk of multiple gestation. The ovulation rates, pregnancy rates and live birth rates are higher with letrozole as compared to clomiphene citrate. The ovulation rates are 75%and pregnancy rates are 25 % with letrozole[16].

When letrozole is compared to gonadotrophins, there is a lower incidence of Ovarian hyperstimulation and multifetal gestation with letrozole. It is a cheaper alternative to gonadotrophins and when combined with them ,the overall dose of gonadotrophins needed and thus the cost are reduced.

Side effects associated with Letrozole occur only after long term suppression. They are bone pain(20%),hot flushes(18%),back pain(17%),nausea (15%)and dyspnea(14%) .

Anastrazole is a third generation class II Aromatase inhibitor .There are no advantages of the drug over clomiphene citrate and has a weaker effect on follicular growth than clomiphene. [17,18,19]

❖ **Clomiphene citrate -** Clomiphene citrate was the first lone drug used for ovulation induction in PCOS until recently. It is still the most widely used drug for ovulation induction[20][21]. It is a selective estrogen receptor modulator (SERM).It competes with endogenous estrogen for estrogen receptor binding sites.There are two chemical types of clomiphene-Zu clomiphene and En clomiphene. Clomiphene citrate circulates in the body for 2 weeks[22] thus having a cumulative antiestrogenic effect on the endometrium and cervix after multiple back to back cycle usage.

It competes with endogenous estrogen for its receptor binding sites thus creating a hypoestrogenic environment. This allows gonadotrophin release from the pituitary for follicular growth and recruitment . The starting dose is 50 mg per day for 5 days from cycle day 3 to cycle day 7 to a maximum of 150 mg per day for 5 days.It's use is allowed for a maximum of 6 cycles in a lifetime because the -

- cumulative pregnancy rate after 6 cycles is 65%[23].
- The ovulation rates vary from 75% to 80%
- The pregnancy rates in ovulatory cycles is 22%.

This discrepancy seen is due to the hypoestrogenic effects seen on the cervix and endometrium. Clomiphene citrate is still the most commonly and easily available drug for ovulation induction. It leads to multifollicular development as compared to monofollicular development with letrozole. It is cheap, orally administrable and a safer alternative to gonadotrophins but the ovulation and pregnancy rates are lower due to clomiphene resistance and failure. Clomiphene resistance is failure to ovulate after 150 mg per day dose of the drug and is seen in 15 to 40 % of PCO cases[24]. Gonadotrophins do not have the associated antiestrogenic side effects and lead to higher live birth rates and over all pregnancy rates as compared to clomiphene citrate[25].

❖ **Gonadotrophins -** Recombinant Follicle stimulating hormone (r FSH), Urinary Follicle stimulating hormone (u FSH) and Human Menopausal Gonadotrophin(HMG) are the commonly used gonadotrophins for ovulation induction in clomiphene or letrozole resistant or failure cases. According to the Cochrane review ,there is no difference in the live birth rates and incidence of Ovarian hyperstimualtion rates between rFSH ,uFSH and HMG preparations[26]. Treatment outcomes depend upon the administered dose rather than the nature of gonadotrophins[27].

Gonadotrophins are used as second line pharmacologic treatment for ovulation induction in PCO. They are indicated in PCO patients who either fail to ovulate or fail to conceive after letrozole or clomiphene citrate. They form first line drug for ovulation induction in older anovulatory women [28].

Gonadotrophins can be used in a step up or a step down protocol. The type of protocol chosen is based on the age of the patient ,duration of infertility and tests of ovarian reserve like AMH and AFC.In a step up protocol ,the starting dose is 37.5 IU to 75IU per day[23] .Based on the response after 7 days ,the dose titration is done .Monofollicular ovulation rate is 70 % and pregnancy rate is 20%[23]. In the step down protocol, we start with a higher dose and the dose is reduced based upon the response.

The ovulation and pregnancy rates of gonadotrophins are higher as compared to letrozole and clomiphene . The time to pregnancy is shorter with a higher live birth rate. Gonadotrophins are expensive and need closer monitoring by a specialist using ultrasound and serum hormones . The risk of ovarian hyperstimulation and multifetal gestation is higher.

Second line surgical management –laparoscopic ovarian drilling - Laparoscopic ovarian drilling (LOD)involves reducing the ovarian cortical tissue and the associated androgenic environment using laser or heat in patients with PCOS. It involves making 3-8 punctures in the ovarian cortex using heat (monopolar or bipolar cautery)[29] or laser to reduce the androgenic mileu. 600 to 800 J of heat energy is used . The levels of inhibin also reduce.

LOD should be considered after considering the prognostic factors and carrying out a risk –benefit cost balance[29]. It is used in clomiphene or aromatase inhibitor resistant cases[23] or as an alternative to gonadotrophins in patients with a BMI <30 Kg/m2 and serum LH levels of >10 IU/L.It can be combined with other laparoscopic surgeries for infertility like checking the tubal patency in doubtful cases.

Laparoscopic ovarian drilling reduces androgens and serum LH levels. Levels of FSH increase . It improves the blood flow to the ovaries by increasing post surgery local growth factors thus improving the response to gonadotrophins. LOD also improves insulin sensitivity. All this improves the follicular recruitment, growth, dominance and ovulation.

In many cases ,there is a theoretical reduction in the ovarian reserve although recent studies are contrary to this fact. LOD causes post operative adhesions in the peri ovarian area [30] especially if large number of punctures are used[23]. There is an associated risk of infection and anesthesia related complications. Rarely, bowel perforation and hemorrhage requiring laparotomy are encountered.

Factors which predict success with LOD are the absence of obesity, duration of infertility<3 years, basal LH>10IU/L ,Testosterone <4.5 nmol/L and basal AMH <7.7 ng/ml[31] . PCO patients with increased LH either naturally or in response to clomiphene benefit from LOD[23].

There is no data on the role of repeated LOD and such practice should be avoided[23].

ORAL HYPOGLYCEMIC AGENTS – METFORMIN AND INOSITOLS AND THEIR APPLICATION IN INFERTILITY

Metformin - Metformin was first introduced in 1957 and is commonly used in the treatment of insulin resistance manifesting as Type 2 diabetes or polycystic ovarian syndrome (PCOS). With an increasing number of these patient conceiving, its use in and around pregnancy has increased.

Pharmacodynamics & Pharmacokinetics - Metformin is a dimethyl biguanide - only biguanide that is used now days.

Insulin stimulated flux of glucose into cells depends on IP3 – increasing activity and cycling of GLUT-4 glucose transporting protein. Metformin augments insulin dependent (GLUT 4) and insulin independent (GLUT4 and GLUT 3) cellular uptake of glucose.

Mechanism of Action - It has antihyperglycemic effect by following mechanisms →.

1. Increased peripheral cellular glucose uptake.
2. Reduced hepatic gluconeogenesis – contributing to post absorptive and postprandial plasma glucose lowering effect.
3. Reduced absorption of glucose
4. Reduces basal hepatic glucose output in patients with Type 2 DM, providing an important mechanism through which the drug lowers fasting plasma glucose concentration.

Actions of Metformin in PCOS

- Reduces hyperinsulinemia
- Decrease in intraovarian androgens
- Reduction in Estradiol levels
- Favours orderly follicular growth in response to exogenous gonadotrophins.
- Decrease in testosterone, free testosterone, DHEAS, Androstenedione LH
- Normalization of LH: FSH ratio
- Increase in SHBG.

Indications for Metformin use -

1. PCOS patients with increased androgens
2. Documented ovulation induction failure after clomiphene with BMI > 25.According to SOGC guidelines 2010[32], Metformin can be added to Clomiphene citrate for ovulation induction in women who are older and have visceral obesity.
3. Documented insulin resistance by blood sugar and serum insulin values.According to Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group[23] there is no clear role for insulin sensitising and insulin lowering drug in the management of PCOS, and should be restricted to those patients with glucose intolerance or type 2 diabetes rather than those with just insulin resistance.

Cochrane review on the use of Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility[33].

Forty-four trials (3992 women) were included for analysis, 38 of them using metformin and involving 3495 women.There was no evidence that metformin improved live birth rates, whether it was used alone (pooled OR 1.80, 95% CI 0.52 to 6.16,3 trials, 115 women) or in combination with clomiphene (pooled OR 1.16, 95% CI 0.85 to 1.56, 7 trials, 907 women). However,clinical pregnancy rates were improved for metformin versus placebo (pooled OR 2.31, 95% CI 1.52 to 3.51, 8 trials, 707 women) and for metformin and clomiphene versus clomiphene alone (pooled OR 1.51, 95% CI 1.17 to 1.96, 11 trials, 1208 women). In the

studies that compared metformin and clomiphene alone, there was evidence of an improved live birth rate (pooled OR 0.3, 95% CI0.17 to 0.52, 2 trials, 500 women) and clinical pregnancy rate (pooled OR 0.34, 95% 0.21 to 0.55, 2 trials, 500 women) in the group of obese women who took clomiphene. Metformin was also associated with a significantly higher incidence of gastrointestinal disturbances than placebo (pooled OR 4.27, 95% CI 2.4 to 7.59, 5 trials, 318 women) but no serious adverse effects were reported.

Cochrane review on the use of Metformin during ovulation induction with gonadotrophins followed by timed intercourse or intrauterine insemination for subfertility associated with polycystic ovary syndrome[34]

Five RCTs (with 264 women) comparing gonadotrophins plus metformin versus gonadotrophins alone were included . The gonadotrophin used was recombinant FSH in four studies and highly purified FSH in one study. The results were as follows-

Metformin plus FSH was associated with a higher cumulative live birth rate when compared with FSH (odds ratio (OR) 2.31, 95%confidence interval (CI) 1.23 to 4.34; two RCTs, n = 180; I2 = 0%; low-quality evidence). This suggests that if the chance of live birth after FSH is assumed to be 27%, then the chance after addition of metformin would be between 32% and 60%.Also Metformin use was associated with a higher ongoing pregnancy rate (OR 2.46, 95% CI 1.36 to 4.46; four RCTs, n = 232; I2 = 0%; low-quality evidence) and a higher clinical pregnancy rate (OR 2.51, 95% CI 1.46 to 4.31; five RCTs, n = 264; I2 = 0%; low-quality evidence).There was no evidence of a difference in multiple pregnancy rates between metformin plus FSH and FSH (OR 0.55, 95% CI 0.15 to 1.95; four RCTs, n = 232; I2 = 0%; low-quality evidence) and no evidence of a difference in rates of miscarriage or OHSS.

Cochrane review on the use of Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome[35]

Nine randomised controlled trials involving a total of 816 women with PCOS. When metformin was compared withplacebo there was no clear evidence of a difference between the groups in live birth rates (OR 1.39, 95% CI 0.81 to 2.40, five RCTs,551 women, I2 = 52%, low-quality evidence). It suggests that for a woman with a 32 % chance of achieving a live birth using placebo, the

corresponding chance using metformin treatment would be between 28% and 53%.When metformin was compared with placebo or no treatment, clinical pregnancy rates were higher in the metformin group (OR 1.52;95% CI 1.07 to 2.15; eight RCTs, 775 women, I2 = 18%, moderate-quality evidence). This suggests that for a woman with a 31%chance of achieving a clinical pregnancy using placebo or no treatment, the corresponding chance using metformin treatment would be between 32% and 49%.

The risk of ovarian hyperstimulation syndrome was lower in the metformin group (OR 0.29; 95% CI 0.18 to 0.49, eight RCTs, 798women, I2 = 11%, moderate-quality evidence). This suggests that for a woman with a 27% risk of having OHSS without metformin the corresponding chance using metformin treatment would be between 6% and 15%.Side effects (mostly gastrointestinal) were more common in the metformin group (OR 4.49, 95% CI 1.88 to 10.72, for RCTs, 431women, I2=57%, low quality evidence).

Initiating and monitoring therapy with metformin - Metformin has potential advantage of targeting insulin resistance, thus reducing plasma insulin levels. Metformin also reduces adipose tissue mass The risk of hypoglycemia is much less with metformin as compared to other hypoglycemic agents (insulin).

Metformin should be taken with meals, (to decrease/prevent gastrointestinal side effects). Starting dose of 500 mg twice a day, which can slowly be increased upto 2 gm/day. Patients starting metformin therapy should have baseline liver function test and renal function test. Also, patients should be advised that they may have minor gastrointestinal side effects. These include diarrhea, abdominal discomfort, anorexia, nausea and rarely, a metallic taste in mouth. The symptoms are dose related and reduce if the dose is decreased.

Inositols in PCOS [36] - In 1850 Johannes Scherer isolated inositol from muscle cells and it was formally included in the sugar family. One of these, myo-inositol (MYO) is the most common in all biological systems and both myoinositol and D –chiro inositol are important.They are found in cereals,nuts,fruits and in human cells.

Mechanism of Action – The inositols are important in glucose homeostasis and serve as second messengers in signal transduction cascade of insulin.Once MYO enters the cell, it is immediately converted to phosphatidyl-myo-inositol,precursor of the inositol-triphosphate (IP3)in the cell membranes. IP3acts as intracellular second messenger for insulin as well as for FSH and TSH.

PCO and Inositol Deficiency - In PCO women, the metabolism of inositols is dysregulated . The insulin resistance and compensatory hyperinsulinemia due to dysregulation of inositol metabolism may actually be the major underlying cause of the disorder. It was shown that an increased activity of epimerase in theca cells of ovaries of PCOS women is associated with a reduction in the intraovarian ratio of Myo-Insositol to D-chiro-Inositol .This causes oligo ovulation and poor oocyte quality. Thus,Myo-Inositol and D-chiro-Inositol supplementation in a physiological ratio(40:1) is important to restore normal ovarian function. This is called the DCI paradox according to which Myo-Ins rather than D-chiro-Ins improved oocyte quality in intracytoplasmic sperm injection

cycles. There is a synergistic action of Myo-Ins and D-chiro-Inositol in overweight PCOS women as Myo-Ins improves the ovulatory function and D-chiro-Ins rapidly reduces the peripheral hyperinsulinemia.

It has also been seen that hormonal parameters improved significantly in all PCOS patients treated with Myo-Inositol.There is a reduction in the body weight and circulating leptin levels decreased with an increase in HDL concentrations .This may prove to be cardio protective in PCOS women. The dose of gonadotrophins and the duration of stimulation is greatly reduced when Myoinositol was given to PCOS during IVF cycles. Myo-Inositols also improve the pregnancy rate in PCOS women.Supplementation also reduces the number of germinal vesicles and immature oocytes with an increase in the mature oocyte numbers.

Third line management:

ART in PCOS - Ovulation induction therapies are first and second line in infertility management in women with PCOS, anovulation and no other fertility factors. Resistance to and failure of ovulation induction therapies and inability to overcome other concomitant causes of infertility is an indication for Assisted Reproductive Technology (ART) including In-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

IVF has risks and limitations, yet also offers the opportunity for pregnancy and live birth in these difficult patients. Different challenges exist with the diversity of phenotypes and multiple protocols available for IVF and concerns in PCOS including OHSS, high oestradiol levels, accelerated endometrial maturation and optimal use of "freeze all" interventions. Hence, the recommendation is to use segmental IVF with a gonadotropic/ antagonist protocol, an agonist trigger, and freeze all embryos and a subsequent frozen embryo transfer in an artificially prepared endometrium [37].

CONCLUSION

PCOS is a complex disorder characterized by multiple phenotypes that makes its management difficult. Each patient therefore requires a personalized plan to resolve infertility. Life style modifications with diet and exercise remain the mainstay along with a single or a combined medical – surgical approach.

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Ovulation Induction Protocols

Dr Kamini A. Rao
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- **FSH window means that the follicular growth is maintained as long as the FSH level remains above the follicle's threshold. In a natural,cycle; as the follicle with lowest FSH threshold begins to secrete estrogen, pituitary FSH secretion is suppressed through negative feedback on hypothalamo-pituitary axis. The decline in FSH concentration is insufficient to sustain the development of other follicles with higher FSH thresholds which become non-ovulatory and undergo atresia but the dominant follicle grows.**
- **LH threshold is the amount of LH activity actually necessary for normal follicle and oocyte development. LH ceiling is the amount of LH beyond which it is detrimental for oocyte development. Thus, LH threshold and ceiling is the genesis for the concept of "LH window".**
- **There is good evidence that combination of Metformin and Clomiphene has higher ovulation and pregnancy rates when compared to clomiphene alone but there is no similar improvement in live birth.**
- **In some anovulatory women, addition of glucocorticoids to CC treatment may induce ovulation successfully. The benefit is most notable in women with serum DHEAS concentration of 200µg/dL or more. Dexamethasone 0.5-2mg / Prednisolone 5 mg daily during follicular phase (D5-14) is administered.**

Anovulation is one of the most important causes of female infertility. 18-25% of infertile females have ovulatory disorders [(1)]. Anovulation as the sole cause for infertility marks a good prognosis for pregnancy; as modern ovulation strategies are highly effective.

BRIEF OVERVIEW OF FOLLICULOGENESIS:

The normal menstrual cycle is the cycle of changes that occur in the ovary and uterus resulting in the production of eggs and preparation of the uterine endometrium that is essential for reproduction (Fig 1). It is under the control of the neuroendocrine system and the hypothalamic-pituitary-ovarian (HPO) axis [(3)].

A fixed number of primordial follicles are endowed during early life and are maintained in a resting state (Table 1). Growth of some of these dormant follicles is initiated before and throughout reproductive life (Initial recruitment). Follicles develop through primordial, primary, secondary and antral stages. At the antral stage, most follicles undergo atresia. However; under optimal gonadotropin stimulation that occurs after puberty, a few of them are rescued (Cyclic recruitment) to reach the preovulatory stage[5]. Eventually, depletion of the pool of resting follicles leads to ovarian senescence.

TABLE 1: DIFFERENCE BETWEEN INITIAL AND CYCLIC RECRUITMENT OF OVARIAN FOLLICLES

	INITIAL RECRUITMENT (Initiation of Growth)	CYCLIC RECRUITMENT (Escape from atresia)
STAGES	Primordial	Antral (2-5mm in diameter)
HORMONES INVOLVED	Not determined	FSH
DEFAULT PATHWAY	Remain dormant	Apoptosis
TIMING	Continuous throughout life; begins after follicle formation	Cyclic; starts after puberty onset
OOCYTE STATUS	Starting to grow; not capable of undergoing germinal vesicle breakdown	Completed growth; competent to undergo germinal vesicle breakdown

ROLE OF FSH AND LH IN OVULATION INDUCTION

FSH Threshold: The concept of FSH threshold (Figure 1) was described by Brown [2]. It is the minimum amount of FSH secretion required to induce follicular growth. The follicle whose granulosa cells are most responsive to FSH; that is; lowest FSH threshold becomes first in the cohort to secrete estrogen.

FSH Window: This concept was described by Baird[2]. It means that the follicular growth is maintained as long as the FSH level remains above the follicle's threshold. In a natural cycle as the follicle with lowest FSH threshold begins to secrete estrogen, pituitary FSH secretion is suppressed through negative feedback on hypothalamo-pituitary axis (Figure 2). The decline in FSH concentration is insufficient to sustain the development of other follicles with higher FSH thresholds which become non-ovulatory and undergo atresia. In contrast, maintaining the FSH levels above the threshold of the dominant follicle and widening the window until the final stages of follicular development plays a key role in multifollicular development (Figure 3).

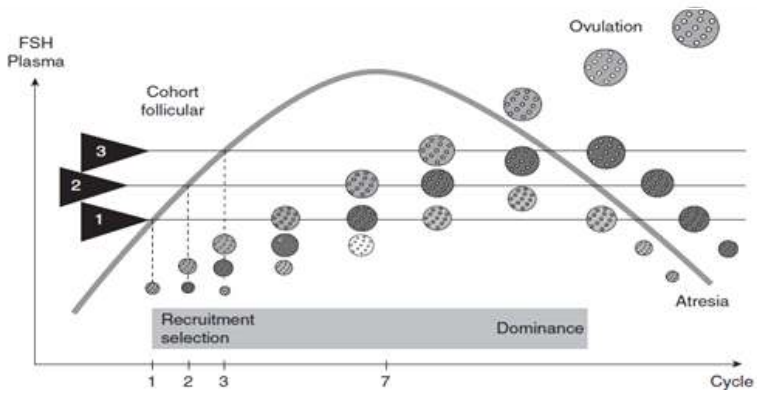


Figure 1: FSH threshold and window concepts

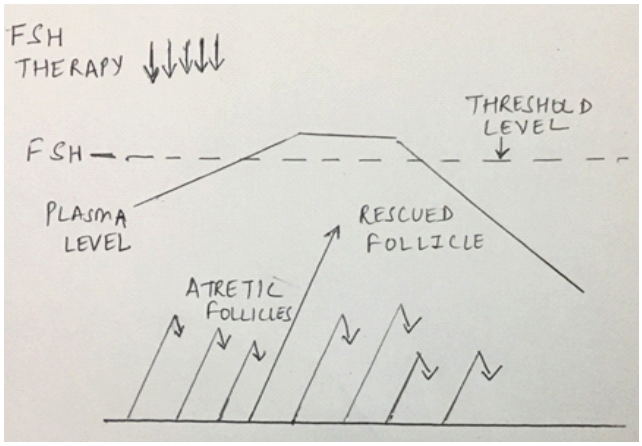


Figure 2: Natural cycle: When FSH is above threshold, one follicle will be rescued and rest will become atretic

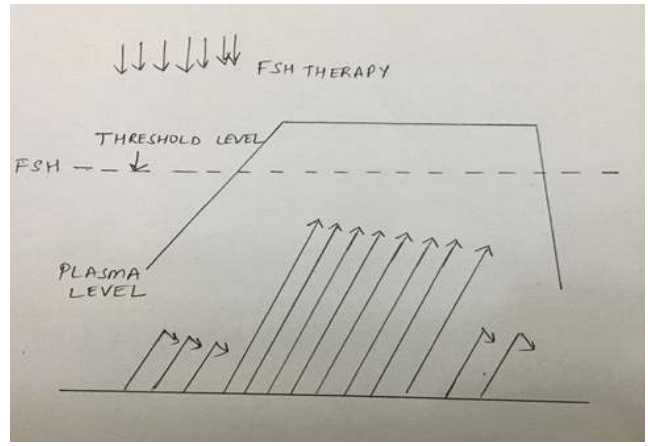


Figure 3: Stimulation of multifollicular development: Maintenance of suprathreshold FSH level during the time of multiple follicular recruitment

LH Threshold and Ceiling: LH threshold is the amount of LH activity actually necessary for normal follicle and oocyte development. LH ceiling is the amount of LH beyond which it is detrimental for oocyte development. Thus, LH threshold and ceiling is the genesis for the concept of "LH window" (Figure 4) which exists during the follicular phase of menstrual and induced cycles. Hence, LH levels should neither be too high nor too low during ovulation induction[2].

