FOGSI FOCUS

Ovulation Induction & IUI

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Foreword

Prof. Dr. Suchitra N. Pandit

Dear FOGSIANS,

Greetings from FOGSI !

FOGSI has always been in forefront for encouraging and disseminating knowledge, education and research in the field of Obstetrics and Gynecology My theme for this year 2014 is 'Empower women : Empower India - Pledge for Excellence!' Women's health at every stage & every aspect of life is important and that is wealth of the Nation. Fertility is highly valued in most cultures and the wish for a child is one of the most basic of all human motivations. When attempts to have a child fail, it can be an emotionally devastating experience One of the most challenging experience is dealing with the emotional ups & downs relating to medical treatment & the uncertainty about outcomes

I wish to congratulate Dr. Roza Olyai, Vice President of FOGSI 2014 and her efficient team for having worked so hard to bring forth this FOGSI FOCUS on 'Ovulation Induction and Intrauterine Insemination' This entire FOCUS is dedicated to the technical nuances of Ovulation induction, optimal use of various protocols, monitoring and also describes simplistically the technique of Intrauterine insemination .

This FOCUS is interesting to read and is very useful .

So friends empower yourself with all the knowledge and practical tips to pledge excellence in treating your patients .

Wishing all of You the Very Best .....!!

Prof. Dr. Suchitra N. Pandit
President FOGSI & ICOG 2014
Sr. Consultant & Head, Kokilaben Dhirubhai Ambani hospital & Research Centre, Mumbai

Message

Prof. C. N. Purandare

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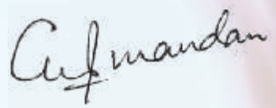
The past three decades have witnessed significant advances in the field of assisted human conception. Following the remarkable perseverance and triumph of Robert Edwards & Patrick Steptoe, numerous scientists and physicians from around the world have worked to develop more effective and safer procedures to treat infertile couples. Along with improvements in the areas of ovarian stimulation, embryo culture and cryobiology, we have seen the introduction of assisted fertilization through intracytoplasmic sperm injection, the development of techniques to remove and perform genetic analysis on polar bodies or blastomeres, and the enhancement of methods for assessing the viability of the developing conceptus.

The basic management of Infertility starts with good knowledge of drugs used for Ovulation Induction & using proper technique of IUI. I would like to Congratulate Dr. Roza Olyai, Vice President FOGSI for bringing out this useful issue of the FOGSI FOCUS.

I am sure the readers will get benefited from the updated topics related to Ovulation Induction & IUI.

With warm regards,



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FOGSI FOCUS ON OVULATION INDUCTION & IUI

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Message from the Editor's Desk...

Dr. Roza Olyai

It gives me great pleasure in bringing out this issue of FOGSI FOCUS on Infertility namely "Ovulation Induction & IUI"

Infertility is generally defined as one year of unprotected intercourse without conception.

Some prefer the term sub fertility to describe women or couples who are not sterile but exhibit decreased reproductive efficiency. Approximately 85–90% of healthy young couples conceive within 1 year, most within 6 months. Infertility therefore affects approximately 10–15% of couples and is an important part of the practice of many clinicians.

A lot of advances have been occurring in the field of infertility over the last decade.

There has also been tremendous increase in the awareness amongst the patients coming for infertility treatment.

This makes it absolutely necessary that all practicing gynecologists keep themselves updated in trends and protocols related to infertility management.

Keeping this in mind we have invited the stalwarts in this field to share their experiences & knowledge.

I hope you will find this issue on Ovulation Induction & IUI of immense benefit in your day to day practice.

I take this opportunity to thank Dr. Suchitra Pandit President FOGSI for entrusting me with this responsibility. I would also like to acknowledge& appreciate the help of my authors who have contributed to this FOGSI FOCUS. Special thanks to Dr. Fessy Louis for helping me compile the articles.

I would specially like to thank Emcure Pharma in supporting this activity, helping to spread the message across the country for the betterment of the infertile patients.

Happy reading!

Roza Olyai

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THE PHYSIOLOGY OF OVULATION

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Introduction

Ovulation is a process where a selected mature follicle breaks and releases an oocyte from the ovary. The ovulation in a woman who has a normal 28-day cycle occurs 14 days after the onset of menstruation. If not fertilized, the oocyte is passed from the reproductive tract during menstrual bleeding, which starts about two weeks after ovulation.

Folliculogenesis

From birth, the ovaries contain a number of immature, primordial follicles each containing an immature primary oocyte. At menarche they undergo a series of histological and hormonal changes. At birth, the number of primordial follicles is about 1 million and at the onset of puberty a few hundred thousand. These progress from primordial through primary, secondary to pre-antral and antral follicles from menarche to menopause, but practically all the follicles (about 99%) will be affected by the phenomenon of atresia at different stages in the course of development. The remaining follicles enter the menstrual cycle, competing with each other until only one follicle is left. This remaining follicle, the late tertiary or pre-ovulatory follicle, ruptures and discharges the secondary oocyte ending folliculogenesis. Folliculogenesis lasts for approximately 375 days. It coincides with thirteen menstrual cycles. The process begins continuously; meaning that at any time the ovary contains follicles in all stages of development, and ends when a mature oocyte departs from the pre-ovulatory follicle in a process called ovulation.

Menstrual cycle

It is divided into three phases: Follicular, Ovulatory and Secretary Phase.

Follicular Phase

In ovary, during follicular phase sequence of events takes place with actions of hormones, autocrine and paracrine peptides that ensures end result as one surviving mature follicle.

This process occur over 10 -14 days. Leading the follicle destined to ovulate through a periods of initial growth from a primordial follicle to pre ovulatory follicle through the stages of pre-antral and antral follicles.

Pre-antral stage

Follicle stimulating hormone (FSH) stimulation takes follicles to the pre-antral stage. FSH induced aromatization of androgens in granulosa results in production of Estrogen. Together FSH as well as Estrogen increase follicular receptors.

At the beginning of each cycle, a group of the most mature follicles (called antral follicles) are recruited. Only the follicles most sensitive to follicle stimulating hormone (FSH) undergo a further development. The remaining follicles undergo atresia.

Antral stage

The rise in FSH concentration stimulates the growth of antral follicles, resulting in an increase of estradiol and Inhibin-B concentrations, producing a negative feedback, i.e. a reduction of FSH concentrations. This combined with rising estrogen concentrations play an important role in the selection of the dominant follicle.

The mid- follicular rise in estradiol exerts a positive feedback influence on LH secretions.

LH levels rise steadily in the late follicular phase stimulating androgen production in theca.

Unique responsiveness to FSH, allows the dominant follicle to utilise the androgen as substrate and further accelerate estrogen production.

Inhibin B secreted by the granulosa cells in response to FSH, directly suppresses pituitary FSH secretion. Activin, originating both from pituitary and granulosa augments FSH secretion and action.

Preovulatory stage

Estrogen concentration becomes sufficient to achieve and maintain concentrations of Estradiol that are required to induce LH surge.In granulosa layer, LH initiates luteinisation and production of progesterone. This preovulatory rise in progesterone facilitates positive feedback action estrogen and may be required to induce the mid cycle FSH peak.

A mid cycle rise in androgens occurs from the theca of unsuccessful follicles.

Ovulatory Phase

Preovulatory follicle through the elaboration of estradiol provides its own ovulatory stimulus. Usually ovulation occur 10-12 after LH peak and 24-36 hours after peak estradiol levels are attained. The threshold of LH concentration is must for 14-27 hours for proper maturation of oocyte. Usually it lasts for 48 hours.

Ovulation occurs primarily in morning during spring and evening during autumn and winter. From July to February n in northern hemisphere about 90% women ovulate between 4-7 pm. During spring 50% women ovulate in between midnight to 11 am.

The main factors responsible for the function of this axis are:

1. Gonadotrophin releasing hormone (GnRH)

GnRH is a decapeptide, synthesized and released by specific neuronal endings in the nucleus arcuatus of the hypothalamus. It is transported through the portal vessels towards the anterior pituitary gland. Small quantities of GnRH are sufficient for effective release of gonadotropins from pituitary gland. GnRH must be released in a pulsatile manner, and it's effects depend on the frequency and amplitude of these pulses. If it is released in a constant, non-pulsatile manner, gonadotropin release is suppressed.

2. Gonadotropins (FSH and LH)

The next step occurs in the pituitary gland. The varying frequency and amplitude of GnRH release determines the pattern of release of the gonadotropins, FSH and LH, during the menstrual cycle, and, subsequently, controls the ovulation and the ovarian steroid production.

3. Ovarian steroid hormones (Estradiol and Progesterone).

The last step of the hormone cascade is localized in the ovaries, where steroid hormones are synthesized caused by the gonadotropins action. These hormones are estradiol, (produced by the growing follicle and the corpus luteum); and progesterone (produced by the corpus luteum), once ovulation has occurred.

Oocyte maturation only occurs within the dominant mature follicle. Until this stage, some inhibit factors such us cyclic adenosine monophosphate (cAMP) and factors increasing it's concentration (e.g. FSH), as well as oocyte maturation inhibitor (OMI) and hipoxantine, keep the oocyte in the immature stage.

Gonadotrophin surge

It stimulates complex series of events causing final maturation of oocytes and decomposition of collagenous layer of follicular wall.

LH surge

It initiates the continuation of meiosis in oocytes, luteinisation of granulosa cells, expansion of cumulus and synthesis of prostaglandins and other eicosanoids which are essential for follicular rupture and rise in the levels of progesterones which act to terminate LH surge by negative feedback. In addition, it increases distensibility of follicle wall.

It changes elastic properties of follicle wall increase rapid increase in follicular fluid volume. Escape of ovum is associated with degenerative changes in collagen i the follicular wall so that follicular wall becomes thin and stretched, FSH LH and progesterone stimulate the activity of proteolytic enzymes, resulting in digestion of collagen in the follicular wall and increase its distensibility. It also releases histamine. Granulosa cells and theca cells produce plasminogen activator. It activates plasminogen to produce plasmin which generates active collagenase to disrupt follicular wall.

Causes of the LH surge

First, the negative feedback of estradiol at the hypothalamic-pituitary level turns to a positive feedback when estradiol concentrations reach a critical point. Then, the pituitary gland becomes highly sensitive to GnRH stimulation, due to the increase of GnRH receptors. Thus, the GnRH surge produces the LH surge. Following ovulation, increasing concentrations of progesterone slow down the frequency of LH releasing pulses. Concentrations of LH once again drop to baseline levels.

The pre-ovulatory LH surge has a number of key functions:

- It triggers ovulation and follicular rupture about 36 hours after the surge,
- It is responsible for the disruption of the cumulus-oocyte complex.
- It induces the production of androgens by cells of the theca follicles.

Role of prostaglandins

Prostaglandins of E and F series and other eicosanoids increase markedly in the preovulatory follicular fluid reaching the peak concentration at ovulation.

They act to free proteolytic enzymes within the follicular wall and the HETEs (Hydroxy Ecosa Tetraenoic acid methyl Esters) to promote hyperaemia and angiogenesis. Thus, the progesterone influenced mid cycle rise in FSH serves to free the oocyte from follicular attachment, to convert plasminogen to proteolytic enzyme, plasmin and to ensure that sufficient LH receptors are present to allow normal leuteal phase.

Causes of ovulation (Speroff 2006; Homburg 2005)

- An increase of intra-follicular pressure,
- Proteolytic enzyme activity on the follicular wall,
- Morphological changes in the stigma,
- Perifollicular ovarian smooth muscle contractions and
- Vascular alterations in the perifollicular vessels.

FSH surge

At mid-cycle, there is a temporary increase in FSH secretion, whose cause and significance is not clear. It may be due to the GnRH surge and may have a function in preparing a cohort of small antral follicles for the next cycle (Homburg, 2005).

The decrease of FSH, during the mid follicular phase, prevents a multiple follicular development, as only the largest of the developing follicles stays above the FSH threshold, has the most FSH receptors, remains most sensitive to FSH and produces most estrogen. The largest follicle becomes less sensitive to the declining FSH concentrations and continuous to develop while the remaining follicles become atretic resulted by a lack of sufficient FSH stimulation.

Role of FSH

- The granulosa cell proliferation and differentiation and the antral follicle development.
- Estrogen production due to the activation of the enzyme aromatase.
- Activation of LH receptors on the dominant follicle.
- Enhancing synthesis of inhibin.

Estradiol

It is the most important type of estrogen in ovulatory cycle.

- After menstruation its concentrations start to increase in the mid-follicular phase.
- When it reaches a critical point, activate a positive feedback mechanism in the hypothalamus causing a massive surge of LH.
- Following ovulation, estradiol concentrations decrease temporarily but are revived by corpus luteum.
- With atresia of the corpus luteum, estradiol concentrations drop to their lowest levels and by a positive feedback, increase FSH levels immediately before menstruation.

The key functions of estradiol

- In the mid-late follicular phase, it suppresses the secretion of FSH leading to the selection of a dominant follicle and preventing multi-follicular development.
- In the follicular phase it is responsible for an increase of thickness of the endometrium.
- In mid-cycle estradiol triggers the LH surge.
- In ovulatory period, it stimulates cervical mucus production.

Changes in body due to Ovulation

1. pH in the vagina becomes less acidic
2. Cervical mucus becomes more copious and less viscous
3. Increase in basal body temperature.
4. Many women experience Mittelschmerz, i.e. pain associated with ovulation.
5. Many women also refer heightened sense of smell and sexual desire.

Luteal Phase

Before ovulation, the granulosa cells begin to increase in size and gain a characteristic vacuolated appearance with accumulation of yellow pigment, called as Leutin, which gives name to the process of luteinisation and the subunit as corpus luteum.

In the luteal phase, the corpus luteum secretes both, estradiol and progesterone.

The corpus luteum maintains itself for 14 days. Luteal phases of less than twelve days may make it more difficult to achieve pregnancy. In early pregnancy HCG rescues the corpus luteum maintaining luteal function until placental steroidogenesis.

Progesterone is the main hormone in the luteal phase. Progesterone concentrations rise to a peak 7-8 days following ovulation and fall rapidly with the demise of the corpus luteum. The rise of progesterone preceding LH surge, may play a role in LH surge (Homburg 2005).

Functions of progesterone secreted by the corpus luteum are:

- To induce a secretary endometrium, capable to enhance embryo implantation.
- To maintain the endometrium throughout the first weeks of pregnancy.
- To interfere in the expression of genes needed for implantation at the endometrium level.

Suggested reading

Speroff Textbook of Clinical Gynaecologic Endocrinology and Infertility.

STRESS IN INFERTILITY IS EVOLUTION STRONGER THAN PSYCHOLOGY?

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Stress is defined as a stimulus, which produces physiological reaction may be associated with anxiety or suffering and may be perceived as a threat provoking a fight or flight response to allow survival or overcome the situation. Stress is taking a toll on people contributing to health problems, poor relationships and lost productivity at work, according to a survey released by the American Psychological Association (APA) in 2007.(1) Fifty-seven per cent of workers in the corporate sector in India reported an increase in stress over the last two years, according to a survey by workplace solutions provider Regus PLC in November 2009.

Factors that contribute to increasing stress includes lifestyle changes, work habits, targets to achieve with stiff competition, high desires, coping with inflation and rising costs, poor eating habits, irregular hours, lack of sleep/ exercise, environmental pollution and very importantly inability to spend quality time with family.

Parenthood is one of the major transitions in adult life for both men and women. Fertility is highly valued in most cultures and the wish for a child is one of the most basic of all human motivations. When attempts to have a child fail, it can be an emotionally devastating experience, associated with anger, depression, anxiety, marital problems, sexual dysfunction, and social isolation. Couples experience stigma, sense of loss, and diminished self-esteem in the setting of their infertility and so they promptly opt for consultation and treatment options due to which the stress levels are bound to increase further. Thus, it's a vicious cycle – stress contributes to infertility and infertility adds to stress.

Infertility involves invisible losses, such as miscarriages, failed medical treatments, or adoptions gone awry. Infertility is an interruption of the family life cycle. Infertility is the obstacle blocking

normal family role transitions and preventing family members from assuming new developmental roles.

So, today's generation already has a predisposition to stress due to various factors as discussed.In Vitro Fertilisation (IVF) is a demanding and stressful treatment for patients, requiring daily hormone injections, ultrasound scans, semen analysis & invasive procedures, such as oocyte retrieval. Stress significantly reduced the probability of conception each day during the fertile window, possibly exerting its effect through the sympathetic medullar pathway. Stress reduces conception probabilities across the fertile window. (2)

There is evidence that stress levels influence the outcome of infertility treatment, as well as contribute to patients' decisions to continue treatment (3). Stress also affects patients' reactions to pregnancy loss during infertility treatment and pregnancy complications. Moreover, psychological distress is associated with treatment failure and interventions to relieve stress are associated with increased pregnancy rates.

Stress and stress hormones can cause infertility in the following major ways which, includes impaired follicle health and development. Stress reduces the secretion of estrogen from the follicle, which reduces the thickness of the endometrium and the fertile mucus. It also causes reduction in the secretion of progesterone from the corpus luteum in the luteal phase, and thus affects implantation. Stress can cause luteal phase defects. It affects the surge of luteinizing hormone (LH) from the pituitary gland, which is responsible for stimulating ovulation. It increases prolactin secretion by the pituitary gland, which inhibits ovarian function. It negatively impacts many other health concerns which may impair fertility, such as thyroid health, autoimmune conditions, allergic conditions, PCOS, endometriosis, and gastrointestinal concerns.

The proposed mechanisms which links stress with infertility involves physiology of the depressed state such as elevated prolactin levels, disruption of the hypothalamic-pituitary-adrenal axis, and thyroid dysfunction. A number of studies have found that the incidence of depression in infertile couples presenting for infertility treatment is significantly higher than in fertile controls, with prevalence estimates of major depression in the range of 15%-54% (4,5,6,7) Anxiety has also been shown to be significantly higher in infertile couples when compared to the general population, with 8%-28% of infertile couples reporting clinically significant anxiety (7,8).

Another study in which, the samples were analyzed for cortisol and alpha-amylase, two biomarkers of stress. High levels of alpha-amylase, a breakdown product of epinephrine, were strongly linked to decreased "fecundity," or the odds of getting pregnant each month (9)

Cortisol, a major stress hormone has been shown to affect reproduction in multiple ways. It interferes with the surge of luteinizing hormone (LH) from the pituitary, delaying it and making the surge less powerful. LH is responsible for the final development of the follicle into the corpus luteum and the release of the egg. This has many negative impacts on healthy ovulation and on the hormones required to sustain implantation. Formation of a healthy corpus luteum is required to produce progesterone which allows for full development of the endometrial lining and hence, implantation. High levels of glucocorticoids (stress hormones) are also known to reduce estrogen secretion by the follicle. Low estrogen levels will reduce fertile mucous and the development of the endometrial lining. The reduced estrogen output by the follicle also indicates that its development may not be normal or adequate.

Since psychological factors play an important role in the pathogenesis of infertility, exploration of this is also an important task to manage this devastating problem, which has cultural and social impact. It is important to find ways to break this vicious cycle and use measures for de-stressing by relaxation, exercises, weight reduction, meditation, regular eating habits, spending quality time with partner, accepting failures gracefully without getting frustrated and avoid smoking, alcohol or chewing tobacco.

There are numerous methods for decreasing stress, including learning relaxation techniques and stress management strategies doing an introspection and reorganisation of one's lifestyle .

Relaxation Response Training

The relaxation response is a state of deep rest. This is the direct opposite of the fight-or-flight response, the physical response to danger.

On eliciting the relaxation response, heart rate, blood pressure and breathing rates decrease. Individuals who elicit the relaxation response on a regular basis report that they not only feel more relaxed and less anxious during the actual relaxation, but also feel calmer throughout the day. Those who elicit the relaxation response during medical procedures report less anxiety, pain and medication use.

The relaxation response can be elicited through a wide variety of relaxation techniques, including progressive muscle relaxation, deep breathing, meditation and imagery.

Meditation requires focusing on a word or phrase as you breathe. And imagery can mean a variety of things, ranging from imagining a pleasant safe spot to focusing on your body.

While stress does not cause infertility, infertility most definitely causes stress. Infertile women report higher levels of stress and anxiety than fertile women, and there is some indication that infertile women are more likely to become depressed. This is not surprising since the far-reaching effects of infertility can interfere with work, family, money and sex.

The difficulties of life are intended to make us better, not bitter. As said by Robert Brault, "When life takes the wind out of your sails, it is to test you at the oars."