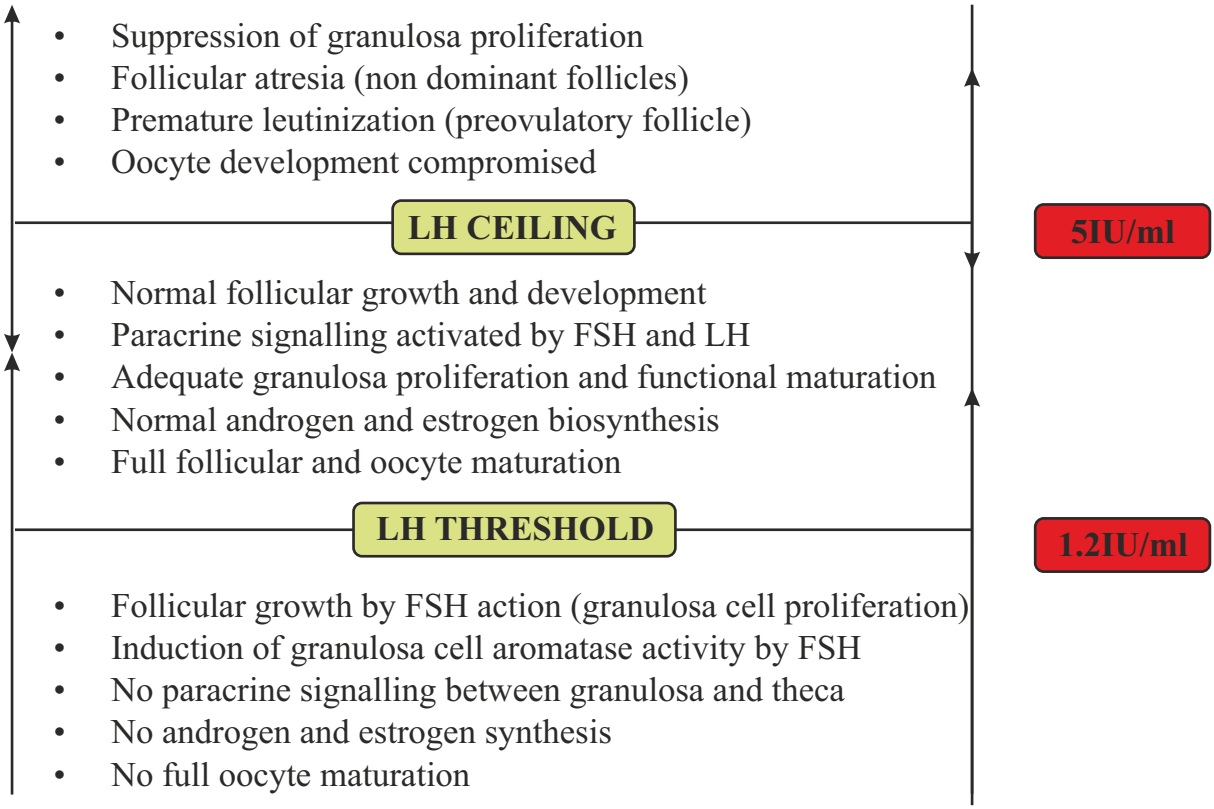


Figure 4: The LH threshold and ceiling concept

PRETREATMENT EVALUATION AND TREATMENT

The causes of anovulation are varied like thyroid disease, hyperprolactinemia, adrenal disease, polycystic ovarian syndrome (PCOS), pituitary or ovarian tumours, eating disorders and obesity. Treatment should be directed at the underlying cause. Anovulatory women should be screened for thyroid disorders (serum TSH) and hyperprolactinemia because both require specific treatment. Screening for impaired glucose tolerance and diabetes is recommended for all obese women anovulatory women; as 35% exhibit impaired glucose tolerance and 7-10% have type 2 diabetes mellitus[1].

Before beginning ovulation induction, screening semen analysis should also be done as male factors contribute to 20-40% of infertility. Additional preliminary investigation includes hysterosalpingography (HSG) to establish tubal patency; especially in women with history of previous pelvic infection or surgery, ectopic pregnancy, pelvic pain or other symptoms of endometriosis. Preliminary HSG and transvaginal ultrasound are recommended when there is a suspicion of co-existing uterine or tubal factors for infertility, women over 35 years of age and when ovulation induction requires treatment with exogenous gonadotropins [1].

The best initial treatment for obese anovulatory women is weight loss and lifestyle modifications; as even 5-10 % of weight loss often restores ovulatory cycles.

GROUP	INCIDENCE	TYPE OF ANOVULATION	HORMONAL LEVELS	EXAMPLE
GROUP I	5-10%	HYPOGONADOTROPIC HYPOGONADAL	↓ or normal FSH Low E2	Kallmann syndrome, Sheehan syndrome, physical, nutritional or emotional stress , Isolated Gonadotropin deficiency
GROUP II	75-85%	EUGONADOTROPIC EUESTROGENIC	Normal FSH Normal E2	PCOS
GROUP III	10-20%	HYPERGONADOTROPIC	↑ FSH ↓ E2	Premature Ovarian Failure
GROUP IV Hyperprolactinemia	5-10%	HYPERPROLACTINEMIC	Low to normal FSH Low E2 High Prolactin	

Table 2: WHO classification of ovulatory disorders

OVULATION INDUCTION is defined as stimulation of ovulation indicated for women who do not ovulate on their own regularly, with the aim of achieveing one dominant follicle in one cycle.

SUPEROVULATION is defined as stimulation of ovulation in an already ovulating woman with the aim of achieveing at least 2 dominant follicles in one cycle.

OVULATION INDUCTION IN WHO CLASS I GROUP:

Ovulation induction is done with Urinary derivatives of HMG contain 75 IU of FSH and LH and are used as substitution therapy in women with primary hypogonadotropic hypogonadism and secondary idiopathic hypogonadotropic hypogonadism. Alternatively, recombinant FSH and LH can be used in combination, although the costs are vastly greater. A dose of 75 IU rLH needs to be supplemented with 150 IU of rFSH, as per the dose finding study by European recombinant Human LH study group 1998 [2,6]. Ovulation induction can also be done with pulsatile GnRH therapy. GnRH is administered intravenously in low doses (2.5-5µg/pulse) at a constant interval (every 60-90 min). It is successful in achieving ovulation rates upto 90% and cumulative pregnancy rates of 96% after 6 cycles.

OVULATION INDUCTION IN WHO CLASS II GROUP:

This is the commonest type of anovulatory disorder comprising almost 75-85%; PCOS being the commonest cause. Anovulation in PCOS is best explained by Lacker's model (7). It demonstrates that follicular dynamics in PCOS women is different from normally ovulating females as in PCOS, there are periods of amenorrhoea with interspersed normal cycles.

According to this model, each follicle has two properties: (i) its initial maturity as it enters the terminal phase and (ii) its sensitivity to gonadotropins for any given level of maturity. In anovulatory cycles, one or more follicles with higher sensitivity are relatively more mature enter the beginning of the selection phase resulting in arrest of all follicles. The only way to obtain a model exhibiting ovulation of a single follicle and arrest of a number of follicles is to have a population of follicles with mixture of different sensitivities. Uniformly "low sensitivity" follicles give rise to normal ovulatory cycles and uniformly "high sensitivity" results in follicular arrest leading to anovulation. The oocytes in follicles of PCOS patients do not have normal developmental potential. Superovulation helps in these cases as these ovaries also contain sufficient number of healthy follicles.

OVULATION INDUCTION IN PCOS:

1. ORAL OVULOGENS : CLOMIPHENE CITRATE
   AROMATASE INHIBITORS : LETROZOLE, ANASTRAZOLE
   SERMS : TAMOXIFEN
   INSULIN SENSITIZERS : METFORMIN
2. INJECTABLE : GONADOTROPINS
   GnRH ANALOGUES
3. LAPAROSCOPIC OVARIAN DRILLING

Other indication where ovulation induction can be tried with oral or injectable ovulogens is in cases of unexplained infertility.

ORAL OVULOGENS

CLOMIPHENE CITRATE (CC) :

Clomiphene citrate is a nonsteroidal triphenylethylene derivative exhibiting both estrogenic and anti-estrogenic properties. Estrogenic agonistic properties are exhibited only when endogenous estrogen levels are very low. As currently manufactured, CC is a mixture in a ratio of 3:2 of two geometric isomers, enclomiphene and zuclomiphene. Enclomiphene is a more potent isomer primarily responsible for ovulation induction[8].

Mechanism of action :

It acts at the hypothalamic level and binds to nuclear estrogen receptors(ER) for an extended period of time and ultimately depletes ER concentrations by interfering with the normal process of ER replenishment. Reduced estrogen feedback alters the pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion to stimulate increased pituitary gonadotropin release and in turn increased ovarian follicular activity. In ovulatory women, CC increases GnRH pulse frequency whereas in PCOS; where the frequency is already high, CC increases GnRH pulse amplitude. After CC administration, there is rise of both FSH and LH and then they fall after the typical 5-day course is completed. LH surge occurs 5-12 days after the last dose of CC [8].

Treatment Regimens:

1. Standard Therapy :

Clomiphene citrate is administered orally, typically for 5 days from Day 2 to Day 6 after the onset of spontaneous or progestin induced menses. The starting dose is usually 50mg/day and can be increased upto 150mg/day (FDA approved). Ovulation rates with increasing dose of CC (Table 3):

Dose	Ovulation Rate
50mg	52%
100mg	22%
150mg	12%
200mg	7%

Table 3: Ovulation Rates with Clomiphene citrate

Dose	Conception rate after 3 months	Conception rate after 6 months
50mg	50%	62%
100mg	45%	66%
150mg	33%	38%

Table 4: Cumulative Pregnancy Rates after 3-6 months with Clomiphene citrate

The overall cumulative pregnancy rate with this conventional CC step up regimen is 55-73%.

2. Stair Step Protocol :

In this protocol (Figure 5), once failure to ovulate is recognized by day 14-21, higher dose of CC is started immediately without inducing a withdrawl bleed. This protocol has the advantage of achieving ovulation in a shorter time when increasing doses of CC are required. The time to ovulation was 32-53 days less with the stair-step protocol compared with a traditional regimen. Dose-dependent ovulation rate was 64% at 100 mg with the stair-step protocol compared with 22% with a traditional regimen[8,9].

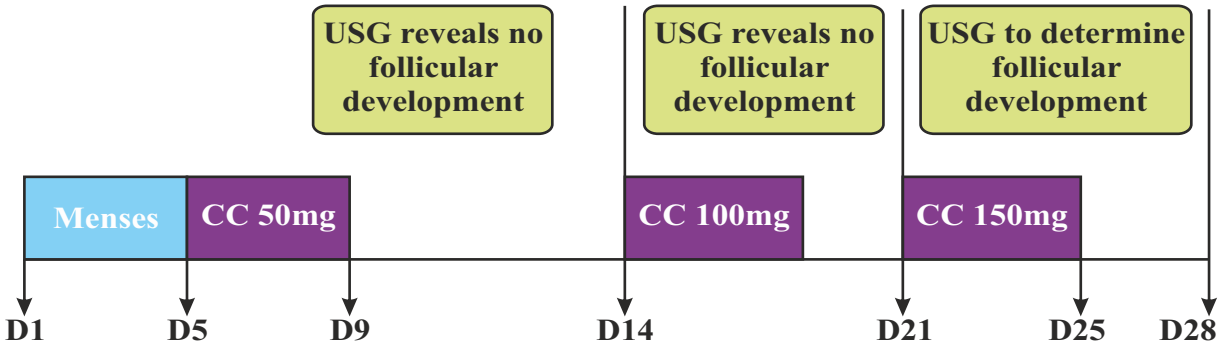


Figure 5: Stair Step CC Protocol

3. Extended CC Regimen :

Those who fail to ovulate with traditional 5-day course, extended treatment for 7-10 days is sometimes useful; although there is no conclusive evidence to support this regimen[8].

Side Effects of Clomiphene Citrate:

1. Mood Swings (Most common – 64%-78%)
2. Hot flushes (10%)
3. Breast tenderness, Pelvic discomfort, nausea – 2-5%
4. Transient visual disturbances – indication to stop CC
5. Optic neuritis – Rare
6. Peripheral Effects - Clomiphene citrate has anti-estrogenic effects on endometrium and cervical mucus which is probably responsible for pregnancy rate of 30-40% despite ovulation rate of 70%[4].

CC Resistance : Clomiphene resistance is defined as failure to ovulate despite using CC of 150 mg /day for 5 days for 3 cycles.

Treatment of CC Resistance :

1. CC and Metformin
2. CC and Glucocorticoids
3. CC and Gonadotropins

CC and Metformin:

Some anovulatory women with PCOS may respond to CC combined with metformin. Two well designed RCTs have shown superior ovulation and live birth rates with Clomiphene when compared to Metformin alone [10, 11]. There is good evidence that combination of Metformin and Clomiphene has higher ovulation and pregnancy rates when compared to clomiphene alone but there is no similar improvement in live birth[10,11].

Clomiphene Citrate and Glucocorticoids:

In some anovulatory women, addition of glucocorticoids to CC treatment may induce ovulation successfully. The benefit is most notable in women with serum DHEAS concentration of 200µg/dL or more. Dexamethasone 0.5-2mg / Prednisolone 5 mg daily during follicular phase (D5-14) is administered. Two large trials evaluated CC resistant anovulatory patients with normal DHEAS levels. Those treated with dexamethasone and CC had ovulation rate of 75-88% with 40% conception rates whereas those treated with CC alone had 15-20% ovulation rate and 5% conception rate. Treatment can be continued for 3-6 cycles when it is successful and should be discontinued immediately if not [8].

Clomiphene Citrate and Gonadotropins:

Sequential CC/gonadotropin therapy is given in CC resistant women and those with unexplained infertility. The typical cycle includes standard CC treatment regimen, followed by low dose human menopausal gonadotropin (hMG) or FSH (75-250IU/day) for 3 days. The gonadotropins can also be administered on alternate days following standard CC therapy. CC resistant anovulatory women are extremely sensitive to low doses of gonadotropins and treatment should be aimed at achieving ovulation of a single mature follicle[8].

CC FAILURE:

Clomiphene failure is defined as failure to conceive after 3 cycles of CC therapy despite ovulation. The treatment includes change of ovulation induction agents like aromatase inhibitors or gonadotropins.

AROMATASE INHIBITORS:

Aromatase or "estrogen synthase" is the enzyme catalysing rate limiting step in estrogen synthesis and is thus a good target for selective inhibition. Aromatase enyme is expressed in ovaries, brain, muscle, liver, breast tissue and malignant tumours like breast tumours. Ovaries are the main source of estrogen during reproductive age whereas, after menopause, most of the circulating estrogen comes from adipose tissue [4].

	AROMATASE INHIBITORS	INHIBITORS (SUICIDAL INHIBITORS)
MECHANISM OF ACTION	Works by temporary (reversible) inactivation of aromatase enyme	Works by permanent (irreversible) inactivation of aromatase enzyme
First Generation	Aminoglutethimide	NA
Second Generation	Rogletimide Fadrozole	Formestane
Third Generation	Letrozole Anastrozole Vorozole	Exemestane

Table 5: Generations of Aromatase Inhibitors[4]

Most commonly used aromatase inhibitors for ovulation induction are non-steroidal belonging to third generation, that is letrozole and anastrozole.

Mechanism of action: Aromatase inhibitors act via both central and peripheral mechanisms. By reducing whole body estrogen synthesis and lowering circulating estrogens releases the hypothalamus and/or pituitary from negative feedback of estrogen on the production and release of gonadotropins. There is no depletion of estrogen receptors unlike clomiphene citrate. Peripherally, aromatase inhibition increases ovarian follicular sensitivity to FSH stimulation. This results from intraovarian accumulation of androgens due to inhibition of aromatase enyme blocking the conversion of androgens into estrogens [4].

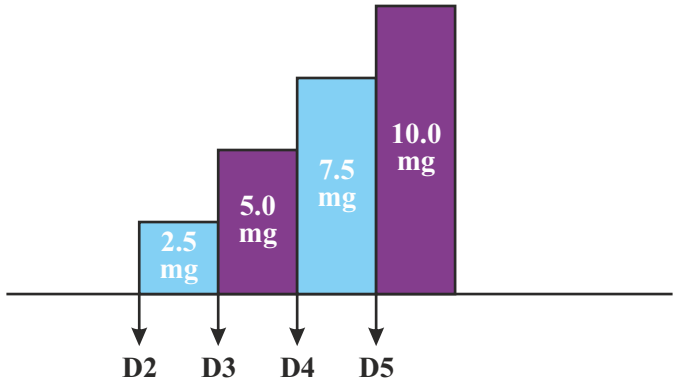
Treatment Regimens:

1. **Conventional Regimen :** Letrozole is administered orally in a dose of 2.5-5mg/day for 5 days from day 2 to day 6 after the onset of spontaneous or progestin induced menses. It is rapidly eliminated due to its shorter half-life of 45 hours; hence there is late follicular rise in circulating estrogen thereby enhancing endometrial development and subsequently increased chances of pregnancy. The rising estrogen levels may also result in shorter FSH window; mimicking the physiological cycle with subsequent ovulation (mono-ovulation) and a lower risk of multiple pregnancy[3,12].

   Ovulation Rate: 70-84%
   Pregnancy Rate: 20-27% per cycle
2. **Letroz Step-Up Protocol :** It involves administration of gradually increasing dose of letrozole from day 2 to day 5 after onset of spontaneous or progestin induced menses.

   This regimen leads to prolonged suppression of estrogen levels. In the first few days of administering aromatase inhibitor, rising levels of endogenous gonadotropins stimulate proliferation of granulosa cells with the induction of more aromatase expression and

breakthrough estrogen production. To prevent rising estrogen from suppressing endogenous FSH and to extend the window of increased endogenous gonadotropins, more aromatase inhibition is required which is accomplished by increasing the dose of aromatase inhibitor. The increased duration of elevated FSH results in multifollicular development[13].



3. **Letrozole with Gonadotropins -** Gonadotropins can be added after a conventional letrozole therapy or a step-up letrozole therapy. They can be administered on a daily or an alternate day regimen. There is a significant reduction in the gonadotropin dose (45-55%) when letrozole is added to gonadotropin regimen. This protocol can also be practiced in mild stimulation IVF regimen which significantly reduces the cost of infertility treatment by decreasing the requirement of gonadotropin dose [4].

Letrozole Versus CC - Letrozole is now recommended as the first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates. Where letrozole is not available or use is not permitted, other ovulation induction agents should be used [15].

In a double blind, multicentre trial [14], involving 750 women, the cumulative ovulation rate is higher with letrozole (61.7%) as compared to clomiphene citrate (48.3%). There is also increased cumulative live birth with letrozole (27.5%) as compared to clomiphene citrate (19.1%). The likelihood of live birth is increased 40-60% with letrozole compared to clomiphene.

The other third generation aromatase inhibitor used is Anastrozole. 1mg of anastrazole is equivalent to 2.5 mg of letrozole in estrogen suppression. It is equally efficient as letrozole with respect to ovulation rate and pregnancy rate, at similar costs.

Side Effects :

1. Hot flushes (Most common – 18%)
2. Gastrointestinal side effects like nausea and vomiting – 15%
3. Bone pain and leg cramps
4. Back pain
5. Dyspnea

These side-effects are mainly observed in women with advanced breast cancer who receive

aromatase inhibition for a longer period of time. In women receiving aromatase inhibitors for ovulation induction mainly experience hot flushes and PMS like symptoms.

INSULIN SENSITIZERS (METFORMIN) :

Metformin is a biguanide (dimethylguanide) is an oral hypoglycemic agent. It is well known that insulin resistance plays an important role in pathogenesis of PCOS. Hyperinsulinemia leads to hyperandrogenism by increasing androgen production and decreasing sex steroid binding globulin. Also, hyperinsulinemia leads to estrogen hyper response resulting in an early FSH drop. This leads to follicle growth arrest in the early follicular phase[4].

Mechanism of action - Metformin lowers insulin resistance and hyperandrogenism which normalizes ovarian hyperresponsiveness and thus promotes restoration of ovulatory cycles [4]

Dose - Metformin is started in a daily dose of 500mg 2-3 times a day to a maximum of 2000mg/day[4]. Metformin per se is not used as an ovulation induction agent. It can be used as a second line agent along with CC in CC resistant PCOS. Addition of metformin to CC results in 50% ovulation rate[4].

Addition of metformin to gonadotropin results in a more physiological ovarian response and reduced amount of gonadotropins. Addition of metformin helps to lower the risk of OHSS.

A recent metaanalysis analysing 12 studies and 1516 participants showed that the use of metformin significantly reduced the risk of OHSS in PCOS patients[16].

In a recent Cochrane review based upon 8 RCTs with 798 women, it was noted that there was a decreased risk of OHSS with metformin use (OR 0.29, 95% CI 0.18-0.49) [17].

Metformin along with lifestyle modifications could be recommended for treatment of weight, hormonal and metabolic outcomes in PCOS women[15].

Side Effects :

1. Gastrointestinal side effects : Nausea, vomiting, diarrhoea
2. Lactic acidosis (Uncommon)

These side-effects diminishes when metformin is used for a longer period of time.

SERMS: TAMOXIFEN

Tamoxifen is a selective estrogen receptor modulator (SERM).

Mechanism of action: It binds to hypothalamic estrogen receptors, blocks the negative feedback mechanism and thus increases the FSH secretion [3]. It is administered in a dose of 40mg/day for 5 days starting from 2nd day of the menstrual cycle. A prospective randomized trial comparing the efficacy of tamoxifen and clomiphene citrate for ovulation induction in anovulatory women showed that overall ovulation and pregnancy rates were similar in both groups. Tamoxifen may be superior to CC in that it does not have an anti-estrogenic effect on the endometrium. It has been shown to successfully induce ovulation in clomiphene citrate failure cases. However, its role in superovulation is yet to be ascertained [3].

GONADOTROPINS:

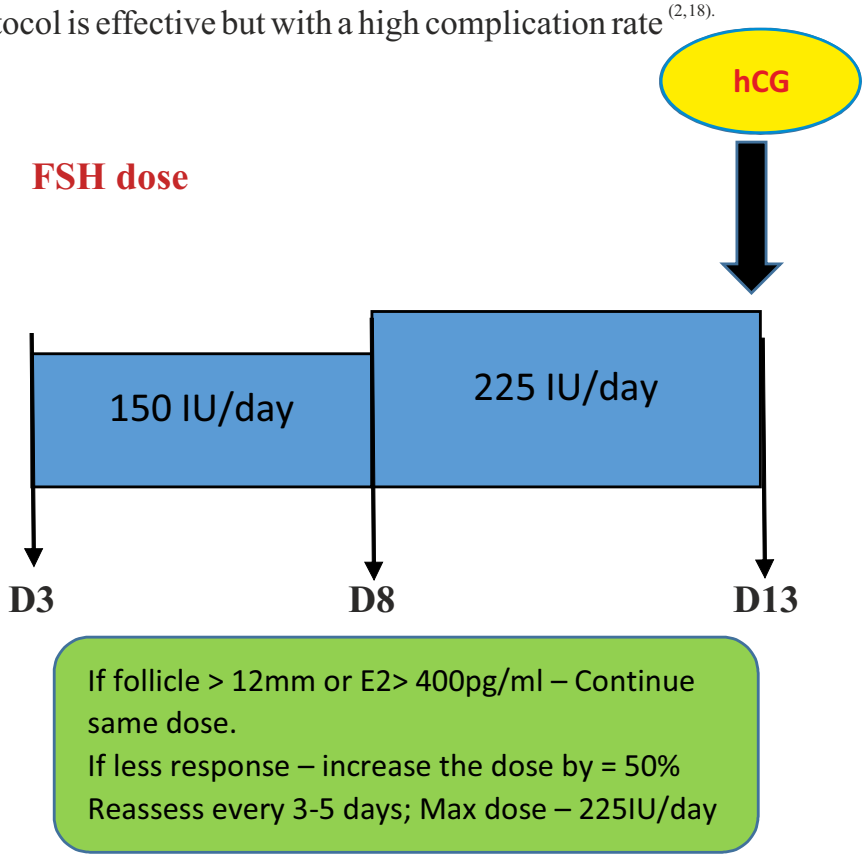
Gonadotropins either in urinary or recombinant form like human menopausal gonadotropin (hMG) or recombinant FSH or LH (rFSH or rLH) can be used for ovulation induction. The underlying principle for their use involves initiation and maintenance of follicle growth by transient increase of FSH threshold and FSH window. This helps in recruiting a limited number of developing follicles[3].