References

1. “Stress a Major Health Problem in The U.S., Warns APA” October 24, 2007
2. Germaine M, Buck Louis et al - Fertil Steril Vol 95, No 7, June 2011
3. Campagne DM. Should fertilization treatment start with reducing stress? Hum Reprod 2006; 21:1651.
4. Domar AD, Zuttermeister PC, Seibel M, Benson H. Psychological improvement in infertile women after behavioral treatment: a replication. Fertil Steril 1992; 58(1):144-147.
5. Demyttenaere K, Bonte L, Gheldof M, Vervaeke M, Meulman C, Vanderschuerem D, D'Hooghe T. Coping style and depression level influence outcome of in vitro fertilization. Fertil Steril 1998; 68(6):1026-1033.
6. Lukse MP, Vacc NA. Grief, depression, and coping in women undergoing infertility treatment. Obstet and Gynecol 1999;93(2):245-251.
7. Chen TH, Chang SP, Tsai CF, Juang KD: Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004; 19:2313-18.
8. Anderson KM. Sharpe M. Rattray A. Irvine DS. Distress and concerns in couples referred to a specialist infertility clinic. Journal of Psychosomatic Research 2003; 54(4):353-5.
9. Stress and infertility linked in study. Chances of infertility almost double when women are stressed - by Dr. Meera Dalal, CBC News Mar, 2014

MANAGEMENT OF MALE FACTOR INFERTILITY

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The causes of male infertility may be divided into 3 basic groups

1) No identifiable and treatable cause

- Testicular Dysfunction syndrome.(70%)

2) Identifiable cause but not treatable

- Y micro deletions,
- Klinefelters Syndrome,
- Translocations (5 %)

3) Identifiable and treatable causes (25%)

Testicular dysfunction Syndrome is a condition thought to be due to the in co-ordination of function between different cells types of testis.It is possibly due to secondary effects of abnormal oestrogen levels during intrauterine period.The defect occurs during spermatogenesis and its manifestation in adulthood ranges from mild OAT to Azoospermia. There are no diagnostic tests. It may be suspected only by exclusion of other causes. Any form of treatment is questionable for this entity. The next group consists of identifiable but not treatable causes. This includes Y chromosome Micro deletion, Klinifelters syndrome and some translocations (5%). No specific treatment is available for this group of patients also.

The third one is the identifiable & treatable group. It comprises about 25% of the patients with male infertility. It includes varicocele, Pyospermia, Diabetes, Thyroid abnormalities etc. These affect the final stages of development of spermatozoa (spermiogenesis) or fully matured sperms. Hence it is amenable to treatment. The effects produced include loss of membrane integrity, acrosome abnormalities, DNA fragmentation etc. Therefore our duty is to identify this particular group and treat them.

The diagnosis of male infertility mainly is from history and clinical examination. A detailed history needs to be elicited regarding duration of infertility, sexual abnormalities, medical conditions like diabetes, hypertension, obesity, psychiatric illness, epilepsy and other chronic illnesses. Special attention need to be given for childhood diseases like mumps, cryptorchidism etc. Some drug intake may be the causative factor and has to be carefully recorded. A proper surgical history regarding any trauma or surgery to pelvic organs should be noted. Smoking, alcoholism and exposure to heat or chemicals also should be thought of. And most importantly, the frequency of sexual life should be recorded as it determines the chances of conception even if all factors are normal.

The physical examination consists of assessing the size and consistency of testes. The Epididymis should be looked for any distension/ beading or scarring. The vas should be examined for its presence/absence, abnormal thickness, discontinuity or beaded feel. The presence of varicocele should be done and clinical grading of it should be done before planning any intervention. The penis also should be examined for any abnormalities.

The basic tests include semen analysis, blood sugar estimation, endocrine evaluation, semen microbiology and ultrasound. The advanced tests include sperm function tests, antisperm antibodies, DNA fragmentation assay, Y Chromosome Microdeletion and evaluating for reactive oxygen species (ROS).

Semen analysis is the most important and basic test in evaluating male infertility. However it has some disadvantages.

a) Parameters vary from sample to sample, technician to technician, lab to lab.
b) Normal report do not confirm fertility potential of a patient.
c) Conception possible even with a very bad sample.
d) Man may be fertile to one female and infertile to another female.

The main points to be noted in performing semen analysis are to exclude recent febrile illness, advice abstinence period of 2-3 days only and not more than that. Analysis should be done after complete liquefaction only in a well equipped lab & by a dedicated technician. Staining for morphology assessment should be a standard practice. The most important parameters are motility & morphology. It will also give an idea about possible collection problems.

However, there are some problems with the latest (2010) WHO Reference values for Semen analysis. The cut off values for volume, sperm concentration, total motility, vitality and morphology recommended in 2010 as against 1999(given in brackets) are 1.5ml (2ml), 15 million (20 million), 39% (50%), 58% (75%) and 4% (14%) respectively. The reason for the lower cutoff values are probably due to a different way in generating data. They studied a different population and higher QC standards and strict criteria were employed. However it is not representative of global fertile male population. Hence about 38% of males classified as infertile according to 1999 criteria would now be classified as fertile. So how far we are able to strictly follow these values is a matter of debate.

Computer Assisted Semen Analysis (CASA) provides a more objective and reproducible measurement. It also gives superior documentation of laboratory values and a better assessment of sperm motility. However it is not reliable if sperm density is $< 2x10^6$/ml or $> 50x10^6$/ml or presence of lots of debris/immotile sperms. The parameters are not standardized between laboratories and hence it is difficult to interpret the results. It did not provide any improvement on the manual method in distinguishing fertilizing capacity of semen.

Post-coital Test is also not a well accepted method today. However a normal PCT will indirectly tell you that semen parameters are normal and there are no sexual problems or cervical or vaginal hostility. It can also rule out presence of anti sperm antibodies.

FSH estimation is one of the cornerstones in male infertility evaluation. It can differentiate hypogonadotropism (< 2) from Normogonadotropism (2-8) and hypergonadotropism (> 8). FSH values are greatly useful in diagnosis and management of Severe OAT and azoospermia. Other blood tests that may be useful are TSH, PRL, Blood Sugar estimation etc. Scrotal USG and TRUS are done by some but may not provide any additional information than that from a thorough clinical examination. Semen microbiology also has no much role in routine workup. Tests for Anti sperm antibodies are advocated by some people. The antibodies are of two types. One is surface antibodies and the other is serum antibodies. Of these, surface antibodies are the only clinically significant type. The tests available are MAR test, ELISA tests, Antibodies detection in cervical mucus etc. However agglutination of sperms, abnormal motility, bad PCT, history of trauma or infection, Pyospermia etc will indirectly tell you about a high possibility of Anti sperm antibodies.

There are some new diagnostic tests beyond the basic tests. These include assessment of sperm DNA integrity, Presence of Reactive oxygen species (ROS), Assessment of Y chromosome microdeletions etc. DNA fragmentation assessment may be indicated in unexplained infertility, RPL or recurrent ART/ IUI failure. The tests available include SCSA (sperm chromatin structure analysis), TUNNEL assay [Terminal deoxynucleotide transferase mediated dUDP nick-end labeling] , COMET assay, DBD-FISH [DNA breakage detection-fluorescence in-situ hybridization and sperm chromatin dispersion tests. DNA Fragmentation Index (DFI) is another one in which fragmentation level is expressed by a DFI Value. Higher values are suggestive of presence of higher percentage of sperms with fragmented DNA.

Y chromosome micro-deletion screening is recommended in severe OAT and Non obstructive azoospermia patients. It is diagnostic as well as it can predict chances for surgical sperm retrieval. They have described three areas of deletions in Y chromosome. These are labeled as AZF a, AZF b and AZF c. Deletion in AZFa and AZF b tells that there is no possibility of sperm retrieval. However AZFc deletion patients can undergo successful retrieval in upto 70% cases.

Presence of ROS can affect fertility by multitude of factors. ROS can be assayed by some methods like colourimetric analysis of semen or seminal plasma. It is also not indicated as a routine step in evaluation.

Even though many newer tests are available, the standard tests (history, clinical examination, semen analysis and endocrine evaluation) are still the Gold standard. The recent WHO references for semen analysis have been lowered and it is advisable to exercise caution to interpret results because they have important shortcomings. The new diagnostic tests allow assessment of sperm DNA integrity, seminal ROS and Y-chromosome related genetic infertility and these probably helps in unexplained infertility. The real picture is that these test results may not aid in the clinical management nor have prognostic value in ART. Hence the old concept of “stick to the basics” holds really well in dealing with assessment and management of male factor in infertility.

CLOMIPHENE IN IUI FOR OVARIAN STIMULATION

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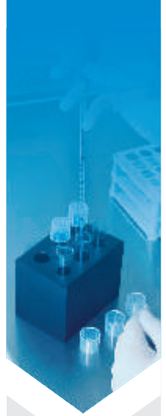

Ovulation induction is a significant step prior to intrauterine insemination (IUI) that aims at multifollicular development to enhance the fertilization and pregnancy rates. Ovulation induction + IUI is indicated as a simple, first-line, cost-effective treatment option in couples with oligo/anovulation, cervical, mild male factor, and unexplained infertility. Several drug regimens, such as Clomiphene citrate (CC), gonadotropins, aromatase inhibitors (Letrozole), and tamoxifen have been used for controlled ovarian hyperstimulation (COH) prior to IUI; however, there is as yet, no ideal stimulation protocol.

Clomiphene citrate (CC)

Clomiphene citrate has been used extensively in reproductive medicine for over 40 years for ovulation induction in anovulatory, ovulatory, unexplained and male factor infertility owing to its ready availability, affordability (1), efficacy and low complication rate.

Dose of Administration

Clomiphene citrate is administered in dosage varying from 50 to 250 mg per day for 5 days in the early follicular phase (day 2 to day 5 of menstruation). Though CC may be initiated on different days of the cycle, the recommended daily dose generally is 50-100/day, the lowest dose being 25 mg/day for hyper- responders and the highest being 250 mg/day in CC-resistant cases.(2) The dose of CC may be increased by 50 mg per cycle till ovulation is achieved, however, the cumulative conception rate does not increase beyond the 150 mg dosage, as the anti estrogenic properties of CC manifest more with the greater dosage and in high doses CC

interferes with implantation and pregnancy. (3)

Clomiphene citrate can be used in two different ways: either for ovarian stimulation, if given before day 6 of menstrual cycle, in which case, it may have a negative impact on the endometrium and implantation or, after day 6 in which case, it only has an inhibiting effect on the luteinizing hormone (LH) surge and ovulation, but probably no negative impact on the endometrium.(4) If administered at a dose of 25mg from day 7 in patients with a pathologic premature LH rise, it can result in improved ovulation, follicle maturation and oocyte quality. (5)

Mechanism of Action

Clomiphene citrate is a selective estrogen receptor modulator (SERM) with anti-estrogenic properties that has competitive antagonist effects on the binding of ovarian estrogens at the hypothalamic and pituitary receptors sites. Blockage of estrogen receptors deactivates the estrogenic negative feedback on the hypothalamus and/or pituitary resulting in an increase in gonadotropin releasing hormone (GnRH) pulse frequency and pituitary sensitivity to GnRH. This action consequently leads to an elevation of endogenous gonadotropin secretion leading to enhancement of ovarian follicular development. (6)

Side Effects

Clomiphene citrate is generally well tolerated and its side effects include hot flushes, mood swings, abdominal discomfort, nausea and vomiting, breast discomfort, headaches and visual disturbances. Many of these side effects are transitory and typically abate after the cessation of treatment. CC is cleared through the liver and excreted in the stool. (7)

Clinical Outcomes

Oligo/Anovulation

In oligo/an-ovulatory infertility, the use of CC results in ovulation in majority of the women (75–80%) but pregnancy is achieved in only 35–40% of the cases.(10) The anti-estrogenic effect of CC on the endometrium and cervical mucus has been suggested as the main reason of this discrepancy between ovulation and pregnancy rates.(8,9) Multiple pregnancy rates have been reported in the range of 5-10% and almost exclusively twins in CC/IUI cycles. (8)

Unexplained infertility (UEI)

While CC has been shown to be effective for ovulatory infertility,(10) randomized studies found no evidence that CC was more effective than no treatment or placebo in women with unexplained infertility undergoing IUI.(11) In patients with UEI, pregnancy rates of 6–8% per cycle have been reported following CC+IUI/CC without IUI cycles, only slightly better than the 2–4% chance for pregnancy without CC treatment.(2) Patients with unexplained infertility, randomized to clomiphene citrate, IUI or expectant management showed comparable results for all three arms in terms of delivery rate.(12)

Advantages of CC over gonadotropins

The advantages of CC over gonadotropins for IUI cycles include a low cost, oral administration, less need for close monitoring, and lower incidence of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS).(8)

CC - Resistance

Patients who fail to respond to CC stimulation are considered as CC-resistant and gonadotropins, aromatase inhibitors, or combination therapy (CC + gonadotropins) may be considered a good option.

Gonadotropins

Significantly higher pregnancy rates have been reported with gonadotropin regimens, using hMG or low dose purified follicle-stimulating hormone (FSH) compared to CC regimens in IUI cycles in patients with male or unexplained subfertility, however, the live birth rate rates showed no significant difference, demonstrating the lack of superiority of gonadotropins over CC.(2) Hence, the higher cost of gonadotropins, discomfort of daily administration and the high multiple pregnancy rate even with conventional doses, should be weighed prior to choosing gonadotropins over CC for stimulation. Despite the reported superiority of the low-dose rFSH protocol in anovulatory polycystic ovary syndrome (PCOS), compared to CC in terms of clinical outcomes,(13) these cannot be extrapolated to male factor and unexplained infertility women in which, comparable results have been reported. (2) Though the low-dose rFSH regimens might be a reasonable strategy to overcome the risk of multiple pregnancies attributed to gonadotropin use, further studies are needed to clarify this issue. Until further large series demonstrate otherwise, CC may be reasonable choice for COH, owing to its advantages like ease of use and affordability. Nonetheless, the choice should be based on hospital facilities, economical conditions, and patient preferences. (2)

Aromatase inhibitors

The use of aromatase inhibitors (Letrozole) is indeed promising, especially in patients who have failed to respond to CC, either because of CC-resistance or a thin endometrium. Letrozole inhibits the enzyme aromatase that converts androgens to estrogens, thus decreasing the estrogen production. The reduced estrogen levels release the hypothalamus and pituitary from the estrogen negative feedback, resulting in increased gonadotropin production and stimulation of ovarian follicles. Unlike CC, Letrozole does not have any adverse effect on the endometrium or cervical mucus because of the absence of estrogen receptor depletion and its short half life.(14) CC-resistant patients respond well to aromatase inhibitors, with good ovulation rates, thicker endometrium, and good pregnancy rates.(15,16)

Clomiphene citrate with gonadotropins

Sequential use of CC and gonadotropin [human menopausal gonadotropin (hMG) or FSH] therapy has become an increasingly utilized method for COH for patients who fail CC therapy. In this protocol CC (100 mg) is administered from day 2 to day 6 and Inj.FSH/hMG 75/150 units is given on day 6 and day 8. Transvaginal sonography is done from day-8 onwards and in case the follicle growth or number is inadequate, additional FSH/hMG injections are administered.(3). A combination of CC with gonadotropins i) yields a higher pregnancy rate than CC alone,(17,18) ii) is more cost effective, as the dosage of gonadotropins is reduced,(18,19) iii) has a lower multiple pregnancy rate than with gonadotropins alone, and iv) has a lower incidence of ovarian hyperstimulation syndrome (OHSS), as compared to the conventional regimens. However, the antiestrogenic effect of CC has an adverse pregnancy outcome.

Clomiphene citrate in advanced - aged women

Infertile women of advanced age are a unique subgroup in the broader population of patients diagnosed as having unexplained infertility. In advanced-aged women ≥ 40 years opting for infertility treatments, CC seems to be ineffective with very disappointing pregnancy rates ranging from 0–4% per cycle and delivery rates almost never reported. Delivery rates of gonadotropins and IUI cycles are < 5%. and in vitro fertilization (IVF) seems to be a more effective option although chances of delivery are low in absolute terms. (1) Therefore, while the value of CC, either with or without IUI, for the treatment of unexplained infertility is questionable for all ages, it seems to be worthless for older patients.(1) Considering its known drawbacks, including a possible association with an increased risk of breast cancer,(20,21) CC should be omitted entirely from the ovulation-induction treatment plan in patients ⩾ 40 years of age.(1)

The use of CC is contraindicated in patients with FSH/LH deficiency owing to a dysfunctional hypothalamus / pituitary. These patients have to be stimulated with hMG to achieve follicular growth. (5)

Conclusion

Though CC is an attractive first-line treatment option for ovarian stimulation for IUI in the indicated patient, its antiestrogenic effects compromise its efficacy and pregnancy rates remain low. While patients with anovulatory infertility benefit the most from CC stimulation, gonadotropins may be a suitable alternative in patients with unexplained and male infertility. Nevertheless, in the backdrop of the associated disadvantages of gonadotropins despite their higher pregnancy rates, and the economic and infrastructural conditions in resource-limited medical settings, CC may still have a role in young patients. It is not recommended in advanced-aged women ≥ 40 years owing to the very poor pregnancy outcomes. Aromatase inhibitors are also effective alternatives to CC without the negative effects of CC and clinical outcomes comparable to gonadotropins. The age of the patient and a thorough evaluation of the etiology of infertility, ovarian reserve, and menstrual history is necessary prior to initiating treatment with CC.

References

1. Tsafrir A, Laufer N. First-line treatment for unexplained infertility in women over 40 years of age : ovulation induction and IUI or IVF? In : Intrauterine Insemination-3rd edition (Editor : Allahbadia GN). Jaypee Brothers Medical Publishers (P) Ltd, New Delhi; 2014:pp 54-61.
2. Berker B, Kahraman K. Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing IUI. In : Intrauterine Insemination - 3rd edition (Editor : Allahbadia GN). Jaypee Brothers Medical Publishers (P) Ltd, New Delhi; 2014:pp 93 -103.
3. Dalal R. Ovulation Induction for IUI. In : Intrauterine Insemination - 3rd edition (Editor : Allahbadia GN). Jaypee Brothers Medical Publishers (P) Ltd, New Delhi; 2014:pp 62-73.
4. Wallace KL, Johnson V, Sopelak V, Hines R. Clomiphene citrate versus letrozole : molecular analysis of the endometrium in women with polycystic ovary syndrome. Fertil Steril. 2011;96:1051-6.
5. Nitzschke ME, Stetson SJ, Ruvalcaba LA. Clomiphene citrate-stimulated or natural cycle IUI? In : Intrauterine Insemination - 3rd edition (Editor : Allahbadia GN). Jaypee Brothers Medical Publishers (P) Ltd, New Delhi; 2014:pp 109–115.
6. Dickey RP. Ovulation induction for intrauterine insemination I : oral drugs clomiphene, tamoxifen, letrazole. In : Manual of intrauterine insemination and ovulation induction. New York, Cambridge University Press, 2nded. 2010: p68-79.
7. Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev. 2010; 1:CD000057.
8. Shoham Z, Howles CM. Drug used for controlled ovarian stimulation : clomiphene citrate, aromatase inhibitors, metformin, gonadotropins, gonadotropins - releasing hormone analogs, and recombinant gonadotropins. In : Textbook of assisted reproductive technologies. London, Informa UK ltd., 3rd ed. 2009:p469-488.
9. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti - oestrogens for ovulation induction in PCOS. Cochrane Database Syst Rev. 2009; 4:CD002249.
10. Costello MF. Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. Aust N Z J Obstet Gynaecol 2004; 44:93-102.
11. Hughes E, Collins J, Vandekerckhove P. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev 2000; CD000057
12. Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C, Harrold A, et al. Clomiphene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility : pragmatic randomised controlled trial. BMJ 2008; 337:a716
13. Homburg R, Hendriks ML, König TE, Anderson RA, Balen AH, Brincat M, et al. Clomiphene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome : a prospective randomized multinational study. Hum Reprod. Hum Reprod 2012 (2):468-73.
14. Mitwally M. Casper R. Aromatase inhibitors in ovulation induction. Semin Reprod Med 2004;22:61-78.
15. Mitwally MF, Casper RF. Aromatase inhibition : a novel method of ovulation induction in women with polycystic ovarian syndrome. Reprod Technol 2000;10:244-7.
16. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305-9.
17. Lu PY, Chen AL, Atkinson EJ, Lee SH,Erickson LD, Ory SJ. Minimal stimulation achieves pregnancy rates comparable to human menopausal gonadotropins in the treatment of infertility Fertil Steril 1996; 65:583-7.
18. Kemmann E, Jones JR. Sequential clomiphene Citrate - menotrophin therapy for induction or enhancement of ovulation. Fertil Steril 1983;39:772-9
19. Dickey RP, Olar TT, Taylor S N, Curole DN, Rye PH. Sequential clomiphene citrate and human menopausal gonadotrophin for ovulation induction : comparison to clomiphene citrate alone and human menopausal gonadotrophin alone. Human Reprod 1993; 8:56-59.
20. Lerner - Geva L, Keinan - Boker L, Blumstein T, Boyko V, Olmar L, Mashiach S, et al. Infertility, ovulation induction treatments and the incidence of breast cancer - a historical prospective cohort of Israeli women. Breast Cancer Res Treat 2006; 100:201-12.
21. Orgeas CC, Sanner K, Hall P, Conner P, Holte J, Nilsson SJ, et al. Breast cancer incidence after hormonal infertility treatment in Sweden : a cohort study. Am J Obstet Gynecol 2009; 200:72.e1-7