Treatment Regimens:

1. Step- Up Regimen :

The step-up protocols can be in the form of standard step up protocol, low dose step up protocol or continuous low dose step up protocol.

(a) Standard Step Up Protocol (Figure 6): This protocol involves initial daily dose of 150IU/day, which is increased by ⩾ 50% every 3-5 days until an ovarian response occurs. This protocol is effective but with a high complication rate [2,18].



(b) Chronic low dose step up regimen : This is the preferred method of ovulation induction in PCOS patients (Figure 7). This regimen is based on the FSH threshold concept. The initiation of follicular growth requires only a 10-30% increment in the dose of exogenous FSH and thus small, stepwise increments of FSH is advocated. The first increase in dose occurs only after 14 days [2]. It usually results in mono-ovulatory cycles in 70% cases with pregnancy rate of 20% per cycle. The risk of OHSS is very low (0.14%).

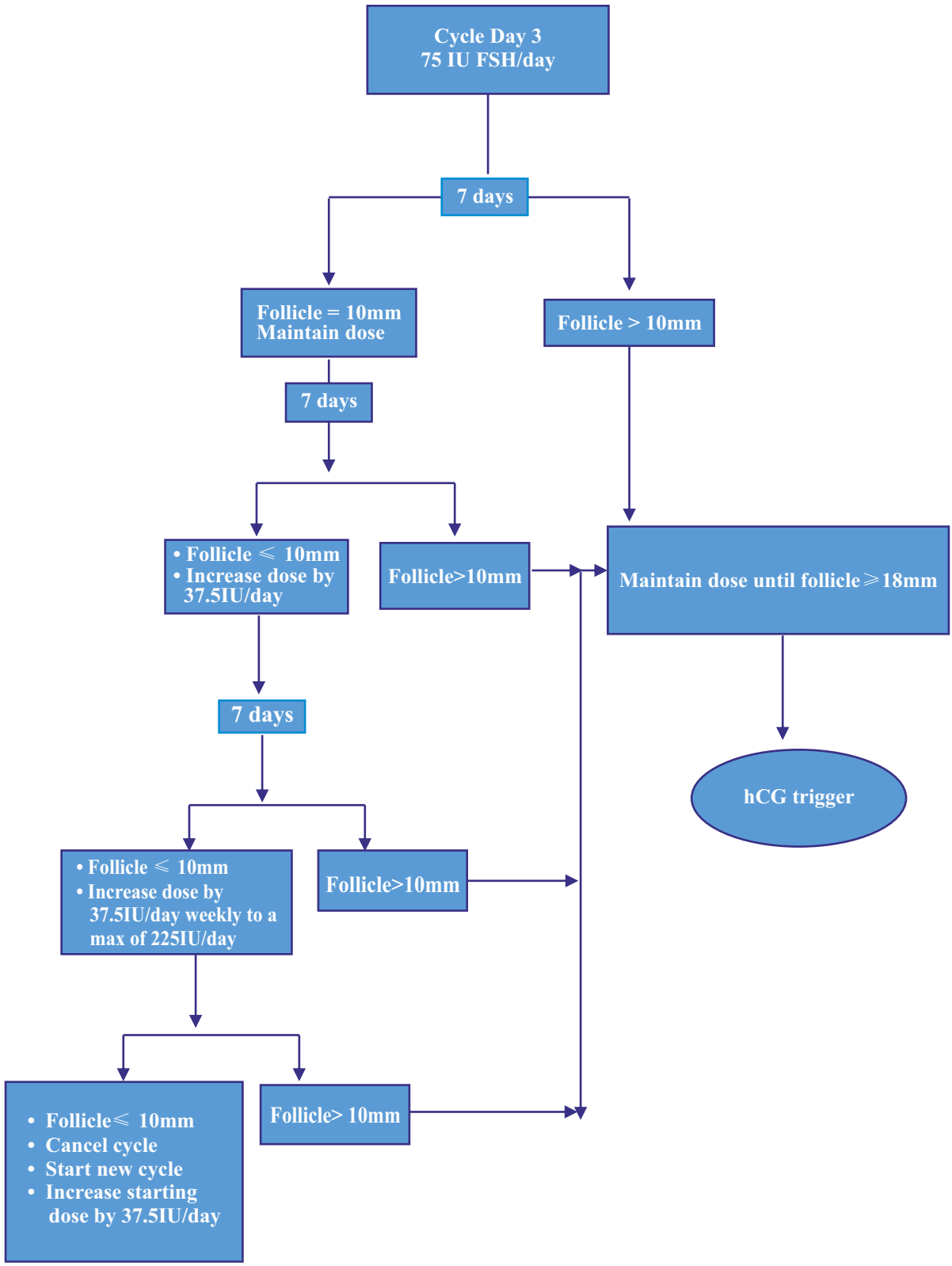
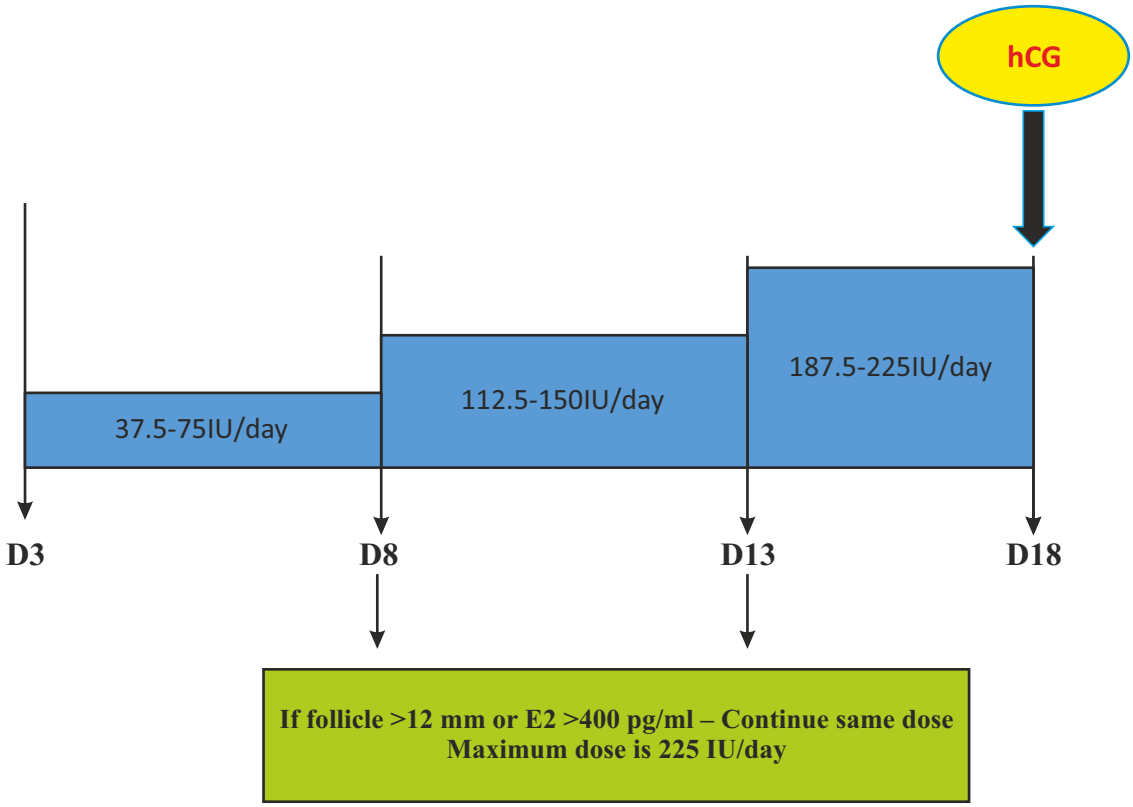


Fig. 7. Chronic low dose step up regimen.

(c) Continuous Low dose Step-Up Regimen (Figure 8) : It involves increasing the dose after 7 days unlike chronic low dose where no change in dose is made upto 14 days [2].



2. STEP DOWN REGIMEN :

The step down regimens can be standard step down or continuous step down regimen.

(a) Standard Step-down Protocol : It uses decremental doses of gonadotropins once ovarian response is established (Figure 9). The starting dose is higher than in step-up approach; as this protocol aims to mimic physiological natural intercycle FSH elevation and subsequently decreasing the dependence on FSH.

However, the monitoring is more stringent than step-up regimen. Also the long half-life of FSH makes it difficult to judge the correct dose adjustments. The step-up protocol is more efficient in obtaining mono-follicular response with reduced risk of OHSS [2].

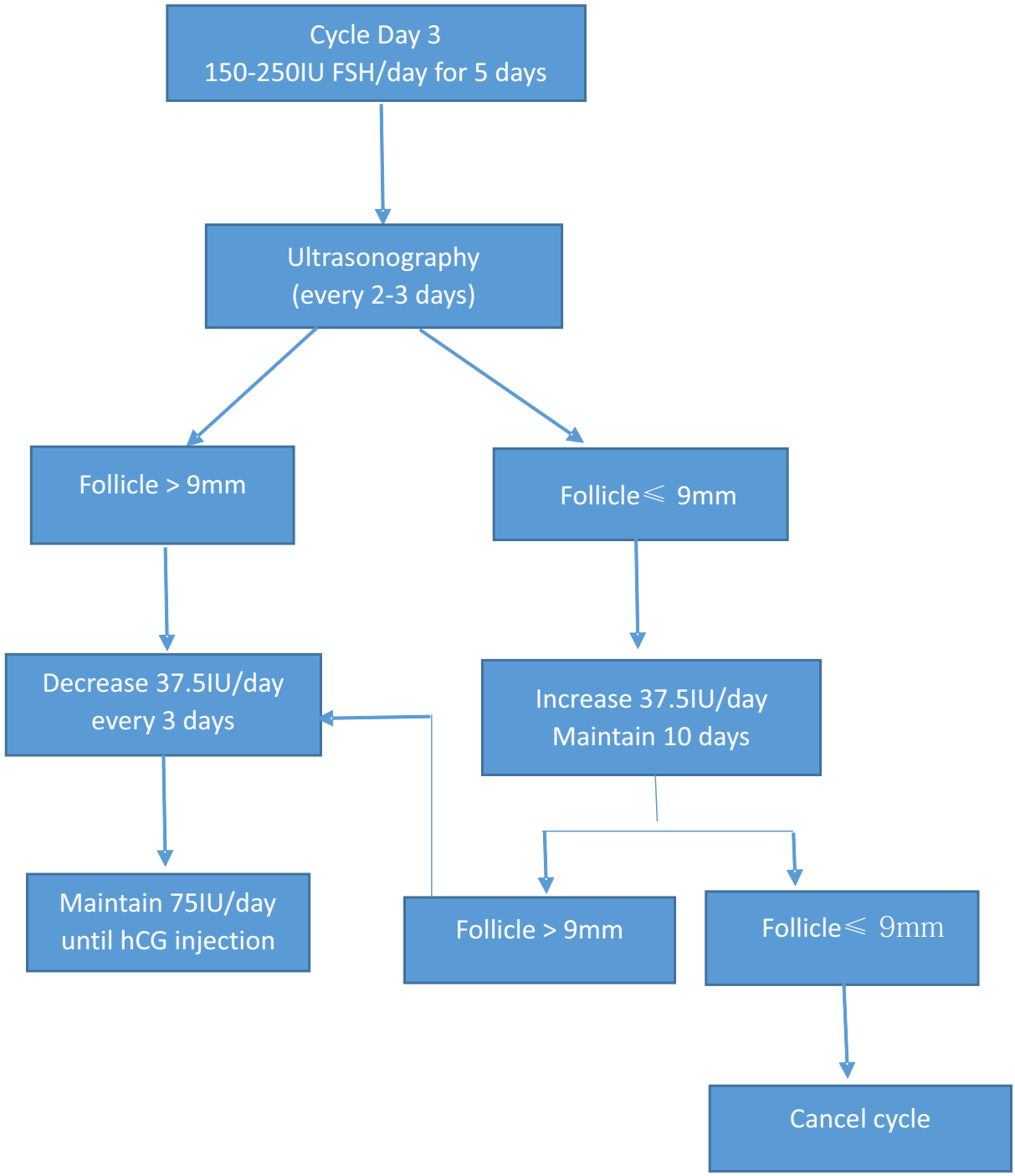
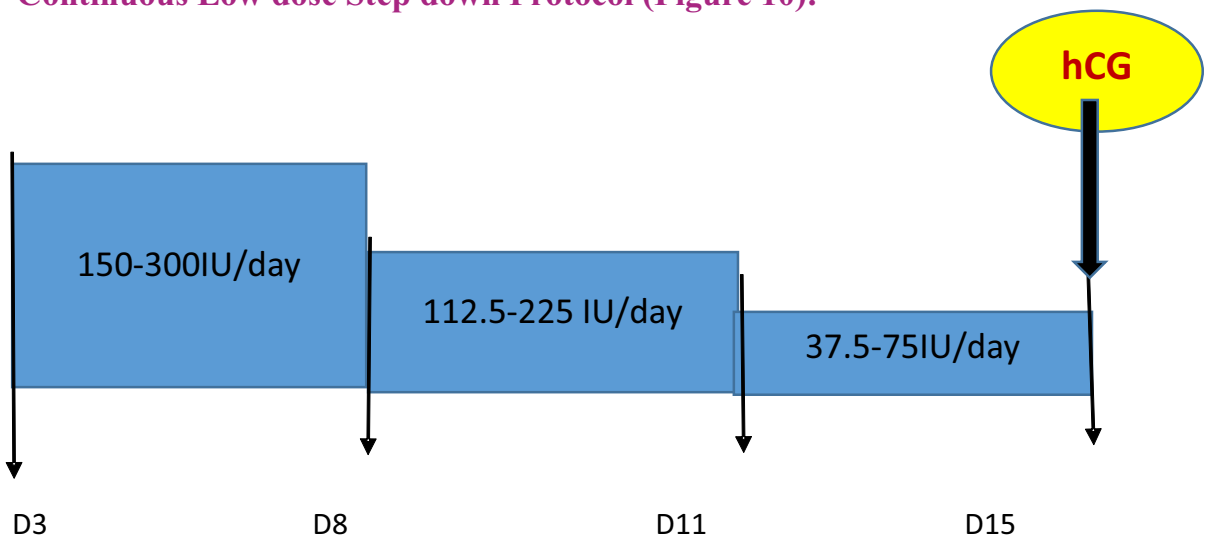


Figure 9 : Standard Step down Protocol

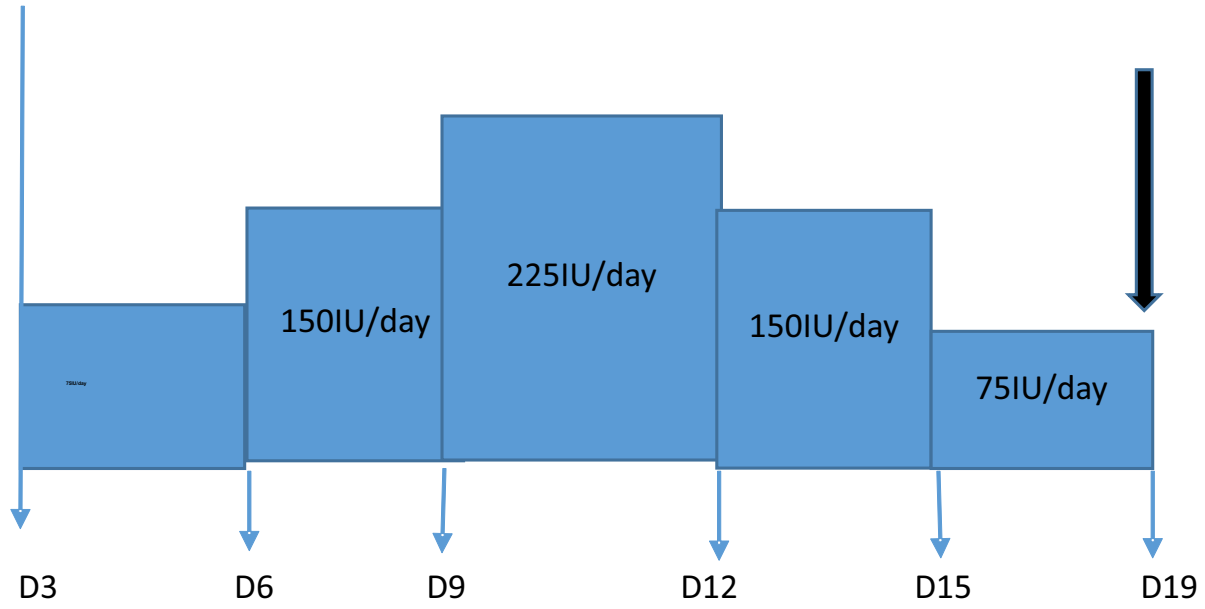
(b) Continuous Low dose Step down Protocol (Figure 10):



If follicle >10 mm or E2 >400 pg/ml – Step down to 112.5 IU & continue for 3 days
Then to 75 IU/day till hCG, if not continue same dose

3. COMBINED STEP UP AND STEP DOWN PROTOCOL:

This protocol uses both step up and step down (Figure 11). Initially the dose is increased till dominant follicle is achieved and then the dose is gradually decreased [2].

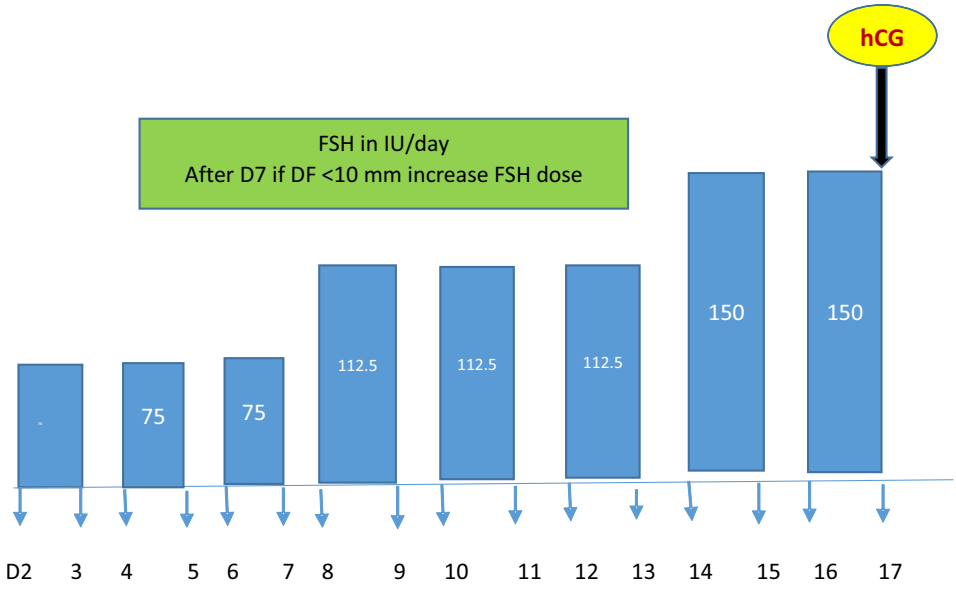


Step Up dose used till lead follicle becomes 14 mm Maximum Dose – 225 IU/day

Figure 11: Combined Step-up and Step down Protocol

4. ALTERNATE DAY GONADOTROPIN PROTOCOL (FIGURE 12) :

It is used in CC resistant PCOS cases. The basic underlying principle behind this protocol is that the half-life of FSH if 30-40 hours. The dose is increased if there is no follicle greater than 10 mm after 7 days.



LAPAROSCOPIC OVARIAN DRILLING (LOD) :

Multiple ovarian punctures performed either by diathermy or by laser is known as "ovarian drilling". Indications for laparoscopic ovarian drilling are:

1. CC resistance
2. LH hypersecretion
3. Anovulatory PCOS who stay far away from hospitals and cannot afford regular monitoring.
4. PCOS patients who require assessment of pelvis.
5. Lean PCO
6. LOD should not be offered for non-fertility indications in PCOS patients

Mechanism of action:

The beneficial effect is due to destruction of androgen producing stroma which results in reduction of intraovarian androgen production and decreased circulating androgen concentrations. The serum LH concentration decreases and FSH concentration increases and thereafter, demonstrates a cyclical rise in keeping with restoration of ovulation. Pituitary responsiveness to GnRH stimulation also decreases. This suggests that procedure has an indirect modulating effect on pituitary-ovarian axis [(4).]

Methods and Dose :

The number of punctures and power required are determined by parameters seen on scan as the volume and stromal thickness. In clinical practice, four to ten punctures are done per ovary as

decided by the parameters such as volume of ovary, body mass index (BMI), nature of cycles, baseline LH levels, previous response to ovarian stimulation, features of hyperandrogenism. Four punctures with 4 mm depth with 4 PW energy is ideal to follow. Repeat procedures are not associated with results and hence are not encouraged[3].

The best results of LOD are seen in the first 6–9 months post procedure. The cumulative ongoing pregnancy rates after 6–12 months post-LOD is comparable with 3–6 cycles of gonadotropin therapy. Ovulation rates after drilling are 56-94% and at least half of the women obtain a pregnancy (43-84%). CC is added if anovulation persists at the end of 12 weeks. Addition of gonadotropins is warranted only if anovulatory cycles persist after 6 months of procedure. LOD significantly reduces the multiple pregnancy rates in comparison with the use of gonadotropins. Miscarriage rates in LOD are comparable with seen in other modes of ovarian stimulation [3,4].

Complications:

1. Laparoscopic complicatons
2. Post operative adhesions
3. Rarely, premature ovarian insufficiency.

OVULATION INDUCTION IN WHO CLASS III GROUP

This category includes women with primary ovarian insufficiency.

A number of treatment strategies like use of CC+ Gonadotropins, only Gonadotropins, GnRH analogues with gonadotropins but with a limited success of 5-10%.

The only reliable treatment is use of donor eggs [3].

WHO CLASS IV GROUP: HYPERPROLACTINEMIA

Prolactin is secreted by lactotrope cells of anterior pituitary and is also present in decidualized endometrium, myometrium, follicular fluid and amniotic fluid. Hyperprolactinemia leads to galactorrhoea, oligo/amenorrhoea with anovulatory infertility.

30% of the women with PCOS can exhibit mild hyperprolactinemia. There are reduced levels of dopaminergic inhibition which leads to elevated serum LH concentrations and consequently anovulation. Dopamine agonists are the treatment of choice for hyperprolactinemic infertile females with ovulatory dysfunction[1].