OVULATION INDUCTION IN HYPOGONADOTROPIC HYPOGONADISM

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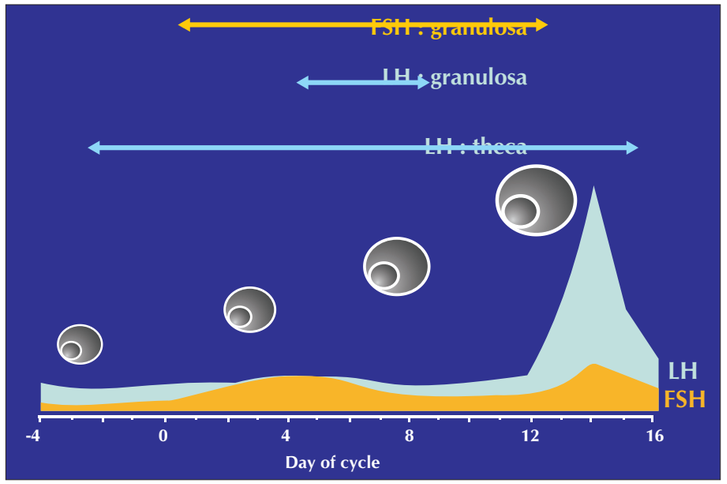
Introduction

We must understand the ovarian cycle well before we know the ovulation induction protocols, as this will help us in selecting the best protocol. The application of new forms of research in recent decades, has contributed to a more in-depth and accurate understanding of the interaction of each of the inter and intracellular structures and mechanisms in the mechanics of human ovarian physiology. On the other hand the use of non-human primate models has also provided invaluable information in the reproductive field related to ovarian function.

Ovulation Induction

Ovulation induction is one of the most common interventions for the treatment of infertility. The aim of ovulation induction is to overcome natural follicular selection process to increase the number of oocytes available for fertilization. Development related paracrine signals set follicular responsiveness to FSH and LH[1]. The action of FSH and LH on the theca and granulosa cell during the follicular phase is essential for the follicular growth (Figure 1 a and b)



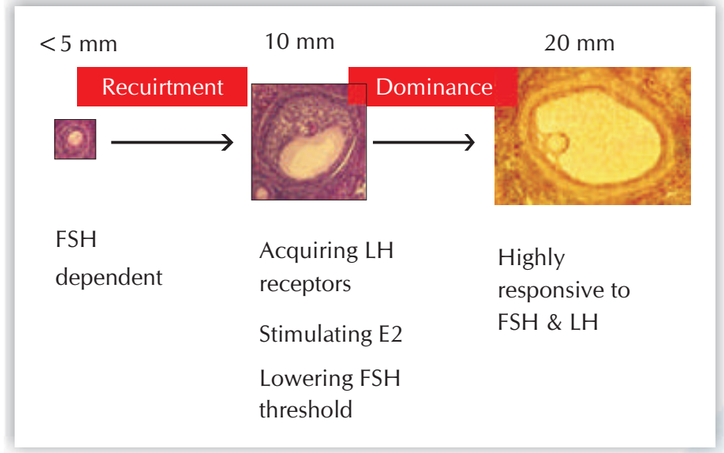


Figure 1 a and b: Development-dependent gonadotrophin action

Before ovulation induction with gonadotrophins it is important to perform ultrasound (USG) for antral follicle count (AFC), ovarian volume, to rule out PCOS and ovarian cyst (physiological or pathological), small ovaries and ovarian tumors

AFC is the sum of antral follicles (2-10 mm) in both ovaries, at a transvaginal ultrasonography during the early follicular phase. A low AFC (range 3 10 total antral follicles) has been associated with poor response to ovarian stimulation and have a lesser chance to achieve pregnancy[2]. On the other hand a high AFC of more than 20 is associated with a higher chance of developing OHSS.

Baseline scan on day 2 or 3 is essential before initiation of any ovulation induction therapy to (Figure 2)

- identify morphology of ovary and adenexal abnormalities - ovarian cyst, hydrosalpinx
- assess the ovarian reserve
- identify uterine abnormalities - myoma, adenomyosis, polyps, intrauterine adhesions, endometrial abnormalities, congenital anomalies
- decide the stimulation protocol for adequate response

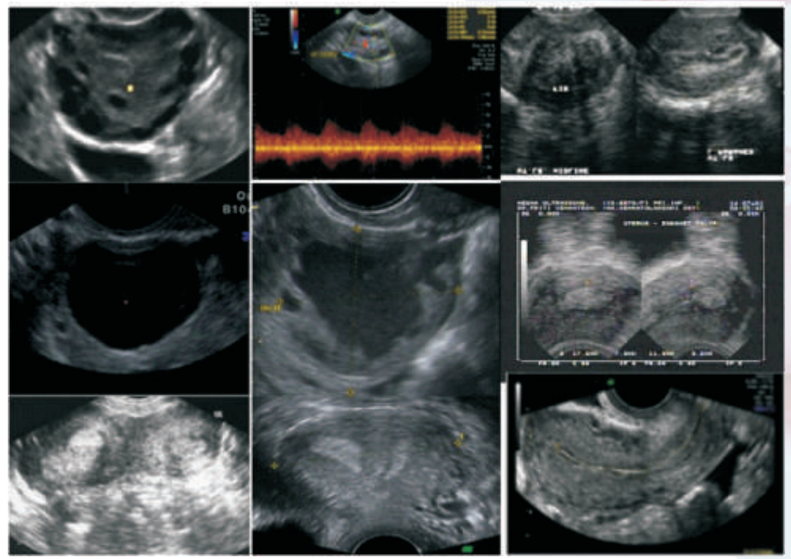


Figure 2: Baseline scan before OI TRO pathology

OI initiated on Day 2/3 only if (Figure 3) the follicular size is < 10 mm, there is absence of ovarian cyst, endometrial thickness <6 mm and estradiol levels are less than 50 pg/ml and progesterone level is less than 1.5 ng/ml.

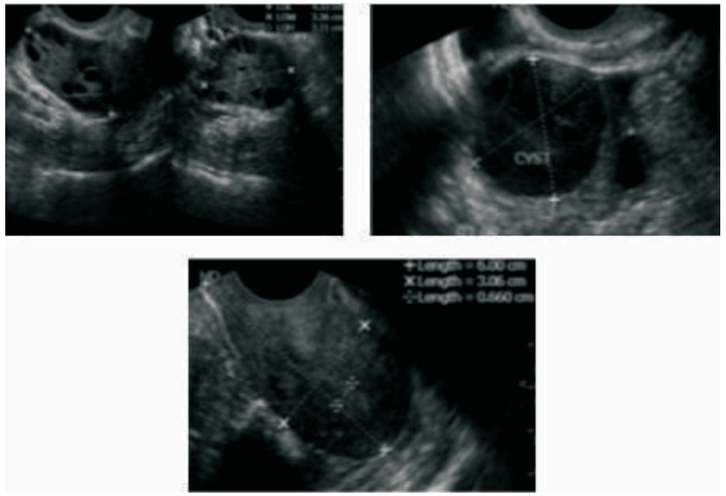


Figure 3: Criteria for initiation of ovulation induction drugs

Ovarian Stimulation Protocols using Gonadotrophins

Rationale for use controlled ovarian stimulation (COH) is to increase in number of oocytes available & increase in steroid production thus increasing the chance of implantation

Response to ovulation Induction is dependent on following factors

1. Good prognosis if baseline FSH levels of 1 – 8
2. Poor prognosis if D 10 FSH levels > 10 after CC challenge
3. Poor results with FSH levels > 20 mIU, independent of age
4. Baseline E2 correlates inversely with number of eggs retrieved
5. Poor prognosis with elevated progesterone levels in follicular phase

Goal of ovarian stimulation (Figure 4)

The ovulation induction protocol will depend on whether ovulation induction is for anovulation or controlled ovarian stimulation so as to have multi-follicular development. So what we need to look at is

- Starting point - the type of patients, whether ovulation induction is done for anovulation or for superovulation
- End point - the aim of the ovulation induction – whether one desires mono follicular or multi-follicular development

Number of follicles to ovulate is determined by length of time that the level of FSH remains above the thresh hold value. In a natural cycle the time period for which FSH remains above the threshold value is less resulting in mono follicular development. If the time period for which FSH remains above the threshold value is extended by administering exogenous FSH in the mid-follicular phase, it results in multi-follicular development.[3]

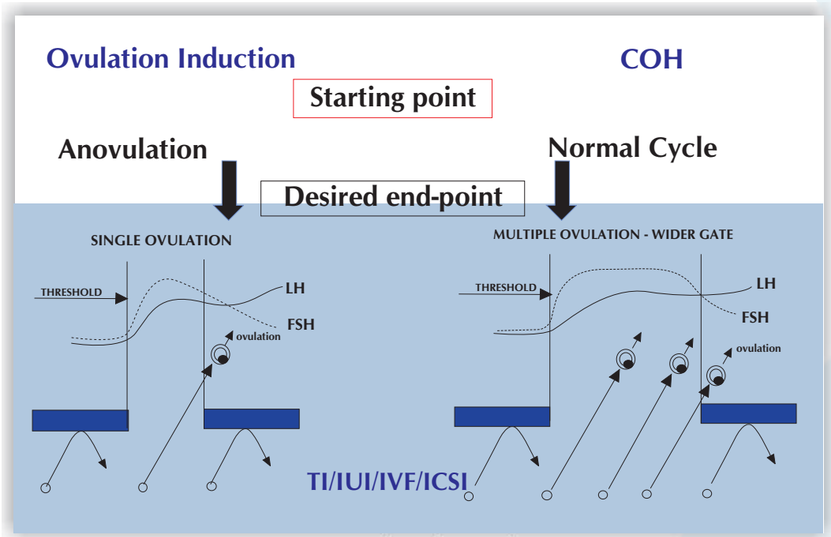


Figure 4: Goal of ovulation Induction

Our goal is to have mono-follicular development for an non-ART cycle and multi-follicular development for ART cycle, which then requires specific protocols and stringent monitoring. (Figure 5)