The drugs most commonly used are bromocriptine and cabergoline. Bromocriptine is given at a dose of 1.25-2.5 mg daily at bedtime to suppress the nocturnal increase in prolactin levels. The treatment is started with low dose to minimize gastrointestinal and cardiovascular side effects. Cabergoline treatment begins at a dose of 0.25mg twice weekly increasing the dose gradually thereafter. Normal prolactin levels are usually restored with a dose of 0.5-1mg weekly. Cabergoline is effective in 70-85% hyperprolactinemic females who are bromocriptine resistant cases or in those who cannot tolerate bromocriptine.

Overall, dopamine agonists normalizes and maintains normal prolactin levels in 60-85% of hyperprolactinemic women with restoration of cyclic menses in 70-90% within 6-8 weeks of initiation of treatment. Ovulatory cycles return in 50-75% of women[1].

Side Effects :

Side effects are more with bromocriptine as as it stimulates both D1 and D2 dopamine receptors and are most severe during the first 2 weeks of therapy, but are generally well tolerated. Nausea, vomiting, dizziness, nasal stuffiness and orthostatic hypotension are most common side effects. These side effects are less with cabergoline as it has higher affinity for D2 receptors [1].

TRIGGERS IN OVULATION INDUCTION:

The trigger acts as surrogate for LH surge to trigger ovulation. In ovulation induction cycle, LH is released spontaneously by pituitary as well in response to positive E2 feedback from mature follicle. So, triggering is basically required not to bring about ovulation but for timing of intercourse or IUI.

The most commonly used trigger is urinary hCG 5000 IU. Timed intercourse is advised for 3 days after hCG trigger and IUI is performed 24-36 hours after hCG administration.

hCG is administered usually when the follicle reaches a size of 18mm or more and is withheld in the following cases in ovulation induction cycles :

(a) Serum estradiol > 1,500 pg/ml

(b) >3 mature follicles

(c) > 2 mature & 5 intermediate (10-14 mm) follicles.

Other triggers which can be used are :

1. Recombinant hCG (equivalent to 6000-7000 IU of urinary hCG)
2. GnRH agonists : 0.5mg leuprolide, 0.2mg triptorelin
3. Recombinant LH

As per a Cochrane review in 2014, there is inadequate evidence to recommend or refute the use of urinary hCG as an ovulation trigger in anovulatory women treated with clomiphene citrate. There have been no trials evaluating the use of ovulatory triggers in anovulatory women treated with other ovulation inducing agents [19].

LUTEAL PHASE SUPPORT (LPS):

Luteal phase support is usually given in the form of Dydrogesterone 10 mg twice daily or micronized progesterone 200mg twice daily for 14 days. The role of LPS is debatable as OI involving 1-2 mature follicles doesn't produce the supraphysiological hormone levels that shut down the corpora lutea but is still practiced by convention.

As per a recent metaanalysis, progesterone support is beneficial in ovulation induction with gonadotropins in IUI cycles but has not shown to be of any benefit in clomiphene cycles [20].

MONITORING OF OVULATION INDUCTION:

1. Serial Transvaginal Ultrasound (TVS) : Baseline USG is performed at day 2 of cycle to assess the antral follicle count and endometrial lining and to rule out any cysts. Ovulation induction is started after deciding the protocol. Serial monitoring is done from Day 8 or Day 9 onwards till the size of the follicle reaches 18mm or more when trigger is administered.

TVS is preferred as it provides a more direct and accurate assessment of follicular development. The follicle grows at a rate of 2-3mm/day once the lead follicle reaches 10-12mm in size.

2. Serial serum Estradiol (E2) monitoring : Plasma E2 levels closely correlate with the stage of dominant follicle. A value of more than 200pg/mL per mature follicle indicates adequate response.

RISKS AND COMPLICATIONS OF OVULATION INDUCTION:

The various risks associated with ovulation induction are :

1. Multifetal gestation
2. Ovarian Hyperstimulation Syndrome (OHSS)
3. Miscarriage
4. Anomalies
5. Cancers

1. Multifetal Gestation : The risk of multiple pregnancy with clomiphene citrate is 8% in anovulatory women and 2.6 – 7.4% in females with Unexplained infertility [4].

The risk of triplets and higher order pregnancies with clomiphene citrate is 0.08%-1.1%. The risk of monozygotic twins with spontaneous conception is 0.3-0.4% and is increased by three fold with the use of gonadotropins (Table 6).

	Multiple Pregnancy (%)
Spontaneous	1.25 (1/80)
CC	5-8
Gonadotropins	15
Gonadotropins + Superovulation	30

Table 6 : Risk of Multiple Pregnancy with Ovulation Induction

2. Miscarriage : The risk of miscarriage with CC is same as that of spontaneous pregnancies, that is, 15%. However with the use of gonadotropins, this risk is increased to 25% especially with increasing age and BMI [4].

3. OHSS : The risk factors for OHSS include young age, lean PCOS, use of higher dose of gonadotropins or previous history of hyperstimulation [2].

In IUI cycles, hCG should be withheld if there are more than 3 follicles $\geqslant$ 17 mm and/or $\geqslant$ 5 follicles $\geqslant$ 14 mm to avoid the risk of hyperstimulation. The risk of mild OHSS in ovulation induction with clomiphene or aromatase inhibitors is upto 13% whereas moderate OHSS can occur in 2-6% of cases.

The risk is increased with IVF. Mild OHSS can occur in upto 20-30% of cases, moderate in 3-6% whereas incidence of severe OHSS is very less, occurring in 0.1-2% of cases.

4. Anomalies : There is no evidence of increased risk of anomalies or developmental delay or learning disability with CC or Gonadotropins[4].

5. Malignancies : No causal relation of any malignancy has been established so far with either the use of CC or Gonadotropins. However, prolonged treatment (>12 cycles) with CC should be avoided as it leads to repeated epithelial injury due to ovulation[4].

CONCLUSION:

In infertility practice, ovulation induction/superovulation poses a great responsibility for the clinician because of wide choice of ovulogens available. It is well known that high-order multifetal pregnancies represent the largest single cause of poor obstetric and perinatal outcome. Thus, ovulation induction regimens should concentrate on the quality output and aim not to exceed three follicles in all induction programs.

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- Dr. Kamini A Rao who is a recipient of the Padma Sri Award, one of India's highest civilian awards
- She has established a strong Quality Audit which has ensured that the success rate exhibited at the parent Centre could be replicated in the newer Centres. This focus on excellence earned her organization, Milann, the distinction of being the No 1 Fertility Centre in India by the Times of India Health Survey, 2016 and Emerging IVF Service Provider by Frost & Sullivan Awards in 2015
- Among Dr. Kamini Rao's early contributions to the field are the establishment of South India's first Semen Bank, India's First SIFT Baby and South India's first babies born through ICSI as well as through Laser Assisted Hatching. A pioneer in the field of medicine, Dr Kamini Rao has recently tied up with Prof. Mats Brannstrom from Sweden to bring the technology of Uterus Transplant to India.
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- President, Indian Society for Assisted Reproduction (2006-2008)
- Editor in Chief, Journal of Human Reproductive Sciences (2009 to 2014)
- Founder Editor, International Journal of Infertility & Fetal Medicine (2010 to date)

Thin Endometrium



Dr. Rishma Dhillon Pai **Dr. Hrishikesh Pai** **Dr. Manisha T Kundnani**

- **The endometrium undergoes a series of changes during the menstrual cycle and prepares itself for implantation[2]. An adequate endometrial thickness and appropriate endometrial pattern are the important pre-requisites for a successful ART outcome.**
- **The significance of endometrial thickness in infertility treatment is conflicting. Though, most clinicians prefer an endometrial thickness of >7mm, pregnancies have been reported with endometrial thickness as less as 4 and 5mm[8,9]. Kasius et al in a systematic review and meta-analysis suggested that endometrial thickness cannot be used as parameter for cycle cancellation, freezing all embryos or discontinuing the treatment[6] as it is not predictive of pregnancy.**
- **Hysteroscopy is an important tool in assessing and treating these adhesions. Electrosurgery can cause thermal endometrial damage and so hysteroscopic scissors are preferred over electrosurgery for adhesiolysis in such cases[12,13].**
- **A number of drugs and supplements known to improve the endometrial perfusion have been used as a treatment option for thin endometrium. These include low dose Aspirin, Vitamin E/pentoxifylline, Sildenafil, L-Arginine and Nitroglycerin.**
- **Thin endometrium still remains a challenge for the reproductive specialist as no definite treatment is yet established.**

INTRODUCTION

A receptive endometrium is crucial for establishment of pregnancy. Thin endometrium, unresponsive to hormonal changes can result in implantation failure and early miscarriages due to inadequate blood supply[1]. The endometrium undergoes a series of changes during the menstrual cycle and prepares itself for implantation[2]. An adequate endometrial thickness and appropriate endometrial pattern are the important pre-requisites for a successful ART outcome. Endometrial thickness is measured in the mid saggital plane of the uterus as the maximal distance between the echogenic interfaces of endometrium and myometrium. An endometrial thickness of <7mm on transvaginal ultrasound is mostly defined as thin endometrium[3], though different cut-offs between

5-8 mm have been used by various researchers[4,5]. An incidence of 1.49-2.5% was reported by Bu et al, however this can vary according to the chosen cut-off. Thin endometrium is found more often in elderly women more than 40 yrs of age due to decreased vascularity[6].

THIN ENDOMETRIUM: CAUSES

The various causes of thin endometrium are enlisted in table -1. These are:

- **Endometritis:** Any infection, acute or chronic, can cause destruction to the basal layer of the endometrium. The subsequent healing takes place by fibrosis and results in poor growth of endometrium. Genital Tuberculosis is the most common infection in India. The other common infections include Chlamydia trachomatis, Ureaplasma urealyticum, and Enterococcus.
- **Iatrogenic:**
  a) Any trauma to the endometrial lining results in development of adhesions between opposite myometrial surfaces causing distortion of the uterine cavity. The most common causes of post surgical intrauterine adhesion formation include repeated and overzealous curettage, intrauterine surgeries (septoplasty, hysteroscopic myomectomy or laparoscopic myomectomy, where the cavity was opened) and Strassman's operation.
  b) Endometrial ablation or radiotherapy below the diaphragm can cause disruption of the uterine blood vasculature, resulting in poor endometrial growth.
  c) Indiscriminate use of Clomiphene Citrate and prolonged progesterone therapy are also sometimes associated with refractory thin endometrium.
- **Idiopathic:** in some cases thin endometrium is due to individual uterine architecture or intrinsic endometrial properties and not secondary to any disease[7].

TABLE-1 CAUSES OF THIN ENDOMETRIUM

Infections: Endometritis: acute/chronic
Iatrogenic:
Surgical: Dilatation and curettage
Intrauterine surgeries
Strassman's operation
Endometrial ablation
Radiotherapy
Prolonged use of clomiphene citrate and progestogens
Idiopathic

THIN ENDOMETRIUM : RELEVANCE IN INFERTILITY AND REPRODUCTIVE OUTCOME

The significance of endometrial thickness in infertility treatment is conflicting. Though, a positive correlation has been found between endometrial thickness and pregnancy rates by many

researchers but many other studies have found no such association. Though, most clinicians prefer an endometrial thickness of >7mm, pregnancies have been reported with endometrial thickness as less as 4 and 5mm[8,9]. Kasius et al in a systematic review and meta-analysis suggested that endometrial thickness cannot be used as parameter for cycle cancellation, freezing all embryos or discontinuing the treatment[6] as it is not predictive of pregnancy. The probability of pregnancy is however reduced with endometrial thickness less than 6mm.

A number of recent studies have suggested that not only the thickness but also the endometrial pattern has a significant effect on the endometrial receptivity and subsequent outcome. Thin endometrium may not necessarily be non receptive. A newer test Endometrial Receptivity Assay (ERA) can help confirm the window of implantation and receptivity of thin endometrium. Mahajan et al observed that in women with endometrial thickness </= 6mm, only 23% had a non receptive endometrium. The overall pregnancy rates in patients with thin endometrium group were 33%[10].

TREATMENT OF PERSISTENTLY THIN ENDOMETRIUM

A number of treatment modalities have been suggested to treat persistently thin endometrium in women undergoing infertility treatments. These can be broadly categorized as hysteroscopic surgical correction, hormonal manipulation, improving endometrial perfusion and the newer options like G-CSF and PRP infusion. Most of these treatments however have a limited effect on the endometrial thickness and subsequent pregnancy rates. The ultimate option left to many of these patients is surrogacy. The current evidence based management does not validate any specific treatment.

1. Hysteroscopy and Adhesiolysis

Hysteroscopic examination of the uterine cavity can help to diagnose previously undiagnosed uterine pathologies. Fatemi et al observed that 40-43% of women, with or without recurrent implantation failure, and with no suspicion of uterine abnormality were found to have uterine pathology on hysteroscopy[11]. Women who have undergone curettage or uterine surgery have a higher incidence of intrauterine adhesions which can compromise endometrial growth. Hysteroscopy is an important tool in assessing and treating these adhesions. Electrosurgery can cause thermal endometrial damage and so hysteroscopic scissors are preferred over electrosurgery for adhesiolysis in such cases[12,13].

Though hysteroscopic adhesiolysis restores the uterine cavity in patients with intrauterine adhesions, pregnancy outcomes are dependent on extent of endometrial fibrosis. Baradwan et al observed significantly higher pregnancy rates and significantly lower miscarriage rates in women with Asherman syndrome with endometrial thickness >5mm[14].

2. Hormonal manipulation

High dose estrogen supplementation is one of the first approaches used in patients with thin endometrium. Estrogen is known to cause endometrial proliferation and facilitates embryo

implantation as it causes spiral artery contraction and reduces oxygen tension in the functional layer of endometrium.[15,16] It can be given in doses as high as up to 16 mg starting from day 1 of cycle. Various routes of administration including oral, vaginal, parenteral and transdermal have been used. The most commonly used route is oral for simplicity reasons. Non –oral routes have the advantages of avoiding the first pass liver metabolism and giving higher serum concentrations.

Extended use of estrogen (14-82 days) has also been used in case of refractory thin endometrium with successful results in some patients17. In fresh IVF cycles, estrogen supplementation in follicular phase is known to improve the endometrial thickness[18].

Other methods of hormonal manipulation to treat persistently thin endometrium have also been researched by various authors. These include addition of low dose of HCG[19] along with estrogen during endometrial preparation and addition of GnRh agonists in the luteal phase[20]. However there is not enough data to recommend these treatments routinely.

Use of alternative drugs for ovulation induction like Tamoxifen instead of clomiphene and addition of gonadotropins to clomiphene citrate is known to improve endometrial thickness in patients with thin endometrium due to prolonged use of clomiphene[21-23].

3. Improving endometrial perfusion

A number of drugs and supplements known to improve the endometrial perfusion have been used as a treatment option for thin endometrium. These include low dose Aspirin, Vitamin E/ pentoxifylline, Sildenafil, L-Arginine and Nitroglycerin.

Low dose aspirin (75mg or 100mg) is known to decrease the impedance of uterine arteries and thereby increases the uterine perfusion. It has been widely used in IVF cycles. Various prospective randomized studies have observed that low dose aspirin increases the implantation rates in patients with thin endometrium, though no significant improvement in endometrial thickness has been observed[24,25]. Cochrane review however did not find any benefit of adding aspirin for endometrial preparation[26].

Vitamin E (1000U) alone or in combination with pentoxiphylline(800mg/day) is another drug used for improving the endometrial perfusion, especially in women with thin endometrium post radiotherapy. Though some trials observed a significant improvement in endometrial thickness, it did not translate into significant improvement in pregnancy rates[27,28].

Sildenafil (100mg) used vaginally has been shown to improve endometrial thickness in patients with thin endometrium[29,30]. Other drugs like L-arginine (6mg) and nitroglycerin have also been used by various authors with limited success and enough evidence is lacking to recommend their routine use for treating patients with thin endometrium.

4. Newer treatment options:

- G-CSF Infusion
- Autologous PRP

- Bone marrow Stem/progenitor cells
- Neuromuscular electrical stimulation

A. Intrauterine G-CSF instillation: G-CSF is a glycoprotein which is known to possess growth factor and cytokine properties. It has been shown to stimulate mesenchymal and hematopoietic stem cells in the bone marrow. Human endometrium contains mesenchymal stem like cells which may be responsible for cyclical endometrial growth. It is proposed that G-CSF stimulates these endometrial stem cells and thus promote endometrial growth. Various authors, in different case series and non-randomised studies have reported significant improvement in endometrial thickness and subsequent pregnancy rates after intrauterine G-CSF instillation in women with refractory thin endometrium[31,32]. However a RCT conducted by Barad et al failed to demonstrate any beneficial effect of G-CSF on either endometrial thickness or pregnancy rates[33].

The usual dose of instillation is 300mcg or 100mcg/0.6ml, administered in proliferative phase or on the day of HCG administration, or on the day of ovulation. Further studies are needed to prove its efficacy and to standardize the dose, timing and frequency of instillation.

B. Autologous PRP infusion is been used for tissue regeneration as it releases cytokines and growth factors like VEGF, transforming growth factor, platelet derived growth factor and epidermal growth factor. Its use in refractory thin endometrium was recently evaluated by Chang et al[34]. The authors observed significant improvement in endometrial thickness and all 5 women enrolled in the study were pregnant after the embryo transfer. PRP infusion may thus be a potential treatment option for women with thin endometrium, though more studies are needed to determine the efficacy and standardize the treatment protocol.

Other treatments like intrauterine administration of bone marrow stem/progenitor cells, pelvic floor neuromuscular electrical stimulation have been evaluated in various case reports. More studies and randomized trials are needed to prove the efficacy of these treatment modalities.

CONCLUSION

Thin endometrium still remains a challenge for the reproductive specialist as no definite treatment is yet established. The treatment options are limited and are not specific to the etiology. There is lack of solid evidence supporting one intervention over the other and more studies are needed to standardize and validate different treatment modalities. The etiology also plays a significant role in subsequent outcome. Thin endometrium secondary to inflammatory process usually remains refractory to treatment and sometimes surrogacy is the only option left to these patients.

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Corrected

Conquer Endometriosis - Surgical Approach

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Dr. Vandana Jain, Dr. Priyanka Bansal

- **(DIE Lesions) Deep infiltrating endometriosis has been directly related to pelvic pain, dysmenorrhea and dyspareunia. Laparoscopy has emerged as a major player in its diagnosis and surgical management.**
- **Diagnosis of deep infiltrating disease may be enhanced by obtaining a CA-125 level during menstruation. Levels above 35 U/ml are associated with endometriosis with a sensitivity of 36% and a specificity of 87%.**
- **Fertility mainly depends on 4 factors.**

  Age of patient, Duration of marriage, Husband semen analysis, Patency of fallopian tubes. In endometriosis there is already low ovarian reserve, hence, immediately after surgery we don't expect good ovarian function. AMH takes 3-6 months for recovery after good surgery.
- **The surgical team must be multidisciplinary, composed of gynecologists, urologists and digestive tract surgeons.**

INTRODUCTION

Endometriosis is an enigmatic disease. In the recent times, lot of attention has been given to elucidating the exact nature, etiopathology and disease symptomatology in relation to chronic pelvic pain. Deep infiltrating endometriosis has been directly related to pelvic pain, dysmenorrhea and dyspareunia. Laparoscopy has emerged as a major player in the diagnosis and surgical management of deep infiltrating endometriosis. **Conquer endometriosis means to conquer pain with infertility.**

Medical therapy is found to be ineffective and temporary with recurrence rate as high as 76.3% whereas surgical treatment is highly effective in relieving pelvic pain and dyspareunia. The old concept of hysterectomy with bilateral salpingo-oophorectomy in relieving pain is ineffective in the face of deep infiltrating endometriosis of rectovaginal space and uterosacral ligaments.

For all endometriotic surgeries we used 5mm trocar via Jain point & optimize 10mm telescope according to surgery.

After visualizing lesion of ovary/rectovaginal septum etc. we ***inject Pitressin in dilution of 20units in 300ml NS*** which we have standardized. It is very useful for decreasing intra-operative blood loss as well as making dissection easier. All endometriotic procedures include peritoneal washing for cytology, inspection of pelvis and peritoneal organs and adhesiolysis.

We have divided this chapter into five parts, each part explaining surgery of one tissue involvement. They are :

1. Peritoneal endometriosis
2. Endometrioma
3. Rectovaginal endometriosis.
4. Endometriosis of urinary tract/ureter
5. Retrocervical and bowel endometriosis.

SURGERY OF VARIOUS SITES OF ENDOMETRIOSIS

1. PERITONEAL ENDOMETRIOSIS:-

It is of three types :

Type I. (Fig.1.a to 1.c) is characterized by a large pelvic area of typical or subtle lesions surrounded by white sclerotic tissue. During excision, deeper disease becomes obvious and grows progressively smaller and deeper like a cone.

Type II. (Fig. 1.d. to 1.e) endometriosis is formed by retraction of the bowel. This is recognized clinically as a small typical lesion associated with retraction. In some women, no lesion is appreciated, but induration is associated with the retraction. Excision usually reveals the nodule.

Type III. (Fig.1.f to 1.h) disease is nodular endometriosis of the rectovaginal septum. These lesions are clinically suspected at the time of rectovaginal examination when painful nodularities are noted. Occasionally, they can be seen as small typical lesions at laparoscopy or as dark blue cysts at the vaginal fornix. This type of disease is most severe. Although the diagnosis of deeply infiltrating endometriosis may be obvious on clinical examination, vaginal inspection or laparoscopic examination, but in some women it is easily missed. Extremely difficult to diagnose are small deep endometriotic lesions that are missed on clinical examination and that are associated with a clean or normal pelvis. Diagnosis may be enhanced if clinical examination is performed during menstruation in women with chronic pelvic pain, severe dysmenorrhea, deep dyspareunia. In most of the cases a nodule may be palpated at that time. Diagnosis of deep infiltrating disease may be enhanced by obtaining a CA-125 level during menstruation. Levels above 35 U/ml are associated with endometriosis with a sensitivity of 36% and a specificity of 87%. Diagnosis seems to be enhanced by transrectal or vaginal ultrasound examination or MR imaging. Treatment of deep infiltrating disease is most commonly surgical because this provides not only therapy but is

instrumental in making the diagnosis. Resection of disease should follow the tissue planes between normal tissue and the nodule. Lesions of 5-6 mm in size are generally flat, whereas deep lesions are elongated. Complete excision may be accomplished laparoscopically in a large number of cases, but laparotomy or vaginal excision may be necessary in others. Whether dissection is accomplished with a CO2 laser or sharply, is a matter of personal preference. Many surgeons choose not to use electrosurgery because of the associated widespread thermal damage and difficulty in recognizing tissue planes.

Ablation of Endometriotic Implants - Vaporization or fulguration of all endometriotic implants on back surface of uterus, cervix, and uterosacral ligaments as carried out after rectal mobilization, lateral clearing and excising adenomyotic nodule using microbipolar forceps. Thorough suction irrigation lavage is done and complete hemostasis achieved.

PERITONEAL ENDOMETRIOSIS

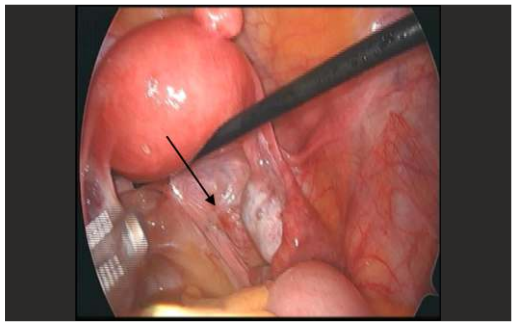


Fig. 1.a. Puckering, scaring of Peritoneum

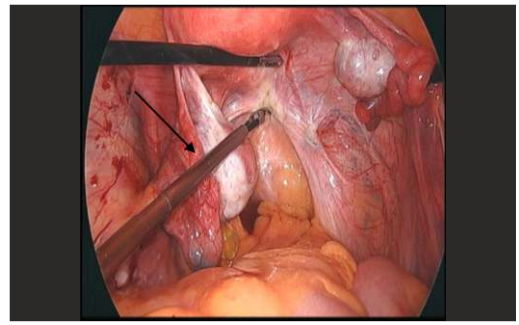


Fig. 1.b. Ablation being done by bipolar

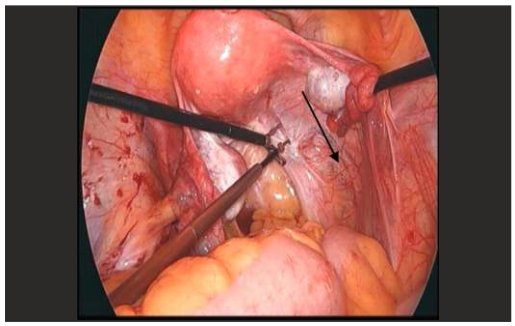


Fig. 1.c Peritoneal window

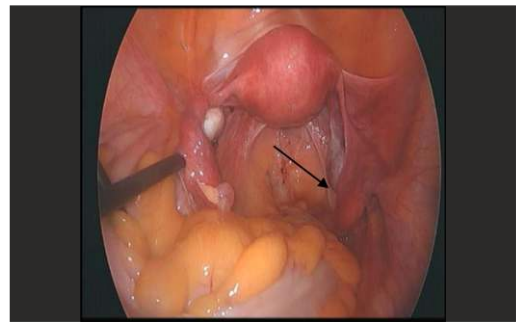


Fig.1.d. Fibrosis and Puckering

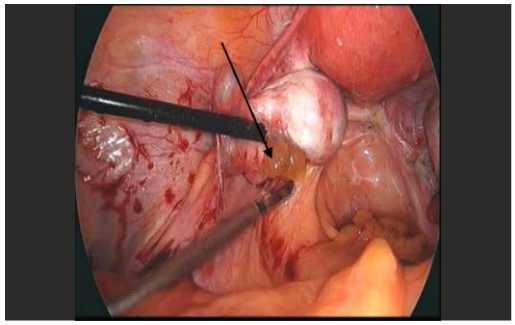


Fig. 1.e. Peritoneal Jelly

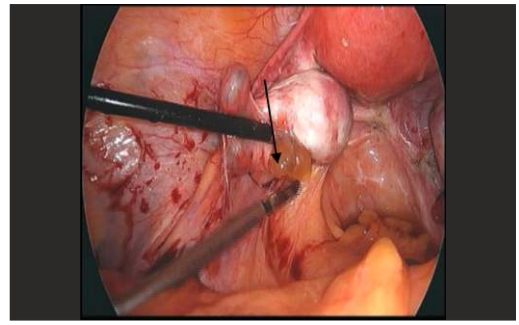


Fig. 1.f. Ablation of Same

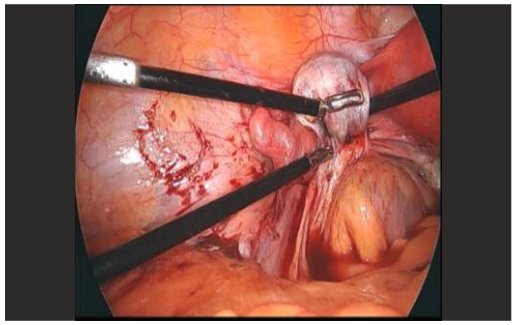


Fig. 1.g. Adhesions between ovary & rectum

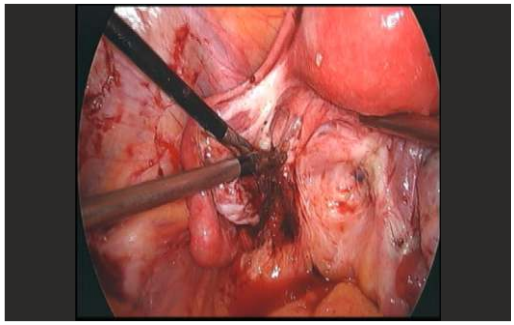


Fig. 1.h. Adhesion being removed by Bipolar

2. ENDOMETRIOMA:-

With sonographic evaluation, taking in consideration the AFS revised 1985, it can be classified according to the extension of disease as follows:

- **Minimal endometriosis (stage I):** There are minimal chances of growth of endometrial tissue outside the uterus.
- **Mild endometriosis (stage II):** Mono- or bilateral endometriomas with diameter < 3 cm; ovaries in normal site, mobile and not adherent to the uterus and surrounding tissues.
- **Moderate endometriosis (stage III):** Mono- or bilateral endometriomas with diameter > 3 cm; at least one ovary in normal site, mobile and not adherent to the uterus and surrounding tissues or one ovary only adherent to the uterus or broad ligament.
- **Severe endometriosis (stage IV):** Mono- or bilateral endometriomas with diameter > 3 cm; ovaries in abnormal site (prolapsed in the pouch of Douglas or dislocated posteriorly, anteriorly or superiorly to the uterus) and adherent to the uterus and surrounding tissues; presence of pelvic adhesions or endometriotic nodules.

SURGICAL TECHNIQUE- (Fig.2.a to 2.e)

Mobilization of ovaries by grasping utero-ovarian ligaments with a 5mm atraumatic grasper.

↓

Sharp adhesiolysis to fully mobilization ovaries

↓

Incise ovary surface in zone of maximum relaxation, possibly on antimesenteric surface distal from fimbrial end.

↓

Cyst is decompressed by suction drainage.

↓

Contents of cyst are carefully washed and inspected introducing the laparoscope inside. (important to rule out vegetation/neovascularization)

Pitressin injected.

↓

With bimanual opposite traction practiced around two places using atraumatic grasper, inner lining of cyst is stripped from normal ovarian tissue.

↓

Using appropriate thermal energy destroy residual cyst capsule.

↓

Achieve complete hemostasis.

ENDOMETRIOMA

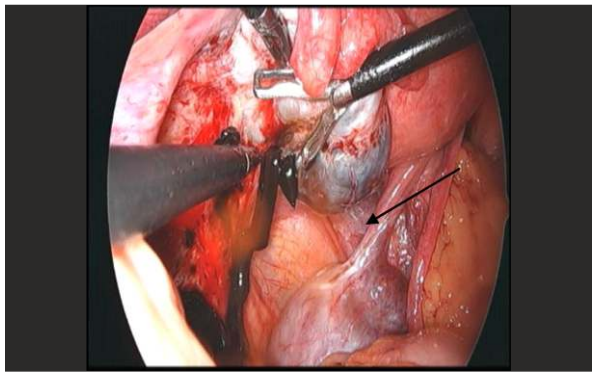


Fig. 2. a. Chocolate cyst being drained

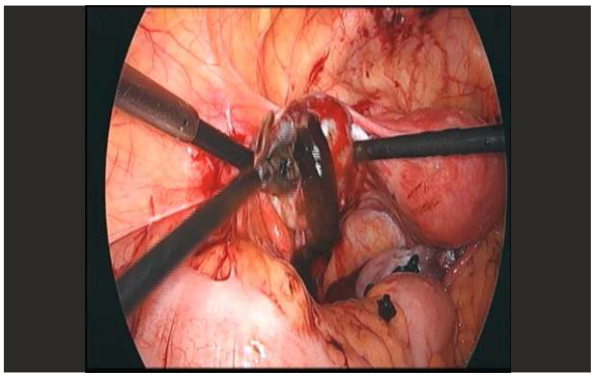


Fig. 2. b. Frank chocolate draining

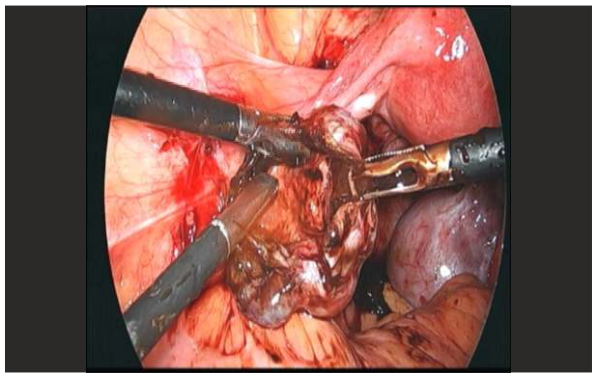


Fig. 2.c Inside of cyst

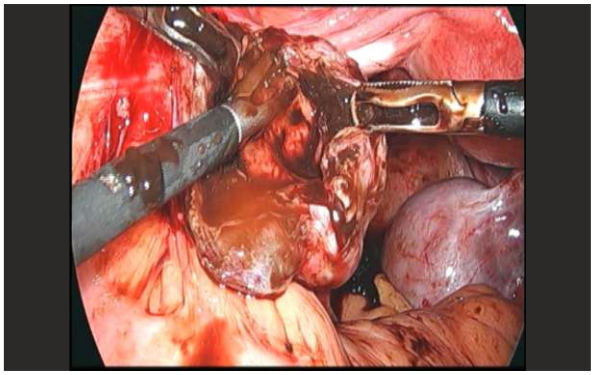


Fig. 2.d. Enucleation of cyst by manual traction

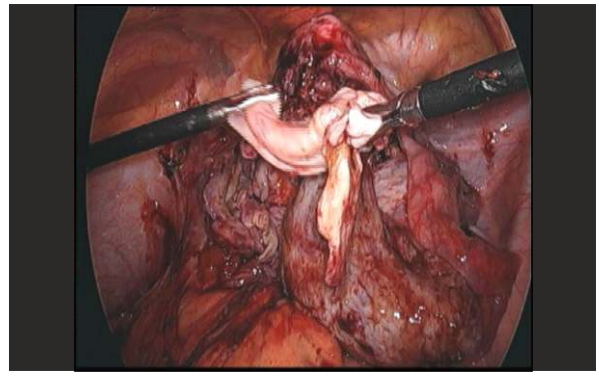


Fig.2.e. Enucleated cyst lining

3. ENDOMETRIOSIS OF RECTOVAGINAL SEPTUM:-

It involves management of adhesions and pain.(Fig.3.a to 3.g)

A. Adhesiolysis:-

Complete dissection of anterior rectum with blunt hook /scissors until the loose fibrofatty tissues is reached.

↓

Open peritoneum covering cul-de-sac between adenomyotic lesion & rectum.

↓

Excise / vaporise deep endometriosis.

- **Pain:-**

Clearing between Utero sacral ligaments & rectum as it carries afferent nerves for pain. We identify & lateralize the inferior hyprogastic plexus, we also trace & lateralize pelvic ureter.

↓

Excise utero sacral ligaments.

↓

Vagina if involved : excise the adenomyotic nodule with **0.5cm disease free margin.**

↓

En-bloc Excision by monopolar Cautery/ harmonic

Suture with 1-0 vicryl.

↓

Rectal check

b) Rectal Excision (Partial / Full Thickness) - is not practiced commonly as there is difficulty in obtaining consent and explanation of need of colostomy in eventuality of a mishap in radical rectal excision. We prefer "radical reproductive surgeries" and mobilize rectum from posterior aspect of uterus, perform lateral clearing and excision of adenomyotic nodules, refraining from unnecessary radical rectal resection.

c) Adhesion Prevention - After such extensive dissection concern for postoperative adhesion formation is real. Use of Interceed® propagated by many, use of fluid barriers is also wide spread, like 4% Icodextrin. In our setup we prefer to use fluid adhesion barriers and 4% Icodextrin is our choice. At times we use only Ringer's lactate and as per Reich et al practice instill three liters at end of such extensive procedure. Patients complain of some bloating for twenty four hours after hydrofloatation but otherwise they tolerate it well. The principle of hydrofloatation works by prevention of opposing surfaces to adhere to each other. On at least three patients we did a second-look procedure and found very low incidence of re-adhesion formation.

Results - As with most surgical treatments, randomized controlled trials of radical excision of deep infiltrating endometriosis are not available. However observational, comparative data and prospective clinical studies are encouraging 66% cure rate by laparotomy excision reported by Wheeler and Malinak Varol reported 57% cured by laparoscopy excision, while Abbott reported 56% cure rates. Postoperative fertility achieved was 43% by Redwine and Wright. According to the two largest published series there are two types of lesions, true infiltrating endometriosis that causes the invasion of very active peritoneal lesions deep in the retroperitoneal space. In cases of lateral peritoneal invasion, the uterosacral ligaments are involved. The other one is adenomyosis of rectovaginal septum which originates from the tissue of rectovaginal septum and consists essentially of smooth muscles with active glandular epithelium and scanty stroma. These two series are by Donnez et al and they assumed that deep fibrotic tissue contains adenomyosis and it was excised from the anterior rectum with aid of multiple rectovaginal examinations. Cul-de-sac dissection was followed by excision of deep fibrotic adenomyosis. They refrained from doing extensive bowel resection and anastomosis in just 3.5% of the large series of 437 cases. Their result showed marked pain relief with the practice of removing the rectovaginal nodule enbloc with vagina whenever vagina was infiltrated with the lesion. So, they feel it is prudent to curtail, rather than encourage, the wide spread use of an aggressive potentially morbid procedure, i.e. bowel resection and anastomosis. In their hands dyspareunia and dysmenorrhea improved significantly and they reserved bowel resection only on cases of rectal bleeding and sigmoid or rectal stenosis. We in our department have stayed with this philosophy and found excellent pain relief with enbloc

dissection of rectovaginal nodule with vagina over period of last twelve years.

ENDOMETRIOSIS OF RECTOVAGINAL SEPTUM

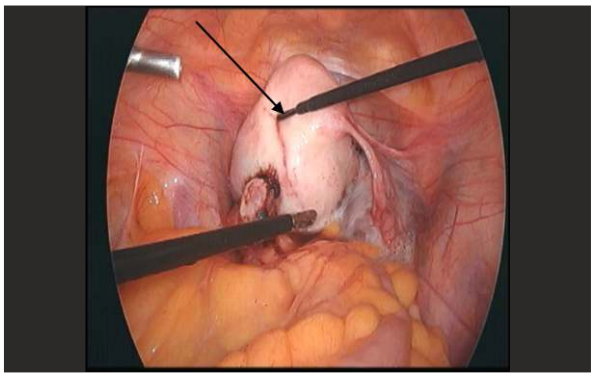


Fig.3.a. Pitressin being injected, note the blanching

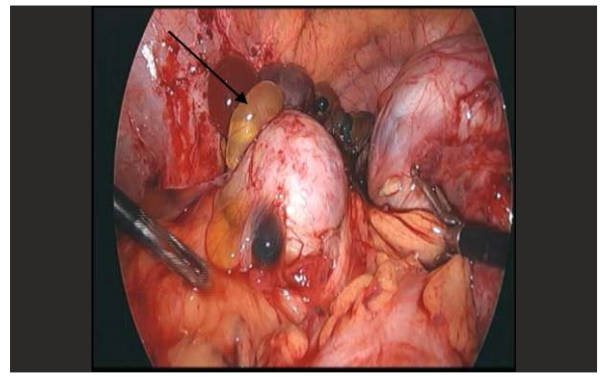


Fig.3.b. Rectovaginal endometriosis with peritoneal jelly

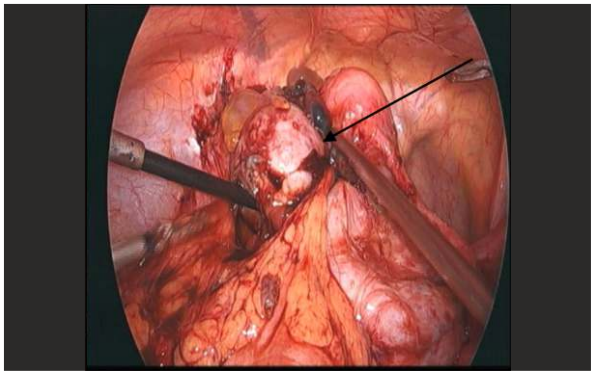


Fig.3.c. Dense adhesions between uterus, ovary and bowel, POD obliterated

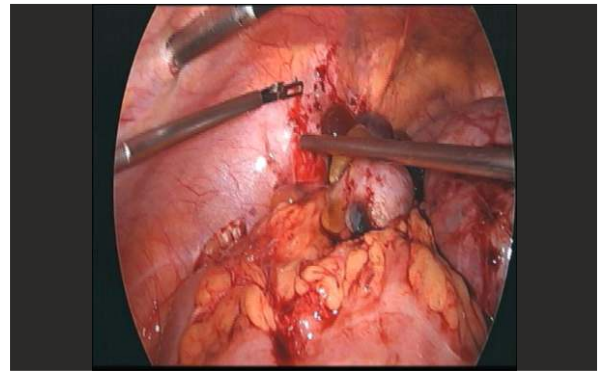


Fig.3.d. Adhesiolysis with bipolar, sharp and blunt dissection

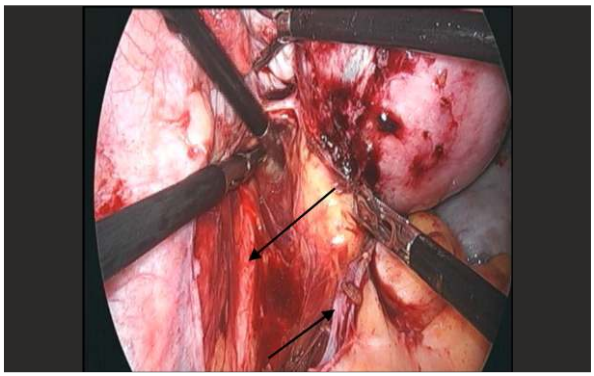


Fig.3.e. Ureter dissection and lateralization of inferior hypogastric plexus

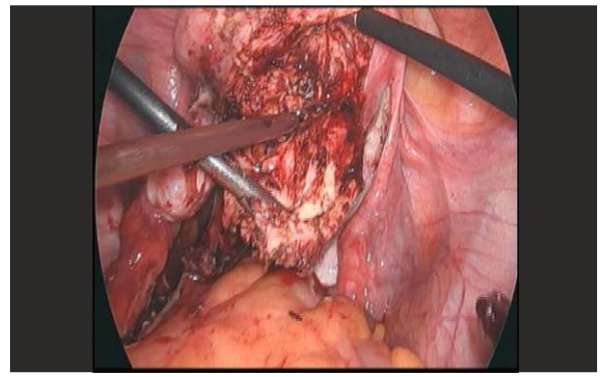


Fig.3.f. Clearing POD

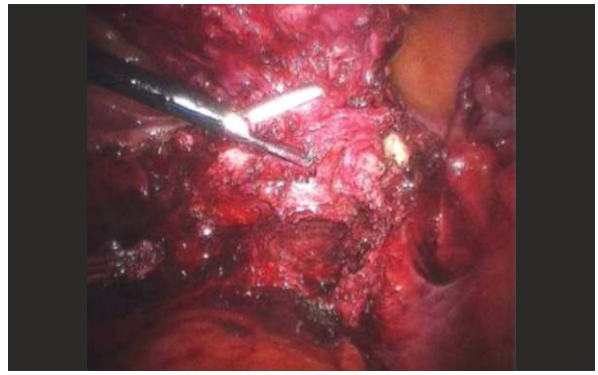


Fig.3.g. Rectovaginal nodule fully exposed and held by tooth grasping forceps

4. (A) ENDOMETRIOSIS OF URINARY TRACT/URETER:-

Multidisciplinary surgical team is required.

- **Bladder**

  Bladder lesions are usually located in roof /post wall of bladder, frequently adherent to the uterine corpus / isthmus.

Preliminary Cystoscopy.(Fig.4.b.)

↓

Identify endometriotic lesions.

↓

Remove by grasper and resecting it either mechanically with scissors or monopolar pure cut mode. (Fig.4.c)

↓

After excising the lesion suture with Vicryl 3-0.
Distend it again to identify any leakage

↓

Catheter for 7 – 14 days.

(b) Endometriosis of Ureter: First identify for extrinsic compression distortion of anatomy / intrinsic disease.

↓

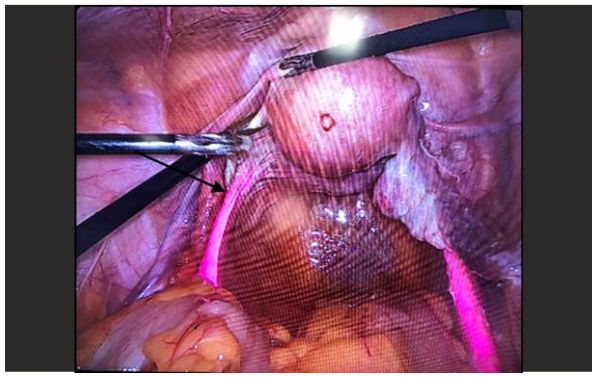
Ureter anatomy delineated by uriglow(Fig.4.a)

↓

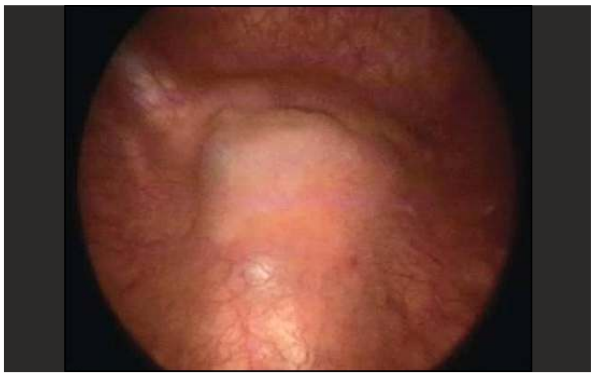
Excise extrinsic adhesions / intrinsic lesion.

- **Adhesiolysis without using electrical energy.**
- Superficial lesion:- sharp scissor.
- Deep lesion:- segmental excision with scissor without any energy end to end anastomosis with 5-0 monofilament.

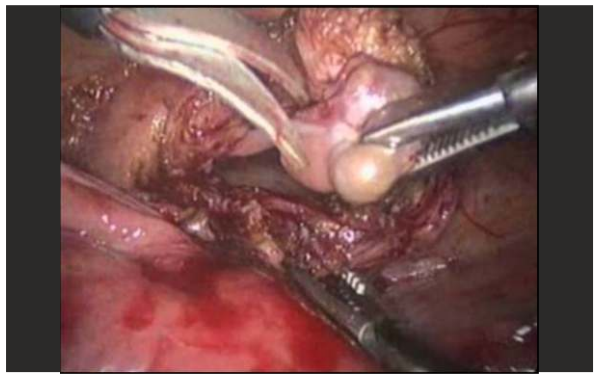
ENDOMETRIOSIS OF URINARY TRACT AND BOWEL



4.a.Uriglow to highlight both ureters



4.b.Cystoscopy with bladder endometriosis



4.c.Laparoscopic treatment of bladder endometriosis

5. RECTO CERVICAL AND BOWEL ENDOMETRIOSIS

Incidence : 3 – 37%

Rectosigmoid involvement – 90%

Required investigation – TVS / MRI

Multidisciplinary approach is required.