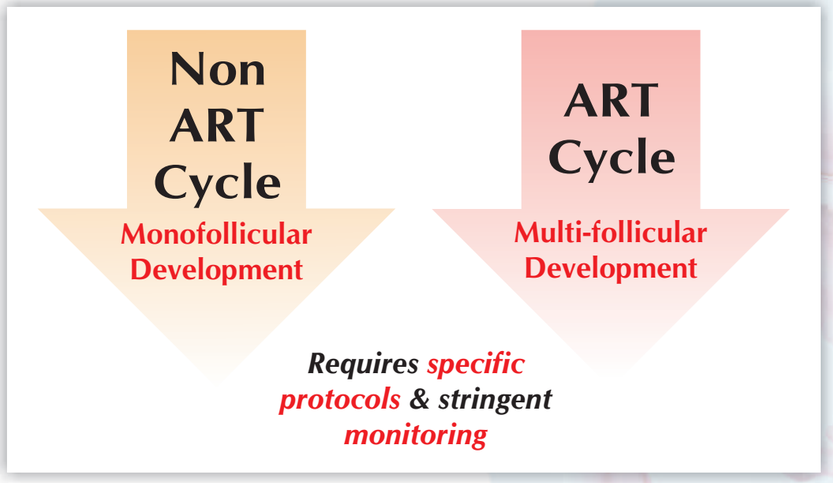


Figure 5: Goal of OI

The choice of gonadotropin and dose will depend on

- ovarian reserve tests: AFC, AMH, FSH
- body weight and BMI
- female age
- presence of other infertility factors
- indication for OI
- genetic: FSH-receptor polymorphism
- past performance to COS
- available resources
- risk tolerance

Indications for use of gonadotrophins for ovulation induction

- Clomiphene/Letrazole resistance
- Clomiphene/Letrazole failure
- Persistent hyper secretion of LH
- Negative post coital test
- IUI and ART cycles

Gonadotropin preparations

- hMG - IM
- Urinary FSH/ Ultra pure FSH (HP) – IM/SC
- Recombinant FSH – SC

Gonadotropin use requires close monitoring with ultrasound, estradiol (E2), LH and progesterone levels . Adjustment of GT dose depends on serial USG findings and E2 levels. Pregnancy rate with gonadotrophins is 35 - 40 %, being slightly lower in PCOS women. But have a very incidence of OHSS with the multiple pregnancy rate being 10 – 15 %.

OI Protocols using Gonadotrophins

Combination protocols

1. CC/Tamoxifen + GT Protocol (Figure 6)

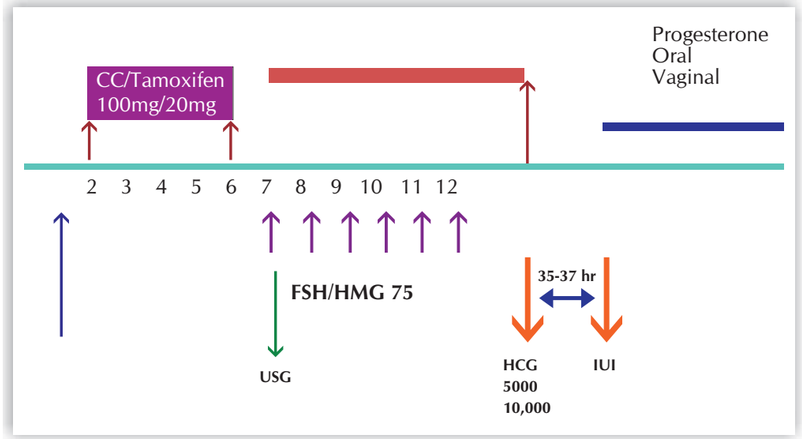


Figure 6: CC + hMG/FSH

CC 100 mg orTamoxifen 20 mg from day 2 – 6 of menstrual cycle
+
hMG or FSH 75 IU from day 7 till hCG

We could also use gonadotrophins in the following protocols along with CC and Tamoxifen which are given from day 2-6

Gonadotrophins can be used as follows

- On day 3, 5, 7, 9, & 11
- Single dose hMG/FSH 150 IU on day 9 or
- hMG / FSH 37.5 - 75 IU D 2 onwards and dose titrated depending on the response
- hMG / FSH 75 IU given 5 onwards daily

Disadvantage

CC/Tamoxifen + Gonadotropin

- 20 % patients have premature LH surge with a high incidence of premature oocyte maturation.
- Higher incidence of OHSS
- Higher incidence of multiple pregnancies

2. hMG/FSH/Recombinant FSH

Conventional Step-up protocol (Figure 7)

Supraphysiological doses of FSH in this protocol provoke initial development of a large cohort, stimulate additional follicles, and even rescue those follicles destined for atresia.

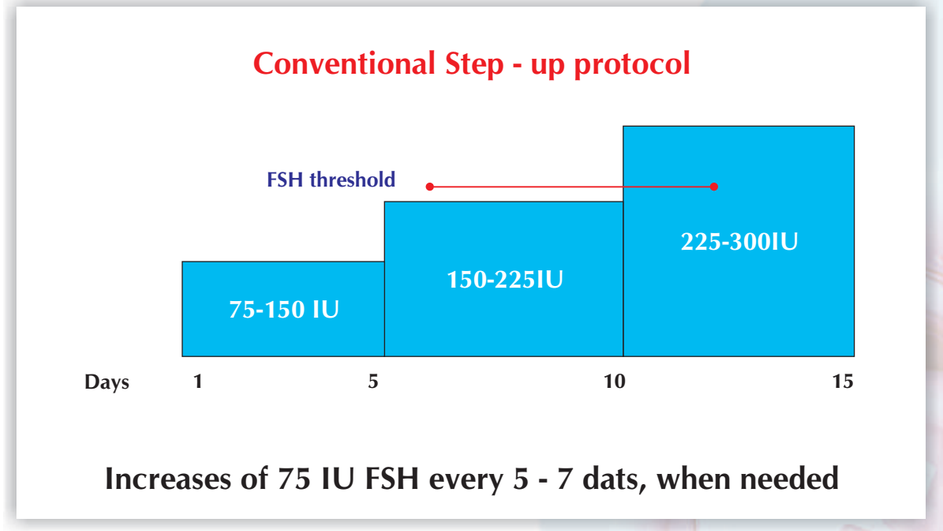


Figure 7: Conventional Step-up protocol

Following are the results with conventional protocol

Ovulation Rate – 70%
Severe OHSS – 7 -14 %
Cumulative Pregnancy Rate - 21 – 75 %
Multiple Pregnancy Rate – 36 %
Low dose protocol (Figure 8)

Gonadotrophins started in the dose of 37.5 to 75 IU, and the first increment in the dose is done on day 7 of stimulation either by 50 % or 100 % depending on the follicular growth. One can achieve mono-folliculogenesis and reduce the risk of OHSS and multiple pregnancies.

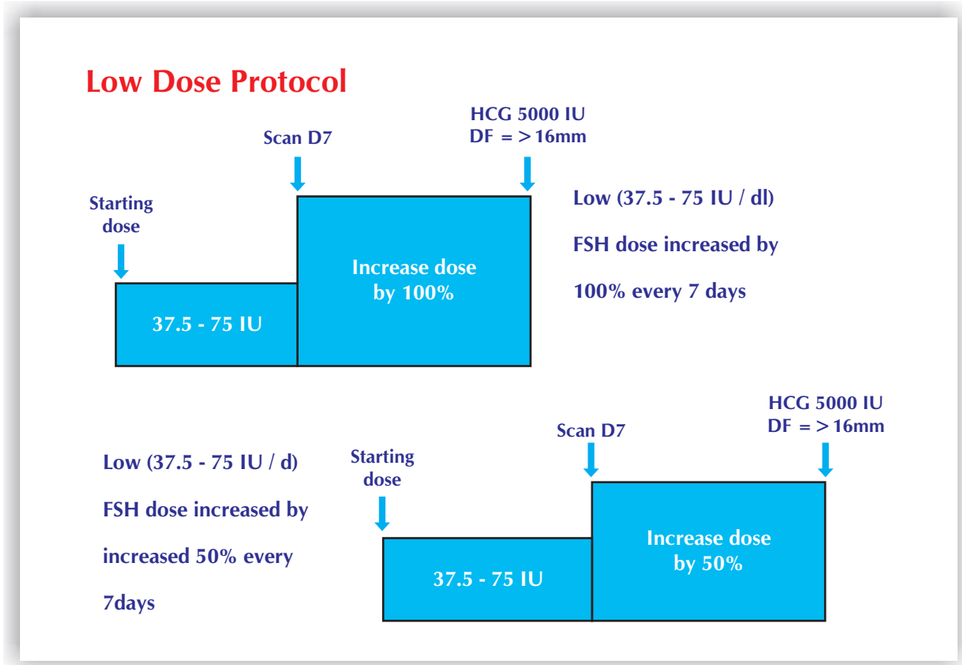


Figure 8 : Low dose protocol

Chronic low dose protocol (Figure 9)

- Low (37.5 -75 IU/d) FSH dose increased by 50% or 37.5 IU after 14 days if no ovarian response
- Any further FSH increment thereafter is made by 37.5 IU - 75 IU at weekly intervals to a maximum of 225 IU/day
- Once dominant follicle emerges, dose of FSH is maintained same until the follicle reaches 18 - 20 mm

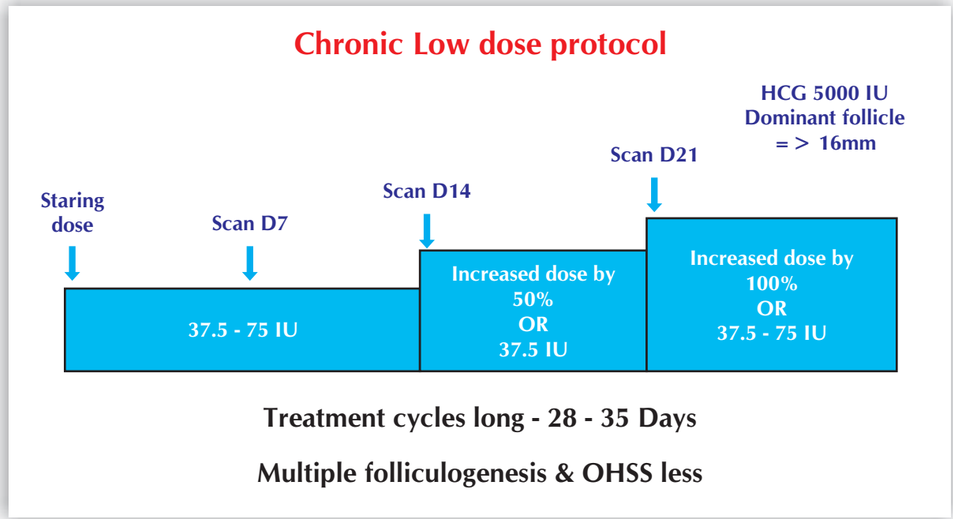


Figure 9: Chronic low dose protocol

Step down protocol (Figure 10)

Loading FSH dose (112.5 to 187.5 0 IU/day) decreased by 37.5IU every 3-5 days till dominant follicle emerges. There after the FSH dose is maintained same till criteria for administration of hCG is reached.

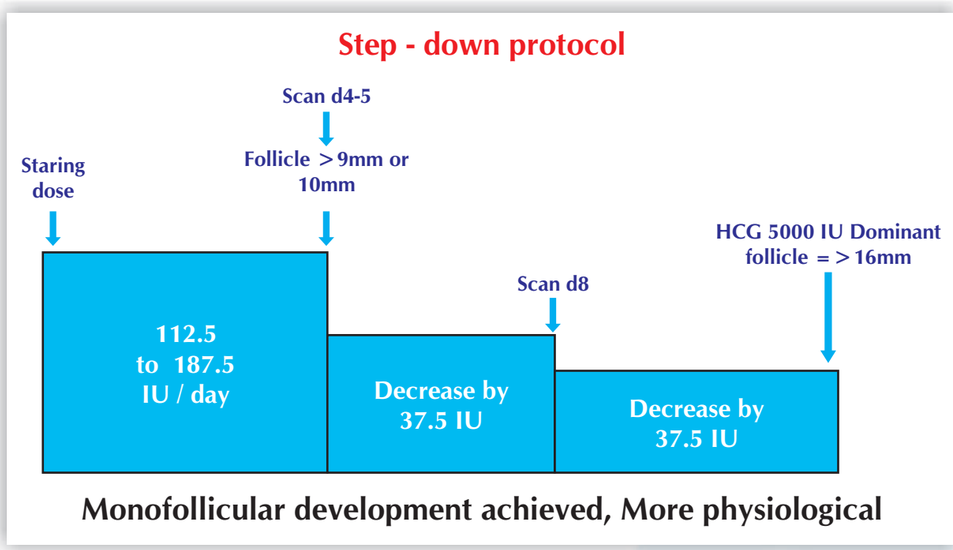


Figure 10: Step down protocol

Sequential protocol (Figure 11)

Principle for using the sequential protocol is as follows

- FSH dependence of leading follicle decreases as follicle grows.
- Decrease in FSH threshold contributes to the escape of the leading follicle from atresia when FSH concentrations start to decrease due to negative feedback of rising E2

Start stimulation with low (37.5 -75 IU/d) FSH dose, which is increased by 50% or 37.5 IU after 14 days if no ovarian response. Thereafter any further FSH increment are made by 37.5 IU – 75 IU at weekly intervals to a maximum of 225 IU/day. Once dominant follicle emerges and reaches a diameter of 14 mm the dose is reduced by 50 %.

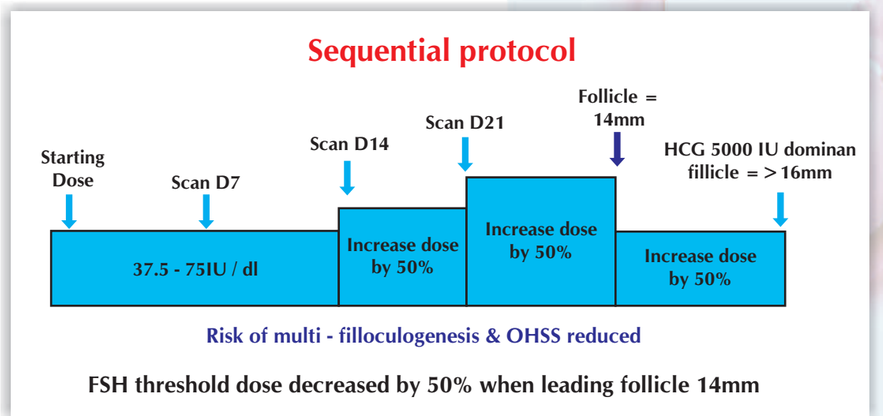


Figure 11: Sequential Protocol

The side effects of gonadotrophins are

- multiple pregnancy (25%)
- breast tenderness
- swelling and rash at injection site
- abdominal bloating
- depression, mood swings
- mild to severe OHSS
- miscarriage and premature deliveries

Contraindications to GT therapy

1. Tumors of ovary, breast, pituitary or hypothalamus
2. Pregnancy or lactation
3. Undiagnosed vaginal bleeding
4. Primary ovarian failure
5. Ovarian cyst
6. Malformation of sexual organs / fibroid uterus incompatible to pregnancy

Disadvantages of COH

1. Time consuming & stressful to the couple
2. Imposes heavy financial burden
3. Result in OHSS – May be life threatening
4. Detrimental effect on embryo implantation due to altered estrogen progesterone balance
5. Higher incidence of multiple pregnancy with its complications like pre-term delivery
6. 8-folds higher incidence of abortions even in singleton pregnancies
7. Women undergoing ovulation promoting medications and especially in those women who are complicated by OHSS are at increasing risk of thromboembolism

Abnormal response to controlled ovarian stimulation includes

1. Premature luteinisation
2. Endogenous surge
3. Poor response
4. Hyperstimulation

Induction of follicular maturation and ovulation : Drugs used for induction of follicular maturation and ovulation are given at a follicular diameter of 16 - 18 mm. They are as follows

1. HCG 5000 – 10,000 IU IM
2. Rec. hCG 250 mcg SC
3. GnRha1 mg SC

Function of these agents is

- Cellular & Nuclear maturation for final meiotic resumption after sperm entry
- Follicular changes for follicular rupture & ovulation
- Induce luteinisation in the granulosa cells of the follicle

Side Effects

Will precipitate mild to severe OHSS if given in patients with hyperstimulated ovaries.

Adjuvant drugs to prevent premature LH surge with gonadotropin therapy

- GnRH agonists in combination with hMG and/or FSH (long, short or ultra short protocol)
- GnRH antagonists in combination with hMG and/or FSH (fixed or variable protocol; single or multiple dose protocol)

Though LH surge is an absolute requirement for luteinization, final maturation of the oocyte and follicle rupture but a premature LH surge can occur in natural cycle[4,5] and in 25 – 30% of stimulated cycles resulting in premature lutenization of follicle, early rupture of follicle so that exact time of ovulation is missed resulting in treatment failures in an timed intercourse and IUI cycle[6-7]. A premature LH surge is defined as premature rise of LH (>10IU/l) accompanied by concomitant rise in progesterone levels(>1 mg/l) [6]

So we need to see whether use of GnRH agonist or antagonist in IUI cycles is a cost effective and helps in improving the outcome.

Moreover when IUI is done with gonadotrophins, the response may vary, ranging from no-response to hyper-response (more than 4 follicles of >12 mm developed). Amongst hyper-responders, where follicular recruitment is excessive, a decision must be made to either cancel the cycle, or allow the multiple follicles to mature and thus risk the incidence of multiple pregnancy and OHSS or convert it into an IVF cycle.

Here is then the role of GnRH analogues, and GnRH antagonist have the advantage over GnRH agonist as they could be

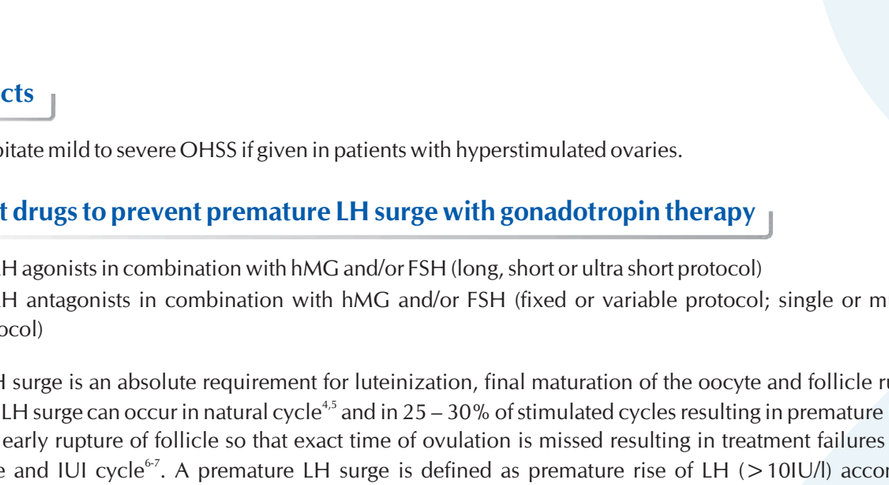


Figure 12: Pituitary function following GnRh analouges

GnRH agonists in ovarian stimulation for IUI

There seems to be no role for GnRH-agonists in IUI programs as they increase cost as the dose of gonadotrophins is increased tremendously. Its use also increases the incidence of multiple pregnancy without increasing the probability of conception. Thus use of GnRH agonists with gonadotrophins should be carefully considered in an intrauterine insemination program. [8]

GnRH antagonists in ovarian stimulation for IUI

When GnRH antagonists are used for ovarian stimulation in combination with IUI[9-10] there may be a small increase in probability of pregnancy and the numbers needed to treat is 20. In addition, they may be helpful in cycle programming and avoidance of inseminations during weekends.

Conversion of high-response gonadotropin-IUI cycles to "rescue" IVF using a GnRH antagonist is a cost-effective strategy that produces better results than regular IVF with relatively minimal morbidity, and shorter duration to achieve pregnancy. Implantation and ongoing clinical pregnancy rates tend to be higher than those from hyper-responder regular IVF patients. Whether or not GnRH-antagonists should be used regularly in IUI programs needs to be determined in future trials.[8]

Conclusion

Ovulatory dysfunction is one of the most common causes of reproductive failure in sub- fertile and infertile couples. In the absence of other significant infertility factors, successful ovulation induction often will restore normal fertility. Clomiphene citrate (CC) is the best initial treatment in majority of anovulatory infertile women.

Gonadotropin therapy is generally used in CC resistant patients and in those patients who do not conceive after repeated courses of clomiphene citrate [11] and those who are for ART.

The aim of ovulation induction with gonadotrophins is to find the threshold dose of FSH required to develop a single preovulatory follicle and to avoid multifollicular recruitment[12-13] for non ART cycles. As the ovarian threshold for FSH response varies among individuals[13] , "step-up protocols" are safest[14-15].

Individualized protocols selected on evaluation of BMI, AFC, AMH and ovarian response in the preceding clomiphene citrate and gonadotropin cycle, reduce duration of treatment, the amount of gonadotrophins administered, the associated risks of cycle-to-cycle variability, multifollicular development, OHSS and multiple pregnancy. This helps in reducing the complexity and cost while improving the success rate.

GnRH antagonists may have a role in ovarian stimulation for IUI but use of GnRH agonist does not improve the outcome in IUI cycles.

Before treatment with gonadotrophins, evaluation should also exclude abnormalities of thyroid function and hyperprolactinemia, and tubal pathology by hysterosalpingography (HSG).