STEPS:-

- Pre-operative bowel preparation.
- Antibiotic prophylaxis.
- **Surgery:-** The surgical technique we employ for laparoscopic segmental resection of rectum affected by endometriosis comprises the following successive steps:

Placement of an umbilical incision.

↓

Insufflation of CO2 through the Veres needle to obtain proper pneumoperitoneum and subsequent insertion of a 10 mm trocar and optics

↓

Insertion of 3 auxiliary trocars, 2 at the iliac fossa (10/12 mm on the right and 5 mm on the left) and a 5 mm trocar in the left flank.

↓

Examination of the abdominal and pelvic cavity and identification of all the sites affected by endometriosis.

↓

Lysis of any adhesions affecting adnexal regions, uterine fundus, posterior cul-de-sac and uterosacral ligaments and relevant bowel adhesions

↓

Release of the sigmoid from the left lateral abdominal wall and from the retroperitoneum, identification of the left ureter up to the level of the pelvic brim

Opening of the mesosigmoid

↓

Mobilization of the rectum by dissecting its anterior wall from the posterior surface of the cervix, following which a linear stapler is applied distal to the area affected by the disease

↓

Thereafter the 10/12 mm incision on the right iliac fossa is enlarged sufficiently to exteriorize the divided bowel enclosing the diseased portion. The proximal stump is sutured to form a pouch; the ogive of the circular stapler is placed inside the stump

↓

The bowel containing the ogive is reintroduced into the abdominal cavity and the abdominal incision is closed(Fig.5.a & 5.b)

↓

The circular stapler is then introduced through the anus and connected to the ogive and the stapler is activated to form the end-to-end anastomosis.

More recently, the possibility of lymph node involvement has been described in cases of endometriosis affecting the rectum and sigmoid. In a series of 40 consecutive segmentary resections, Abrão reported that during pathologic examination of the specimens, in 19 of the 40 cases lymph nodes were detected in the surgical specimens, and in 26% of these 19 cases the lymph nodes were found to have endometriosis. It must be noted that positive lymph nodes were present in 100% of the cases in which the disease was affecting more than 80% of the circumference of the rectum; the thicker the lesion, the greater was the probability of lymph node involvement. These data illustrate the aggressive nature of this disease.

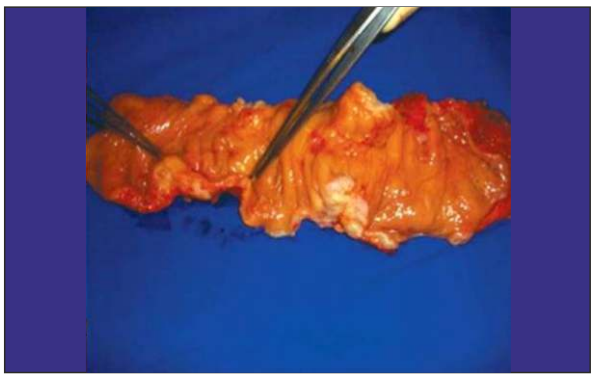


Fig.5.a.Sigmoid endometriosis

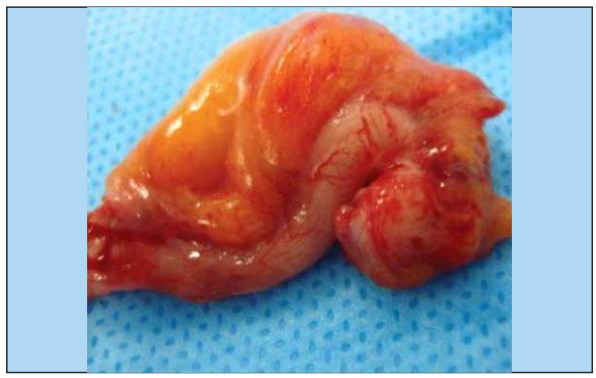


Fig.5.b. Appendix endometriosis

FOLLOW UP FOR FERTILITY:

Fertility mainly depends on 4 factors.

1. Age of patient.
2. Duration of marriage.
3. Husband semen analysis.
4. Patency of fallopian tubes.

In endometriosis there is already low ovarian reserve, hence, immediately after surgery we don't expect good ovarian function. AMH takes 3-6 months for recovery after good surgery.

In grade I & II Endometriosis:-

We don't need to downregulate. Routine follow up is done with controlled ovarian hyper stimulation.

In grade III & IV Endometriosis:-

We downregulate for 2 cycles followed up with controlled ovarian hyper stimulation. If semen analysis & tubal factor patency is favorable then patients is advised for natural conception else we resort to IUI & IVF respectively.

CONCLUSION:

Deep endometriosis requires a thorough preoperative investigation and appropriate, subsequent surgical planning. It is imperative to perform a careful, thorough and critical preoperative analysis of the clinical data and the findings of the various imaging techniques used to plan the appropriate treatment and surgical approach and avoid the surgical team to face a situation it is unable to resolve satisfactorily. Thereafter, the surgical approach for the various parts of the procedure will depend on the symptoms of the patient and the extent of invasion of each organ involved by the disease. The surgical team must be multidisciplinary, composed of gynecologists, urologists and digestive tract surgeons, as necessary, since all visible and palpable lesions of the disease must be excised for the patient to reap any real benefits, bearing in mind that the concept of "one shot surgery" is the best option to avoid persistence of lesions and minimize the rate of recurrence of the disease following surgery.

Suggested reading :-

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3. Valentin L. Pattern recognition of pelvic masses by gray-scale ultrasound imaging: The contribution of Doppler ultrasound. Ultrasound Obstet Gynecol. 1999;14:338.

4. Donnez J, Nisolle M, Casanas-Roux F, et al. Laparoscopic treatment of rectovaginal septum endometriosis. In Donnez J, Nisolle M (Eds): An Atlas of Laser Operative Laparoscopy and Hysteroscopy. Carnforth, UK: Parthenon Publishing. 1994;75- 85.
5. Donnez J, Nisolle M. Advanced laparoscopic surgery for the removal of rectovaginal septum endometriotic and adenomyotic nodules. Baillieres Clin Obstet Gynecol. 1995;9:769-74.
6. Abrao MS, Neme RM, Averbach M. Rectovaginal septum endometriosis: a disease with specific diagnosis and treatment. Arq Gastroenterol. 2003;40(3):192-7.
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ABOUT THE AUTHOR

1. Director of Vardhman Infertility & Endoscopy Centre, Muzaffarnagar, India.
2. Elected Board member of International Society of Gynecological Endoscopy(ISGE) in 2006.
3. Nominated for AAGL Board of Trustees in 2008 to represent ASIA PACIFIC REGION
4. Member of Governing Council of ICMR (Indian Council of Medical Research)
5. Live telesurgery relay of laparoscopic surgery to AAGL 46th annual global congress in Washington DC ,USA on 16th November 2017
6. Author of seven Text Books of Laparoscopic Surgery which are translated in Spanish & Chinese and are very popular world wide. They are on Laparoscopic suturing, pelvic floor repair and General laparoscopy and a video atlas.
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Corrected

A Novel Concept of Management of Poor Ovarian Responder (POR) : The POSEIDON Stratification

Dr. Gita Khanna
Dr. Trishya Reddy, Dr. Farhat Kazim & Dr. Arti Gupta

- **It was concluded that "poor ovarian responders" should be considered patients having at least two of the following criteria:**
  - **Advanced maternal age [> 40 years] or any other risk factor for POR.**
  - **A previous Poor Ovarian Response in ART cycles [<3 oocytes with conventional stimulation protocols].**
  - **An abnormal Ovarian Reserve Test [i.e. AFC 5-7 follicles or AMH between 0.5 – 1.1 ngm/ml].**
- **POSEIDON combines quality and quantity for the stratification of patients with confirmed or expected inappropriate ovarian response.**
- **POSEIDON may allow clinicians to estimate the number of oocytes needed to achieve a new marker of successful outcome, i.e., at least ONE euploid embryo for transfer in each patient.**
- **By using POSEIDON, clinicians would be able to set patient expectations and establish a workable plan to reduce the Time-to-Pregnancy.**
- **POSEIDON concept of low prognosis can help to improve the management of patients undergoing ART by promoting a tailored approach to patient handling**
- **POSEIDON concept may help identifying more homogeneous populations for clinical trials, thereby providing better tools with which to maximize IVF success rates.**
- **Several Tests proposed to Predict Ovarian Reserve -**
  - **Serum FSH - High levels [>12 or >15 mIU/ml] on cycle day 2 or 3.It is only screening test. It is a good predictor only at high threshold >12 mIU/mL**
  - **Serum estradiol [E2] - Elevated levels [>30 – 75 pgm/ml] on cycle day 2 or 3.Limited by its very low predictive accuracy for poor response.**
  - **Serum INHIBIN-B - Decreased levels [45pgm/ml] on cycle day 2 or 3. Accurate only at a very low threshold level.**
  - **Serum AMH seems to be a better predictor of overall ovarian response & poor response.**

INTRODUCTION

Poor ovarian responders are a big challenge to the present era of reproductive medicine and are now categorized separately. The number of oocytes obtained after controlled ovarian stimulation (COS) is of central importance for success in ART.

INCIDENCE

10% of the women undergoing ART will show poor response to gonadotrophin stimulation.[1-3] The incidence of poor ovarian responders among infertile women has been estimated at 9–24% [4]. Data from ASRM/SART registry showed that of 14.1% of initial cycles cancelled at least 50% of these were poor responders [5].

ETIOPATHOGENESIS

Reproductive ageing is a continuous process from before birth till menopause. Women have a finite number of germ cells whose number is maximum at 6-7 million by 20 weeks of gestation. After this throughout reproductive life; an irreversible attrition progressively decreases the germ cell pool of ovaries.

Diminished ovarian reserve is a phenomenon often noted in women in their mid to late thirties, but it may affect younger women as well. It is believed that there is an accelerated decline in follicular pool at the age of 37–38 when it reaches below a critical level of 25,000 [6]. Subsequently, there remains a very limited time for conception with one's own eggs. It is believed that this phenomenon is accompanied by a declining quality due to aging oocytes, and hence, young women with POR may have better chance at conception [7,8]. However, recent evidence challenges this and POR may be associated with low pregnancy rates irrespective of age[9-11] and a high pregnancy loss[12,13].

Women beyond 30 years of age have shown fertility decline gradually due to reducing primordial follicular pool as a result of ovulation but predominantly because of follicular atresia. Non Growing follicular pool (NGF) at different ages may have a differing response to changes in hormone levels associated with age.

Women of all age groups with Non Growing follicles below the normal range would have a suboptimal response to ovarian stimulation and lead to a reduced reproductive life span. These women would undergo an early menopause considering a fixed time interval between end of fertility and menopause.

CAUSES OF EXPECTED POOR OVARIAN RESPONSE (RISK FACTORS)[14]

1) Physiological cause:

- Decline of the "follicular pool" with age

2) Acquired Causes:

- Short menstrual cycle length.

- Previous Ovarian Cystectomy (endometriosis, tumors, other ovarian cysts) or Solitary Ovary
- Unexplained Infertility
- Previous Chemotherapy and Radiotherapy.
- Extensive Genital Tuberculosis
- Diabetes mellitus Type I (Soto et al., 2009)
- Transfusion-dependent B-thalassemia (Chang et al., 2011)
- Chronic Smokers
- Uterine Artery Embolization for Fibroids
- Ethnicity: Indian Women undergoing IVF, Ovarian ageing was found to be approximately 6 years older than Caucasians.

3) Genetic Risk Factors:

- Family history of Premature Menopause
- Fragile X mental retardation 1[FMR1]
- FSH Receptor [FSH R] and LH Receptors [LH R] Polymorphism is considered to be important cause of unexplained Poor Ovarian Response in young women.

HOW WILL YOU DIAGNOSE POR – OVARIAN BIOMARKERS (ORTS)?

It is of extreme importance to predict who will be a poor responder, because stimulation protocols should be ideally individualized accordingly. There are several tests proposed to predict ovarian reserve, which can give an idea about the ovarian response.[15,16,17,18]

1) Static tests - A. Biochemical Testing of ovarian reserve based on a single measurement of early follicular phase [cycle day 2-4].

- Serum FSH - High levels [>12 or >15 mIU/ml] on cycle day 2 or 3.It is only screening test. It is a good predictor only at high threshold >12 mIU/mL
- Serum estradiol [E2] - Elevated levels [>30 – 75 pgm/ml] on cycle day 2 or 3.Limited by its very low predictive accuracy for poor response.
- Serum INHIBIN-B - Decreased levels [45pgm/ml] on cycle day 2 or 3. Accurate only at a very low threshold level.
- Insulin like growth factor 1 (IGF 1) - Low levels of IGF-1 in follicular fluid are poor predictor in follicular fluid.
- AMH - a glycoprotein produced by the granulose cells within preantral and early antral follicles. Serum AMH seems to be a better predictor of overall ovarian response and poor response compared to FSH and age, though it cannot be the absolute predictor, levels of 0.5 – 1.1 ngm/ml is also discriminatory for POR[19].

B. Sonographic Tests -

- **Ovarian Volume -** Decreased ovarian volume is hardly suitable as a routine test for ovarian reserve assessment.
- Antral follicle count (AFC) - AFC is defined as the number of follicles smaller than 10 mm in diameter detected by Transvaginal Sonography in early follicular phase. AFC less than 4 is discriminatory for POR, more likely to have cancelled cycles.

2). Dynamic Tests Clomiphene Citrate challenge test [CCCT], Exogenous FSH ovarian reserve test [FSHORT] and GnRH agonist stimulation test [GAST] are Dynamic tests but evidence suggests that dynamic tests should be abandoned.

DEFINITION OF POOR RESPONDER: ARE WE ON THE RIGHT PATH?

Majority of attempts at definition of POR have considered certain parameters noted during ovarian stimulation for IVF: [20-26].

- The number of mature follicles on the day of human chorionic gonadotropin (HCG) administration (<2 to <5)
- The number of oocytes retrieved (<4 to <6)
- The serum estradiol concentrations (<100 pg/mL on day 5 of stimulation or <300 to <600 pg/mL on the day of HCG)
- The total gonadotropin dose used > 3000 IU and/or the daily stimulation dose >300 IU and/or prolonged duration of gonadotropin stimulation.
- Some define age of > 40 years, previous poor response for diagnosing POR.

DEFINITION OF POOR OVARIAN RESPONSE: THE "BOLOGNA CRITERIA"

The Bologna ESHRE 2011, criteria represent the first real attempt by a panel of experts in reproductive medicine to unify the many definitions proposed to identify poor responder patients by establishing a definite point from which to begin and how to find therapeutic strategies [27].

It was concluded that "poor ovarian responders" should be considered patients having at least two of the following criteria:

- Advanced maternal age [> 40 years] or any other risk factor for POR.
- A previous Poor Ovarian Response in ART cycles [<3 oocytes with conventional stimulation protocols].
- An abnormal Ovarian Reserve Test [i.e. AFC 5-7 follicles or AMH between 0.5 – 1.1 ngm/ml].

What are the pitfalls of "Bologna criteria"? [28,29,30]

1. Heterogeneity of subgroups- the criteria did not cater to the heterogeneity of the population

2. The concept of "sensitivity" is not included – Sensitivity means same age, same BMI and same ovarian reserve but different sensitivity to FSH and LH
3. Age related aneuploidies were not considered

The pitfalls of Bologna criteria lead to the development of POSEIDON GROUP [Patient Oriented Strategies Encompassing Individualized Oocyte Number] which was recently established in 2016 by a group composed of Reproductive Endocrinologists and Infertility Specialists (REI) from 7 countries (Table 1). They proposed a new stratification to classify patients with low prognosis or unexpected inappropriate ovarian response to exogenous gonadotrophins[31].

1.	Carlo Alviggi (Italy)
2.	Claus Y. Andersen (Denmark)
3.	Klaus Buhler (Germany)
4.	Alessandro Conforti (Italy)
5.	Giuseppe de Placido (Italy)
6.	Sandro C. Esteves (Brazil)
7.	Robert Fischer (Germany)
8.	Daniela Galliano (Spain)
9.	Nikolaos P. Polyzos (Belgium)
10.	Sesh K. Sunkara (United Kingdom)
11.	Fillipo M. Ubaldi (Italy)
12.	Peter Humaidan (Denmark)

TABLE 1: POSEIDON WORKING GROUP

Four subgroups of women have been suggested by poseidon, based on the following quantitative and qualitative parameters (figure1)

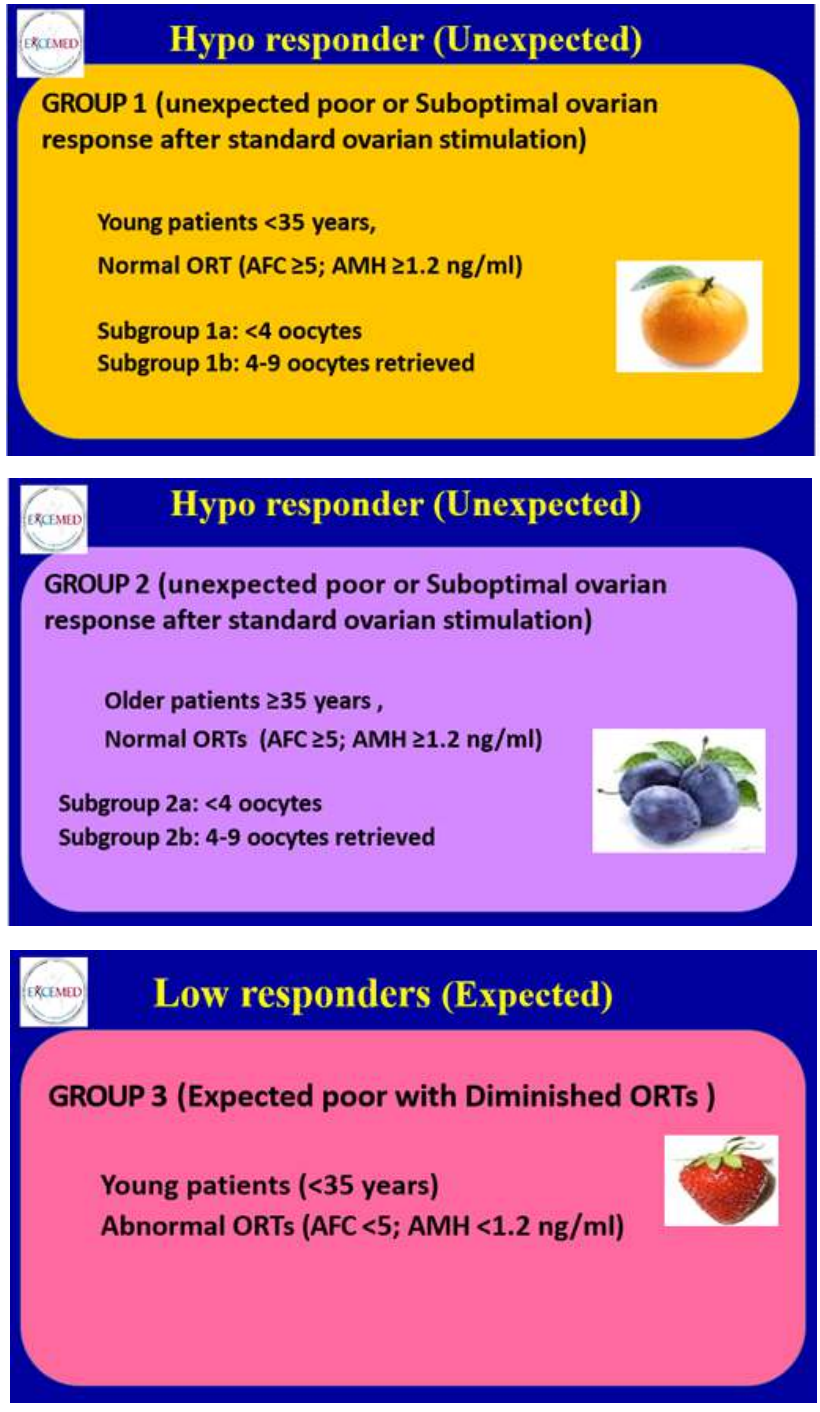
1) Age and expected aneuploidy rate
2) Ovarian biomarkers (AFC and AMH)
3) Ovarian response in previous ART cycle

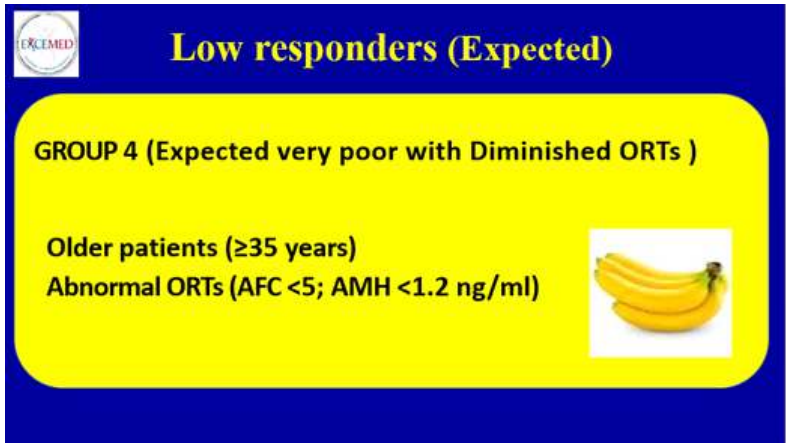
What is unique in POSEIDON classification?[32]

- Introduced the concept of "Low Prognosis" in ART
- Combine oocyte quality and quantity for identification and stratification of the "Low Prognosis" patients
- Included "Hypo-responder" as a distinct category of "Low Prognosis" patients
- Introduced an intermediate marker of success in ART: the ability to retrieve the number of

oocytes needed to obtain at least one euploid blastocyst for transfer in each patient. Hence, transfer of euploidy embryo maximizes IVF efficiency by offsetting the Negative effect of age on implantation and pregnancy.

Figure 1. Four groups of 'low prognosis patients' in assisted reproductive technology according to the POSEIDON's stratification based on oocyte quantity and quality.





What do you mean by hyporesponse or hyposenstivity of ovarian follicles to gonadotropins?[33]

It is important to understand "ovarian sensitivity" when developing an individualized approach to ovarian stimulation. A reduced ovarian sensitivity is typical for hyporesponsive women in whom, despite having a good ovarian reserve, a standard COS protocol proves to be below expectation. There are differences between hyporesponse and POR, and was emphasized in the new Poseidon criteria for the identification of women requiring COS but who have a poor prognosis (Poseidon Groups 1 and 2). In essence, the hyporesponder is a woman in whom we are unable to exploit her full reproductive potential with a conventional stimulation protocol. Indeed, such women typically have good ovarian reserve but an unexpected low response to ovarian stimulation, irrespective of age (Figure 2).

Poor responder (ESHRE, Blogna criteria)	Hypo responder
At least two of the following three features must be present: • Advanced maternal age (≥40 years) or any other risk factor for POR (Turner syndrome, X-fragile mutation, history of chemotherapy etc.) • A previous poor ovarian response (POR) [≤3 oocytes with a conventional stimulation protocol) • An abnormal ovarian reserve test (i.e., AFC 5-7 follicles or AMH 0.5 – 1.1 ng/ml)	• Young, normogonadotrophic women, with normal ovarian reserve who show sub-optimal or unexpected poor response to exogenous FSH • These women even when the ovarian response is normal (i.e., >5 eggs) tend to show an increase in the cumulative FSH dose (i.e > 2500-3000 IU) and in the stimulation length (hypo-sensitivity to FSH)
Ferraretti et al. Hum Repro; 2011	De Placido, et al Hum Reprod 2001: Clin Endocrinol 2004; Hum Reprod 2005; Drugs 2008. Ferraretti, et al. Fertil Steril 2004. Kailasam, et al. Hum Reprod 2004 Alviggi, et al. RBMOnline 2006; RBMOnline 2009; Reprod Biol Endocrinol 2009; 2011

Figure 2: Difference between hyposensitivity to FSH and poor ovarian reserve

What could be the reason of unexpected hyporesponse?[34]

Hyporesponders to FSH are women with normal ovarian reserve who require elevated r-FSH dosage (i.e. >3000 mIU), and who show a reduced response during COS in terms of estradiol levels and/or follicular growth.

Hyporesponse characterizes the interplay between gonadotropins and their receptors, and can be quantitatively evaluated by calculating the woman's Follicle Output Rate (FORT). **The FORT reflects ovarian follicular competence, by calculating the percentage of antral follicles that respond effectively to FSH after COS. A FORT of ~30% denotes poor response (hyposensitivity), and can be noted in 15% of women with good ovarian reserve (Figure3).**

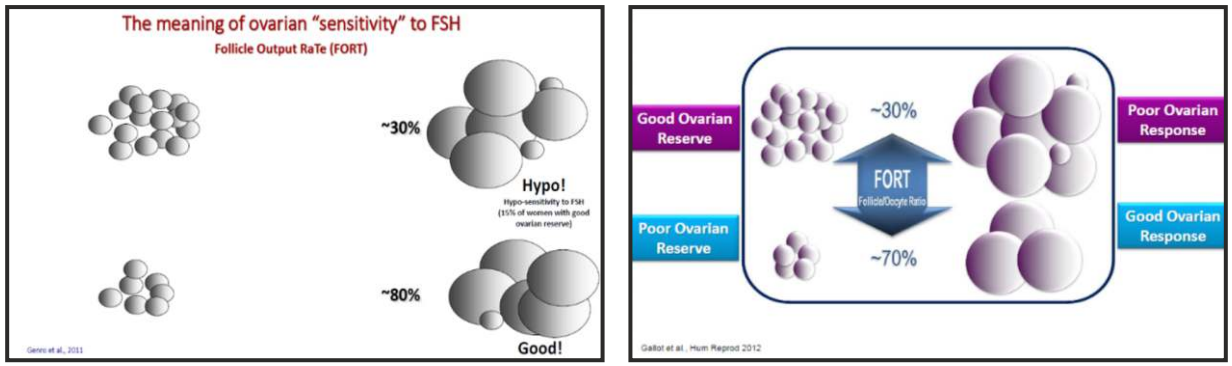


Figure 3: The meaning of ovarian "sensitivity" to FSH

Hyporesponse to COS is associated with specific polymorphisms. In detail, it was demonstrated that FSH-RSer680 and common V- beta LH polymorphism carriers show a reduced sensitivity to exogenous gonadotropin administration. (Figures 4a and 4b). While carriers of the Ser680 polymorphism may achieve a good ovarian response by increasing the gonadotropin dosage, carriers of the common V-LH beta polymorphism may benefit from LH supplementation.

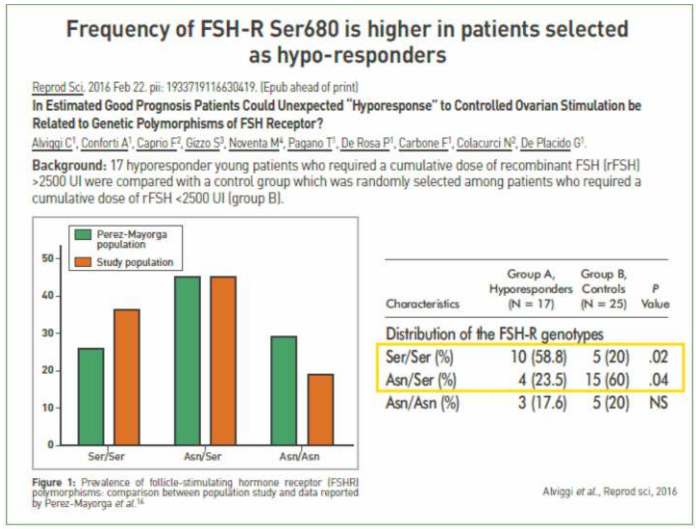


Figure 4a: Hyporesponders and the link with FSH-R SER680

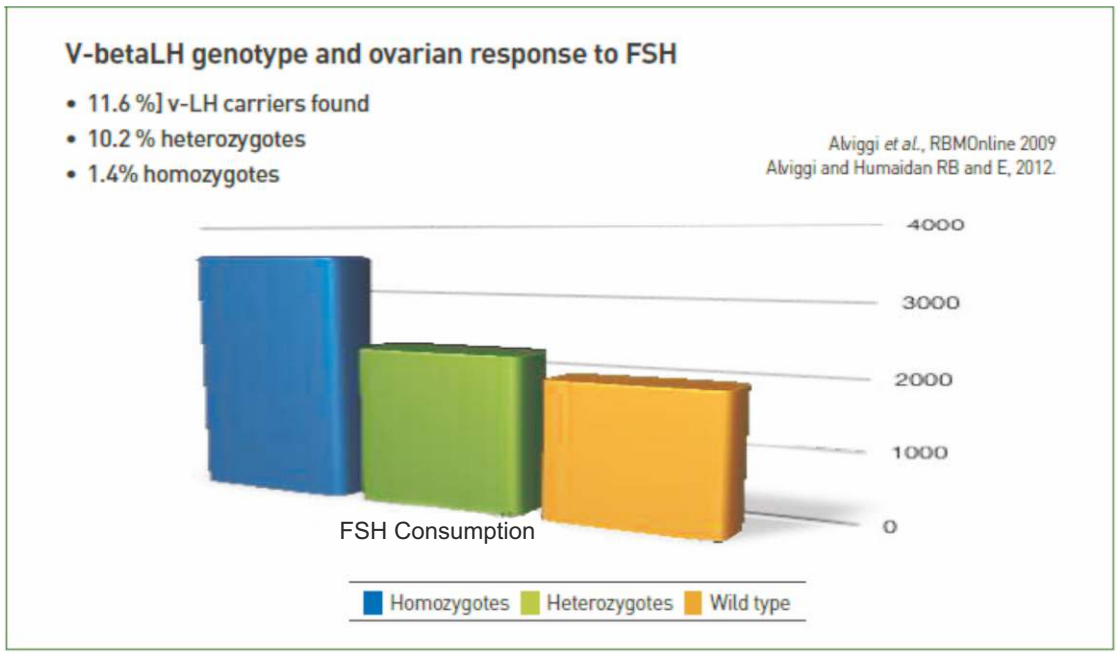


Figure 4b: Hyporesponders and common LH variants

Intermediate marker of success in ART according to poseidon stratification [35]

Estimating the number of oocytes needed for one euploid embryo transfer proposed as an intermediate marker of success in ART.

- It is found that cohort size has no impact on embryo euploidy rate (Figure 5)[36].
- Embryo euploidy rate is independent from the number of obtained blastocysts but not of age (Figure 6) [37].

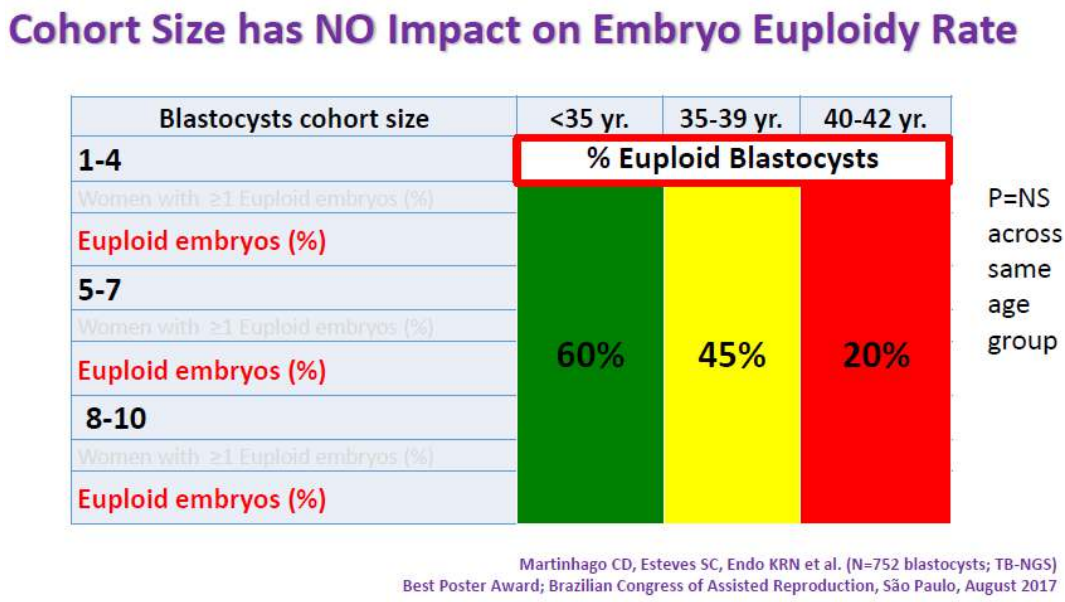


Figure 5: Cohort size has no impact on embryo euploidy rate

Number of blastocysts	% normal embryos				
	<35 y	35-37 y	38-40 y	41-42 y	>42 years
1-3	61%	51%	39%	22%	13%
4-6	60%	52%	38%	23%	17%
7-10	62%	51%	36%	21%	14%
>10	63%	55%	37%	25%	n/a

N. = 4,747 cycles and 29,803 embryos. (Modified from Munne)
Ata, Munne et al. (2012) Reprod Biomed Online and unpublished data

Figure 6. Age related aneuploidies

It is important to remember three things [35]

- Oocyte quantity and oocyte quality are not the same
- Euploid embryo output varies with age
- Transfer of a euploid embryo practically eliminates the age-related decline in implantation rate.

The ART Calculator -

The new ART Calculator based on mathematical function taking relevant predictive factor into account, is an online tool that may be of value in the clinical management of people undergoing ART. It is compatible with the POSEIDON classification, in that it estimates the Poseidon's endpoint, namely, the number of oocytes needed to achieve at least one euploid blastocyst (www.groupposeidon.com).

Computing four common IVF parameters– %MII, &2PN, cleavage (D3) or blastocyte formation rate, and embryo euploid rates – provides a reasonable estimate of the number of oocytes required for achieving one euploid embryo. Other qualifiers like, paternal age, sperm source, use of fresh or frozen-thawed oocytes affect these estimates and have a well-known impact on fertilization and blastulation rates (Figure 7).

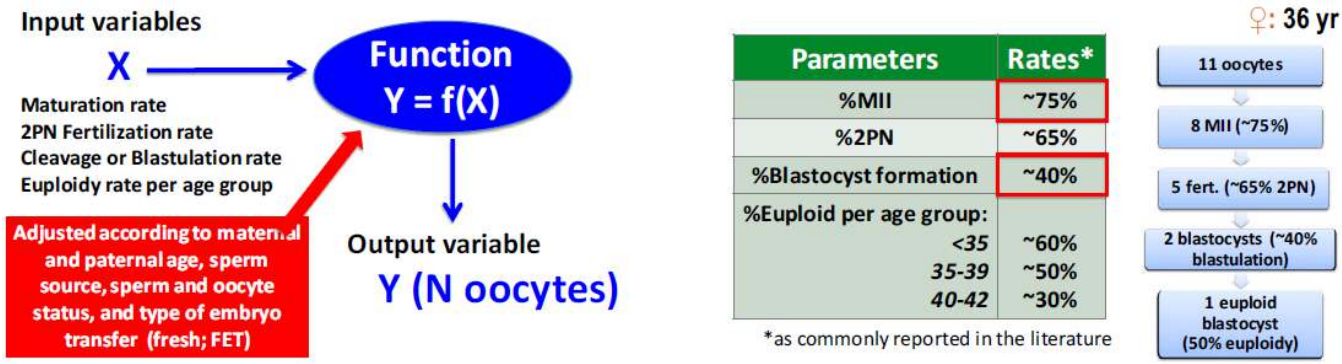


Figure 7: Calculating the number of oocytes likely to be needed to achieve one euploid embryo.

Dr Sandro C. Esteves (Campinas, Brazil) explained these calculations in practical terms: a generalized estimate can be obtained by inputting data into the following formula (Figure 8):

$$\text{N Oocytes} = 1 \Big/ \frac{\text{\% euploid embryos per age group}}{\text{(\% MII)x (\% 2PN)x (\% Blastulation)}}$$

Figure 8: Formula for estimating number of oocytes required to achieve one euploid embryo transfer.

Management of The Poseidon Groups -

Controlled Ovarian Stimulation (COS) strategies to increase oocyte number/quality[38]

Fifteen is the maximum number of oocytes to retrieve, to optimize the likelihood of a live birth. Oocyte/embryo quality declines with age, but not with the number of oocytes/embryos achieved after COS. Professor Peter Humaidan (Aarhus, Denmark) said that the optimum COS protocol should focus on retrieving sufficient oocytes to likely lead to one euploid embryo transfer, without increasing the risk of ovarian hyperstimulation syndrome (Figure 9).

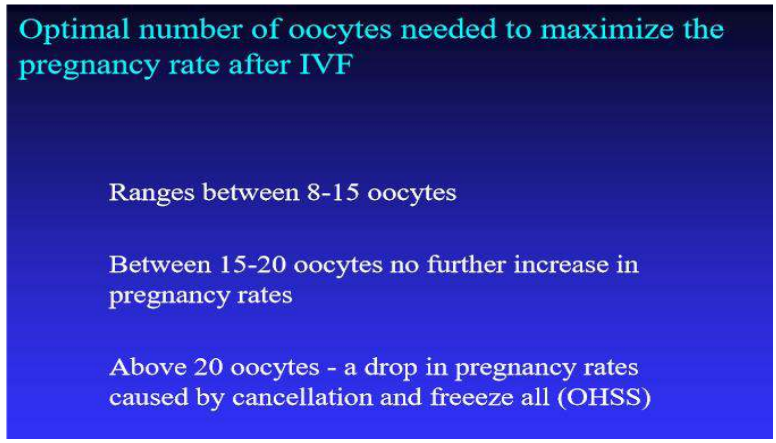


Figure 9 : Advice on the optimum number of oocytes to maximize the IVF pregnancy rate

Protocols for controlled ovarian stimulation for low prognosis cases

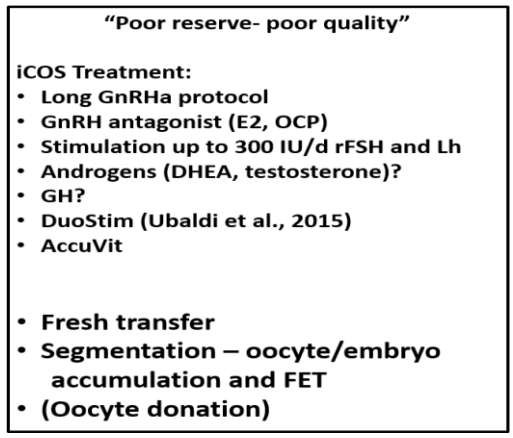


Figure 10 : Possible treatment options for women with poor reserve and poor quality.

POSEIDON is developing protocols for each of four groups of women with POR. Individualized therapeutic approach with the mind set to achieve number of oocytes estimated for obtaining at least one euploid blastocyst.

- GnRH analogue regimen
- Gonadotropin dose and drug type
- Trigger strategy
- Combined strategies (AccuVit; Duostim, etc.)
- Personalized use of laboratory technology
- Personalized luteal phase support

Which POSEIDON groups may benefit from LH supplementation?[39]

1. Increase the dose of Gonadotrophins

When the standard dose of gonadotrophins [225-300 IU] fails to induce proper multifollicular growth, high doses of gonadotrophins have been used. In poor responders; the recruitable follicles are fewer and the gonadotrophins, independently of the dosage administered, can only support, the cohort of follicles receptive to stimulation without manufacturing follicles de novo.

In Hypo-responder patient, LH increases sensitivity of granulosa cells to FSH By enhancing the amount of FSH receptors

Increase rFSH doses or rLH 2:1(FSH/LH)

Group 1 includes women with hyporesponse: rhLH administration may be effective in rescuing the number of follicles/oocytes, and achieving embryo competence, if hyporesponse is identified in days 5−8 of COS.

Group 2 includes older women with normal ovarian reserve, who likely have reduced androgen production: administering LH significantly improves implantation rates, although there is no evidence for improvement in ongoing pregnancy or live birth rates.

The efficacy of rLH in Groups 3 and 4 POSEIDON (women with low ovarian reserve) is under evaluation (ESPART subgroup analyses).

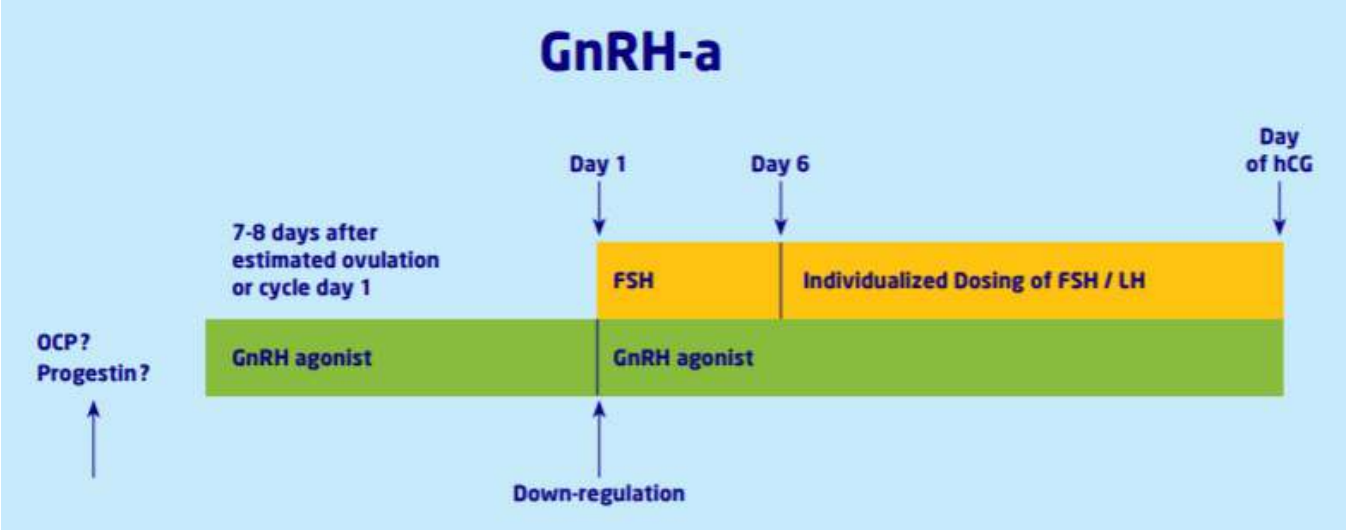
GnRH analogues[40]

From past two decades the combination of gonadotropins and gonadotropin-releasing hormone (GnRH) agonists, started on the late luteal phase of the previous cycle, has been considered the protocol of choice in normo-responder patients. Such approach lowers cancellation rate and raises the number of pre ovulatory follicles and the number of oocytes retrieved and good quality embryos for transfer, leading to better pregnancy rates. However this protocol could have a detrimental effect in poor responders because it may induce an excessive ovarian suppression that could lead to a reduced or absent follicular response. For this reason, in patients with poor ovarian reserve the options could be -

- **To decrease the length of suppression by decreasing the duration of GnRH agonist use (short and ultra- short, mini- and microdose flareup regimens)**
- **To lower or to stop (after pituitary suppression) the dose of GnRH agonists initiated during the luteal phase**
- **To use the GnRH antagonists in combination with gonadotropins to prevent premature LH rise during the mid-late follicular phase.**

The common protocols used are –

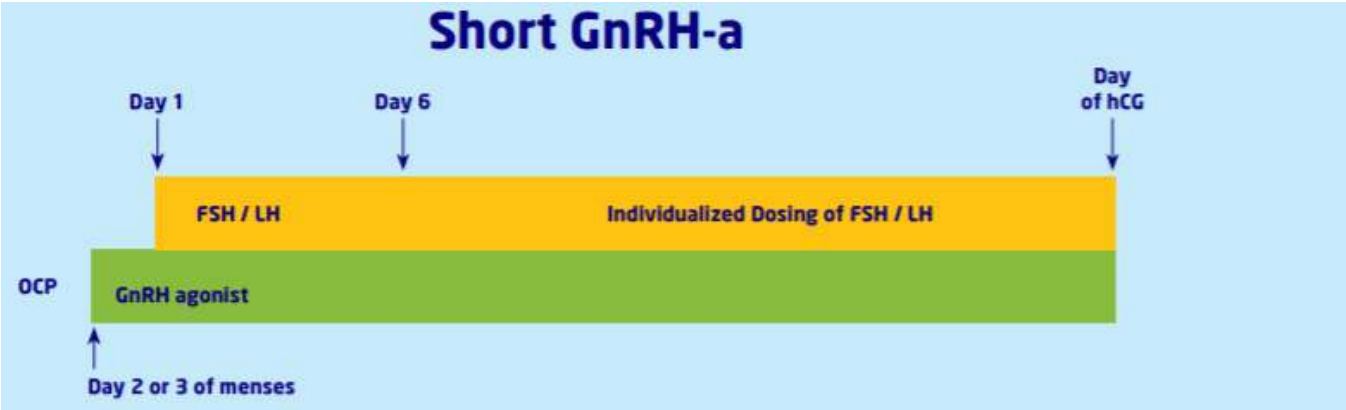
1. Gonadotrophins and GnRH Agonist started in late luteal phase



Limitations

- High Cancellation rate
- Prolonged hormonal stimulation
- High Cost
- Only marginal benefit in yield of mature oocytes

2. Short GnRH agonist protocol

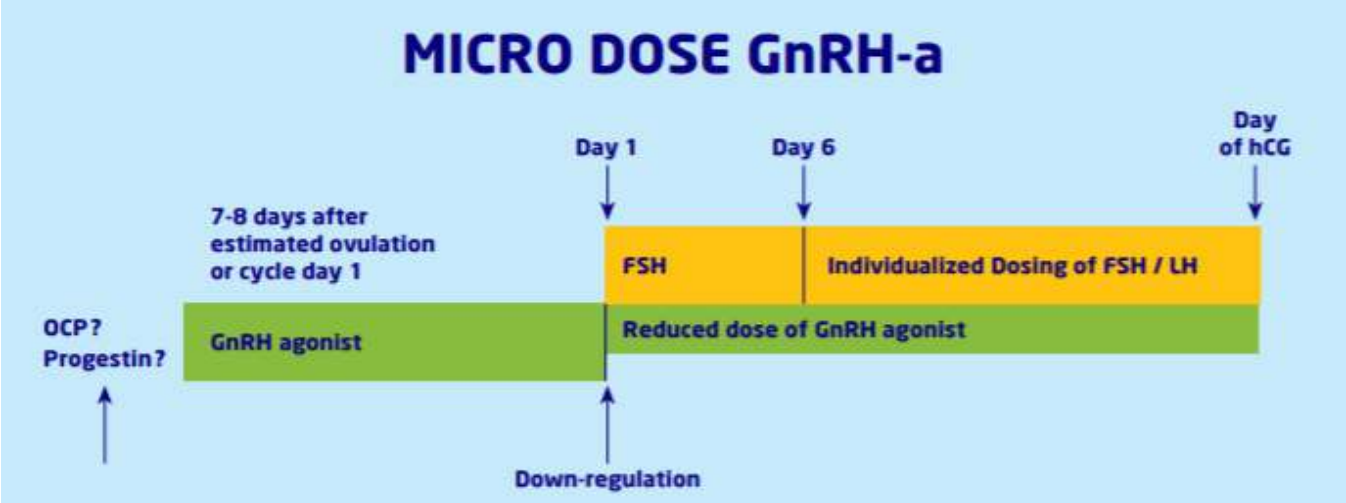


MOA - Initial agonistic stimulation effect on endogenous FSH and LH (Flare up effect)

Advantage

- Decrease in Exogenous gonadotrophin requirement
- Higher Pregnancy rate
- Decrease miscarriage rate Limitations Significant increase in LH and progesterone levels leading to atresia of follicles

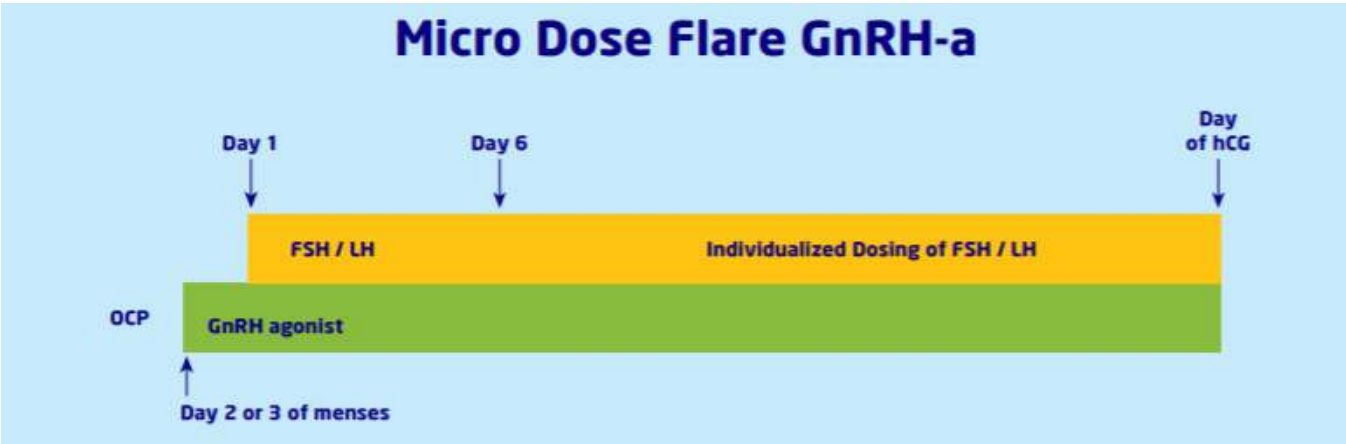
3. Micro dose protocol



Advantage

- Decrease Gonadotrophin requirement
- Shorter duration of stimulation
- Increase E2 concentration on day of stimulation
- Increase number of mature oocytes
- Good quality embryos
- Decrease cancellation rate

4. Micro dose flare up protocol



BASIS - Low dose of leuprolide acetate (25-50ugm) is needed to cause a pituitary flare of gonadotrophins

Advantage

- More physiological
- Rapid rise in E2 levels
- Development of mature follicles
- No premature LH surge

Limitations

- Most studies are retrospective
- Efficiency is yet to be proved

5. GnRH analogue stop protocol

GnRH-a "STOP"

(1) GnRH-a administered as in long protocol from D-21

(2) Withheld once gonadotrophin stimulation has started

(3) No Premature LH Surge

Limitations

Prospective studies, showed that in spite of higher number of oocytes there was no improvement in reproductive outcome.

3. GnRH Antagonist

Advantages

- Suppresses LH surge of late follicular Phase
- Shortens treatment period
- Allows natural follicular recruitment
- Cost effective due to decreased Gonadotropin requirement[41,42,43,44,45,46]

4. DOUBLE STIMULATION (DuoStim)

The application of Double Stimulation (DuoStim) in COS to increase the number of oocytes/embryos in ART [47,48]

The double stimulation approach (DuoStim) could increase the number of available euploid blastocysts within a single menstrual cycle (Figure 9). It consists of both follicular phase (FP) and luteal phase (LP) stimulations, described by Dr Carlo Alviggi (Naples, Italy). This one-round double stimulation protocol may increase the likelihood of achieving competent oocytes and live births in those with a poor pregnancy prognosis following exogenous gonadotropin (e.g. women in Groups 3 and 4 in the POSEIDON stratification).

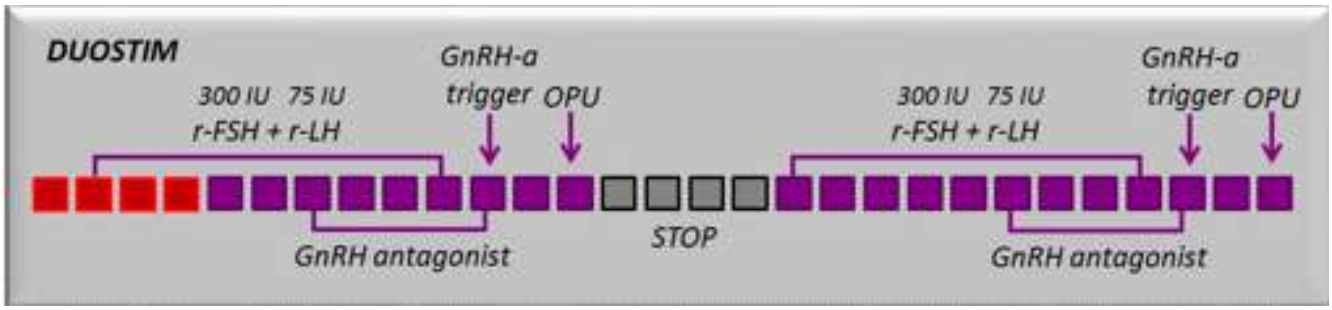


Figure 9. DuoStim may be a useful strategy for women with POR, with poor pregnancy prognosis

DuoStim follows the principle that follicles developing during the luteal phase may have the potential to ovulate in the presence of a LH surge, offering improved possibilities for ovarian stimulation. Two or three follicular waves have been observed in ultrasonographic studies taken during the intraovulatory period. Such waves are characterized by an increase, then decrease, in the number of 5mm follicles, as two follicles reach 6mm. Existing antral follicles in the luteal phase enable ovarian stimulation. Luteal-phase stimulation is already used in cryopreservation strategies, such as in women requiring emergency fertility preservation.

In Group 3 or 4 patients (POSEIDON), oocyte/blastocyst accumulation is an option, and the DuoStim strategy helps to maximize the number of oocytes per menstrual cycle in these women, while taking account of the woman's ovarian reserve.

AccuVit - Accumulation of oocytes and/or embryos by vitrification[49]

Obtaining a large cohort of oocytes in poor responders by accumulating vitrified (AccuVit) oocytes over several cycles of stimulation could result in higher live birth rate per patient and potentially reduce dropout.

CONCLUSION

1. POSEIDON combines quality and quantity for the stratification of patients with confirmed or expected inappropriate ovarian response.
2. POSEIDON may allow clinicians to estimate the number of oocytes needed to achieve a new marker of successful outcome, i.e., at least ONE euploid embryo for transfer in each patient.
3. By using POSEIDON, clinicians would be able to set patient expectations and establish a workable plan to reduce the Time-to-Pregnancy.
4. POSEIDON concept of low prognosis can help to improve the management of patients undergoing ART by promoting a tailored approach to patient handling
5. POSEIDON concept may help identifying more homogeneous populations for clinical trials, thereby providing better tools with which to maximize IVF success rates.

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Ovarian Rejuvenation by Autologous Stem Cells

Dr. Sunita Tandulwadkar **Dr. Shreya Gupta**

- **Various factors that lead to DOR are ovarian toxicants, cigarette smoking, alcohol abuse, nutritional deficiencies, oxidative stress, metabolic disorders, autoimmunity, long term stress-depression, iatrogenic (Pelvic surgeries, chemotherapy and radiotherapy), infections, endometriosis and various genetic mutations. The modern stressful lifestyle, delayed child bearing has also resulted in speedy ovarian aging.**
- **Clinical applications of ABMDSCT is becoming popular for many degenerative diseases and POI. Ovarian instillation of ABMDSC can promote folliculogenesis in women suffering with POI.**

HUMAN OVARIAN RESERVE FROM CONCEPTION TO THE MENOPAUSE

The adult human ovary is devoid of germ line stem cells. As such, female reproductive senescence largely results from depletion of a finite ovarian follicular pool, that is produced during embryonic development[1]. A rapid mitotic multiplication of germ cells begins at 6-8 weeks of intra-uterine life (IUL) and by 16-18 weeks of IUL, a maximum total of 6-7 million oocytes are formed in both ovaries[2].

The primordial follicle is non-growing and consists of oocyte arrested in diplotene stage of meiotic prophase, surrounded by a single layer of spindle shaped granulosa cells. These follicles represent the entire ovarian reserve that a female will ever possess. From a maximum number at 16-18 weeks, the number will irretrievably decrease. The rate of decrease is proportional to the total number present. Therefore the most rapid decrease occurs before birth resulting in a decline from 6-7 million to 2 million at birth and to 300,000 at puberty. From this large reservoir about 300-400 follicles reach maturity and ovulate during the reproductive life span of an adult female[2]. The rest of follicles are lost with apoptosis, which continue during periods when there is no ovulation, such as pregnancy, breast feeding or use of oral contraceptives. The most of oocytes are lost via apoptosis which is more accelerated process in the last 10-15 years before menopause[3]. When a female reaches the mean age of 45 , follicle pool usually decreases below a critical value of 1000 or less follicles and irregular cyclic changes exist as first clinical sign of ovarian aging[4,5].

DIMNISHED OVARIAN RESERVE (DOR) - A GLOBAL CONCERN

DOR is defined as a decrease in quantity and quality of oocytes. It is used to describe women of reproductive age with regular cycles mostly ovulatory, whose response to stimulation or fecundity is reduced compared to women of comparable age. DOR is distinct from premature ovarian insufficiency (POI)[6]. POI is a common cause of infertility and is characterised by amenorrhea, oligomennorhea, hypoestrogenism, low anti mullerian hormone (AMH) level and elevated gonadotropin levels in women under age of 40 years[7,8]. It also indicates a reduction in quantity and quality of oocytes in women of reproductive age group. Various factors that lead to DOR are ovarian toxicants, cigarette smoking, alcohol abuse, nutritional deficiencies, oxidative stress, metabolic disorders, autoimmunity, long term stress-depression, iatrogenic (pelvic surgeries, chemotherapy and radiotherapy), infections, endometriosis and various genetic mutations. The modern stressful lifestyle, delayed child bearing has also resulted in speedy ovarian aging[9,10,11.]

Evaluating ovarian reserve and individualizing the therapeutic strategies are very important for optimizing the success rate for treatment of infertility.

HOW TO OVERCOME DECREASE OVARIAN RESERVE

There is overriding concern that women with DOR and POI have a limited reproductive lifespan to conceive with their own eggs. The vast majority of available evidence on efficacy of various therapeutic interventions in women with DOR is in the context of IVF and shows a lowered pregnancy and live birth rate irrespective of age[12,13,14,15]. Thus, majority of time the only option available to such patients is to receive donor oocyte program. However, many women, due to various religious, cultural or ethical consideration, would also like to use their own eggs.

Various adjuvant therapy in the form of oral dehydroepiandrosterone or transdermal testosterone in poor responders has been explored as it is believed to improve the intrafollicular environment and follicular sensitivity to exogenous FSH. Available evidence shows a modest improvement in various parameters including number of oocytes, embryo quality, and live birth rates.[16,17,18,19]

Autologous stem cell therapy (ASCT) for ovarian rejuvenation and regeneration has opened new door for women with POI.

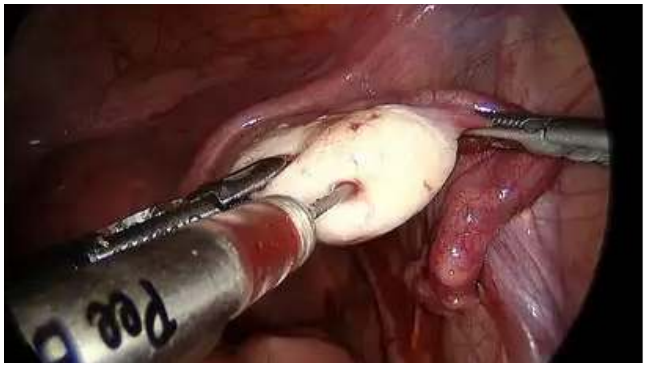
WHAT ARE STEM CELLS

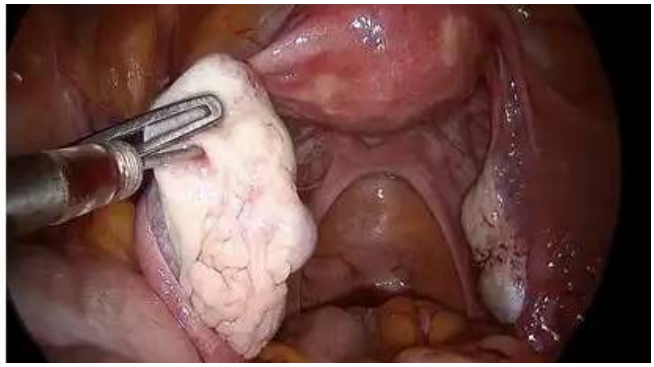
Stem cells (SC) are the foundation cells for every tissue in the body. They are undifferentiated cells that have the potential to develop into specific functioning self sustain cells[20]. Under certain physiologic or experimental conditions, they can be induced to become tissue- or organ- specific cells with special functions.

Resuming oogenesis in-vivo in adulthood still appears a distant hypothesis as there is a lack of concensus about the existence and functionality of adult ovarian stem cells[21]. In presence of all these limitations, use of autologous bone marrow-derived mesenchymal stem cells for follicular recruitment in POI to attain pregnancy has been under trial in various centres across the globe.

PROCESS OF OVARIAN REJUVENATION - STEM CELL THERAPY

The failed ovary needs rejuvenation to produce eggs following stimulation. The bone marrow is easily aspirated from iliac crest which is processed by simultaneous centrifugation and sedimentation to yield mesenchymal stem cells . These stem cell can be instilled either into ovarian artery or directly into ovarian cortex[22] either by transvaginal route under sonography guidance or by laparoscopy.





LAPRAROSCOPIC OVARIAN INSTILLATION OF AUTOLOGOUS BONE MARROW DERIVED STEM CELLS

Another method for ovarian rejuvenation is by fragmentation and re - implantation of ovarian tissue also known as OFFA (ovarian fragmentation for follicular activation)[23].

The improved ovary after stem cell transplantation is complex mix of many unclear factors such as recovering sex hormone function, reducing apoptosis of granuloss cells and increasing the number of follicles. The technique of stem cell therapy has obtained promising results, as even spontaneous pregnancies in women with low ovarian reserve after undergoing bone marrow transplant have been achieved.

Edessy et al[22] proved the therapeutic potential of ABMDSC (Autologous Bone Marrow derived stem cells.) in women suffering from POI. Further researches to determine the efficacy of ABMDSC therapy on ovarian function recovery in subjects with idiopathic and other types of POI are still underway like study by Herraiz et al[24] and ROSE trial(Rejuvenation of premature ovarian failure with stem cells) and their results are still awaited.

In our recent study at Ruby Hall Clinic Pune, we have successfully delivered World's first baby with ovarian Autologous Stem Cell therapy in a perimenopausal woman of age 45 years[25].

Few drawbacks of this therapy are high cost and expertise, lack of long term human studies and lack of universal concensus for use of stem cell therapy.

To conclude, clinical applications of ABMDSCT is becoming popular for many degenerative diseases and POI. Ovarian instillation of ABMDSC can promote folliculogenesis in women suffering with POI. ABMDSC is a novel therapy that improves ovarian function, therefore restoring fertility even in perimenopausal women. It also gives a ray of hope to infertile couples who don't

wish to opt for donor assisted reproductive techniques.

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Empowered Women - Empowering Womanhood

Dr. Madhu Loomba
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Role and rights of women are changing with time & realization but, one thing that has stayed constant is the sheer number of awe-inspiring women that exist all over the world. They all have changed the world.

INDIAN

Neerja Bhanot

Sarla Thakral

Savitribai Phule

Mary Kom

Indira Gandhi

Who: Neerja Bhanot

Why she inspires us : was a flight attendant 22 years old who died while saving passengers from terrorists on board of a hijacked airplane.

What she taught us : Do your duty come what may. Never tolerate injustice and never compromise on self respect.

Who: Sarla Thakral

Why she inspires us: the first Indian women to fly an aircraft and to earn an aviation pilot licence at the age of 21.

What she taught us "Always be happy, it is very important for us to be happy and cheerful. This motto has seen me tide over the crises in my life.

Who: Savitribai Phule

Why she inspires us: established the first women school in India and became the first woman teacher of our country.

What she taught us Awake, Arise and Educate Smash traditions. Liberate.

Who: Mary Kom

Why she inspires us: also called 'Magnificent Mary' is a five-time World Amateur Boxing champion. She is the only woman boxer to have won a medal in all six world championships.

What she taught us - "People used to say that boxing is for men and not for women and I thought I will show them some day. I promised myself and I proved myself."

Who: Indira Gandhi

Why she inspires us: Gandhi was the only female Prime Minister of India, and forged the historic 1972 Simla agreement to end war between India and Pakistan.

What she taught us: 'Forgiveness is a virtue of the brave'.




Lakshmi Sehgal **Shakuntala Devi** **Matangini Hazra** **Arunima Sinha**

Who : Captain Lakshmi Sehgal

Why she inspires us : A doctor, a revolutionary soldier in the Indian struggle for independence, an officer of the Indian National Army, a politician, a social activists, a prisoner of war,

What she taught us : The fight will go on. A doctor who saw patients for charity even at 92 years of age.

Who: Shakuntala Devi

Why she inspires us : An Indian prodigy who holds a record in the Guinness Book for being able to do insanely large mental calculations. Awesome woman!

What she taught us : Nobody challenges me .I challenge myself.

Who: Matangini Hazra

Why she inspires us : 73 years old when while participating in an Indian Independence Movement she was shot dead by the British Indian Police. She held the Indian Flag high and kept chanting Vande Mataram while several bullets pierced into her flesh one after another.

What she taught us : Even in death, the brave heart had ensured that the flag – symbolizing the spirit of freedom – remained unsullied!

Who: Arunima Sinha

Why she inspires us 1st Woman Amputee to climb Mount Everest at the age of 26 years.

What she taught us : She says hardships often prepare ordinary people for an extraordinary destiny.

INTERNATIONAL

Who: Rosa Parks

Why she inspires us : Parks was an NAACP secretary, civil rights activist and 'Mother of the Movement'.

What she taught us: 'Each person must live their life as a model for others'.





Rosa Parks | **Valentina Tereshkova** | **Audrey Hepburn** | **Maya Angelou** | **Margaret Thatcher** | **Jaya Ben Desai**

Who: Valentina Tereshkova

Why she inspires us: Her humble origin as a textile worker, her enthusiasm for parachuting and the fact that she was the first woman to go into space.

What she taught us: Keep reaching for your next goal.

Who: Audrey Hepburn

Why she inspires us: There was nothing Audrey Hepburn couldn't do: she was a humanitarian, dancer, actress and member of the Dutch Resistance.

What she taught us: Endless optimism: 'Nothing is impossible, the word itself says 'I'm possible!''

Who: Maya Angelou

Why she inspires us: Author of 'I Know Why The Caged Bird Sings' and civil rights activist.

What she taught us: 'I've learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel.'

Who: Margaret Thatcher

Why she inspires us: Daughter of a greengrocer, Thatcher rose through the political ranks to become Britain's first female prime minister.

What she taught us: Thatcher lived up to her nickname of 'The Iron Lady'. It may be the cock that crows but it is the hen that lays the eggs.

Who: Jayaben Desai

Why she inspires us: Leader of the strikes in the Grunwick factory dispute, where groups of workers of predominately South Asian heritage went on strike to protest unfair working conditions.

What she taught us: Never ignore the role women who have played in the history of feminism.





Katharine Graham | **Julie Bindel** | **Wangaari Mathaai** | **Vigdis Finnbogadottir** | **Martina Navratilova**

Who: Katharine Graham

Why she inspires us: First ever-female CEO of a Fortune 500 company.

What she taught us: 'To love what you do and feel that it matters – how could anything be more fun?'

Who: Julie Bindel
Why she inspires us: Radical feminist and co-founder of the law-reform group Justice for Women, which supports victims of domestic violence.
What she taught us: To protect our fellow sisters.

Who: Wangaari Mathaai
Why she inspires us: Mathaai was the first African woman to receive a Nobel Peace Prize, which was for 'contribution to sustainable development, democracy and peace.'
What she taught us: The power of grass roots movements – together, women are powerful.

Who: Vigdis Finnbogadottir
Why she inspires us: The world's first democratically directly elected female president, and the longest serving female head of state.
What she taught us: She paved the way for female leaders all over the world. Her personal slogan of 'Never let the women down'.

Who: Martina Navratilova
Why she inspires us: Navratilova has been one of the unrivalled queens of the court for almost 40 years.
What she taught us: How to maintain a successful sporting career over an incredible number of years.


Benazir Bhutto


Princess Diana


Malala Yousafzai


Hillary Clinton

Who: Benazir Bhutto
Why she inspires us: Bhutto served as Prime Minister of Pakistan and was the first woman to head a democratic government in a Muslim majority nation.
What she taught us: The importance of democracy; Bhutto said that it is 'necessary for peace and to undermine the forces of terrorism.'

Who: Princess Diana
Why she inspires us: Her life was tragically cut short, but her inspiring work with AIDs sufferers and anti-landmine campaigns means that Diana truly was 'The People's Princess.'
What she taught us: Everyone in society deserves to have a voice.

Who: Malala Yousafzai
Why she inspires us: Yousafzai 20 years old survived a Taliban assassination attempt as retaliation for her activism for girls' education and went on to be the youngest recipient of the Nobel Peace Prize.
What she taught us: With Malala, When whole world is silent even one voice becomes powerful.

Who: Hillary Clinton:
Why she inspires us: From her championing of the Violence Against Women Act.
What she taught us: Even in the jaws of the most galling defeat, we must learn from our mistakes and carry on fighting for what we think is right.