Our aim is to use proper drugs after proper evaluation, investigations & at a proper time. If a patient has a normal ovarian reserve, determining the potential cause of the ovulatory defect is prudent. In the presence of obesity and chronic anovulation, polycystic ovarian (PCOS) syndrome and in the presence of elevated androgen levels or hyperinsulinemia, the ovulation induction protocols need to be individualized and carefully monitored for hyper- response. Patients with DOR also require modification of conventional protocols, but are usually associated with poor prognosis.

References

1. Hillier SG (2009). Paracrine support of ovarian stimulation. Mol. Hum. Reprod. 15:843-850.

2. Hendriks DJ, Mol BW, Bancsi LF, Te Velde ER, Broekmans FJ. Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle- stimulating hormone level. Fertil Steril 2005;83:291–301.

3. Macklon NS, Stouffer RL, Giudice LC, Fauser BC. The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocr Rev 27[2]:170-207, 2006.

4. Klein NA, Harper AJ, Houmard BS, Sluss PM, Soules MR. Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? J Clin Endocrinol Metab 2002;87:5746-5750.

5. deKoning CH, McDonnell J, Themmen AP, deJong FH, Homburg R, Lambalk CB.The endocrine and follicular growth dynamics throughout the menstrual cycle in women with consistently or variably elevated early follicular phase FSH compared with controls.Hum Reprod 2008;23:1416-1423.

6. Lambalk CB, Leader A, Olivennes F, Fluker MR, Andersen AN, Ingerslev J, Khalaf Y, Avril C, Belaisch-Allart J, Roulier R et al. Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinisation in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial.Hum Reprod 2006;21:632–639.

7. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with sub fertility (Review). Cochrane Database Syst Rev 2007. Art No.: CD005356.

8. Cantineau AEP, Cohlen BJ; Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility (Review); The Cochrane Library 2011, Issue 6

9. Ragni G, Vegetti W, Baroni E, Colombo M, Arnoldi M, Lombroso G and Crosignani PG (2001) Comparison of luteal phase profile in gonadotropin stimulated cycles with or without a gonadotropin-releasing hormone antagonist. Hum Reprod 16,2258–2262.

10. Gomez-Palomares JL, Julia B, Acevedo-Martin B, Martinez-Burgos M, Hernandez ER and Ricciarelli E (2005) Timing ovulation for intrauterine insemination with a GnRH antagonist. Hum Reprod 20,368–372.

11. Clark JH, Markaverich BM. The agonistic-antagonistic properties of clomiphene: a review. Pharmacol Ther 1982;15:467–519.

12. Van Campenhout J, Borreman E, Wyman H, Antaki A. Induction of ovulation with cisclomiphene. Am J Obstet Gynecol 1973;115:321–7.

13. Young SL, Opsahl MS, Fritz MA. Serum concentrations of enclomi- phene and zuclomiphene across consecutive cycles of clomiphene ci- trate therapy in anovulatory infertile women. Fertil Steril 1999;71:639 –44.

14. Kerin JF, Liu JH, Phillipou G, Yen SS. Evidence for a hypothalamic site of action of clomiphene citrate in women. J Clin Endocrinol Metab 1985;61:265–8.

15. Rebar R, Judd HL, Yen SSC, Rakoff J, VandenBerg G, Naftolin F.Characterization of the inappropriate gonadotropin secretion in poly-cystic ovary syndrome. J Clin Invest 1976;57:1320–9.

TRIGGERING OF OVULATION

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Normal menstrual cycle is a complex process of events involving the hypothalamus, pituitary, ovary and uterus. During the follicular phase, there is a rise in the level of FSH hormone which causes increase in E2 and LH levels. Increase in LH causes androgen production in theca cells, which by the help of aromatase enzyme gets converted to E2. As the follicle grows and E2 levels rise, it causes negative feedback on FSH so that the growth of smaller follicles stop and dominant follicle emerges, having maximum E2 levels and highest number of FSH and LH receptors. E2 level rises causing FSH surge, which is followed by LH surge which leads of ovulation[1]. For LH surge to cause ovulation, there should be sustained E2 levels of 200pg/ml for 50 hours. An adequate gonadotrophin surge doesn't always ensure ovulation. The follicle must be at a stage of maturity to respond to the ovulatory stimulus. In a normal menstrual cycle, gonadotrophin release and final maturity of the follicle coincides with the timing of gonadal surge. This is controlled by increasing E2 levels which in turn is the function of follicle growth and maturity.

Normal LH surge lasts for 48-50 hours. It has got three phases: the initial phase of acceleration lasting for 14 hours, plateau phase for 14 hours and phase of deceleration lasting for 20 hours[2].

LH surge causes

1. Resumption of meiosis causing release of first polar body.
2. Release of vasoactive amines which causes rupture of the follicle.
3. Formation of corpus luteum.

Normally during mensturation, there is first preovulatory FSH rise (which leads to increased LH receptor formation, increase in hyaluoronic acid and increase in plasminogen activation) followed by LH surge.

In case of controlled ovarian stimulation, the follicle is stimulated with gonadotrophin and ovulation is triggered with HCG which acts as surrogate for LH. HCG is a glycoprotein like LH with extended plasma half life. It has two subunits and . The alpha subunit is similar to LH and it is the Beta subunit which is different in both of these molecules[3]. Unlike physiologic LH surge which lasts for 48-50 hours, the surge caused by HCG spans several days which leads to increased levels of estradiol and progesterone along with vasoactive amines. This excessive amount of vasoactive amines and steroids leads to an increased OHSS incidence with HCG.

To overcome this life threatening potential complication of OHSS, triggering with GnRH agonist in antagonist cycle came into view.

MECHANISM OF ACTION : GnRH agonist acts at the level of pituitary and displaces GnRH antagonist and activates GnRH receptor which causes a surge of gonadotrophin LH and FSH which leads to ovulation. It is as close to natural menstrual cycle as possible. There is first FSH surge as in a natural cycle followed by LH surge which leads to resumption of meiosis. Unlike natural cycle LH SURGE, GnRH agonist surge is a short surge lasting for 24-36 hours with only two phases unlike three phases of LH surge[4]. So less amount of gonadotrophins are released which leads to early demise of corpus luteum. This is one of the major drawbacks of GnRH triggering, there is deficient corpus lutem leading to deficient luteal phase. This leads to significiantly lower pregnancy rates[5].

Many strategies have been adopted to correct this luteal phase defect. Concept of dual trigger i.e GnRH agonist along with HCG combines the benefit of endogenous release of FSH and LH by agonist trigger and small bolus of HCG to cover early luteal phase insufficiency caused by agonist trigger. *Peter Humaidan (2012)*[6] in his study gave 1500 IU of HCG along with GnRH agonist to correct this luteal defect at the time of egg retrieval and got good pregnancy rates.

Engmann et al (2008)[7] supplemented the luteal phase with intramuscular progesterone and estradiol valerate as modified luteal phase support post GnRH Agonist trigger.

According to Cochrane database comparing[8] GnRH agonist with HCG trigger, concluded that agonist should not be routinely used for triggering ovulation in normal responders as it leads to significantly lower live birth rates.

Comparison	GnRH AGONIST trigger	HCG trigger
OHSS	Very rare	High
Cost	Expensive	Cheap
Half life	Short(24-36 hours)	Long(8-10 days)
Luteal phase	Deficient	Adequate
FSH Surge	Present	Absent
Pregnancy rate	Lower	Higher

Indications for use of Agonist Trigger

1. PCOS patients with high risk for OHSS.
2. Patients having previous history of OHSS
3. Donor patient cycle
4. Empty follicle syndrome, repeated IVF failures and repeated retrieval of immature oocytes as a subset of patients who may require FSH surge in addition to LH surge to promote final oocyte maturation (Humaidan 2010)[6].

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication. The incidence for moderate cases is 5% . The incidence of cases requiring hospitalization is up to 2%. With the increasing use of antagonist protocol, the incidence of OHSS has come down drastically. The number of patients with severe OHSS which would require admission is relatively few and occurs most commonly with HCG triggering. To overcome this drawback of HCG trigger, GnRH agonist triggering is recommended in high responders and patients having history of OHSS.

OHSS FREE CLINIC

With the advent of GnRH agonist triggering the concept of OHSS free clinic has come. It is based on the three segment approach to prevent OHSS

- **Segment A**

  It consists of optimization of the ovarian stimulation, including GnRH agonist triggering in a GnRH antagonist cycle.

- **Segment B**

  It consists of optimum cryopreservation methods for oocyte or embryo vitrification.

- **Segment C**

  Includes embryo replacement in a receptive, non-stimulated endometrium in a natural cycle or with artificial endometrial preparation. (PAUL DEVOERY hum reprod 2011)[8]

OHSS Free Clinic

TYPES OF GnRH AGONIST TRIGGER

1. Decapeptidyl : It is used in the doses of 0.2 mg subcutaneously

2. Leupride acetate : 4 mg subcutaneously.

We at bloom IVF give decapeptidyl 0.2 mg subcutaneously trigger to

- Patients with more than 20 follicles on ultrasound.
- Patients with E2 levels > 4000 pg/ml
- Oocyte donor with follicles more than 15 on ultrasound.

In the year 2013, 65 patients were given decapeptidyl trigger with age more than 35 having AMH more than 3.5ng/ml.

We performed a retrospective analysis at Lilavati Hospital from January 2013 to December 2013.

We did 492 ovum pickups out of which 62 were with decapeptidyl trigger.

AMH(ng/ml)	> 3.5	< 3.5
No.of patients	37(59.6%)	25(40.4%)

OVULATION INDUCTION IN HYPOGONADOTROPIC HYPOGONADISM

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Hypogonadotropichypogonadism (HH) is a rare disorder of reproductive system where the defect lies in hypothalamic-pituitary axis. It corresponds to type 1 ammenorrhea according to WHO classification. It is characterized by

(a) Low FSH & LH levels
(b) Hypoestrogenism
(c) Ammenorrhea
(d) Arrested folliculogenesis
(e) No response to progesterone challenge.
(f) Response to combined estrogen & progesterone challenge

The defect lies in either pituitary causing deficiency of FSH & LH or in the hypothalamus causing deficiency of GnRH (1).

Causes of hypogonadotropic hypogonadism

1. Functional hypothalamic disorders : Stress, Dieting, anorexia nervosa, vigorous exercise, Post traumatic stress disorder
2. Genetic causes : Kallman syndrome, Isolated FSH deficiency, isolated LH deficiency
3. Anatomical causes : Craniopharyngioma, pituitary tumors
4. Radiation therapy
5. Endocrine causes : Hypothyroidism, Cushing syndrome, Hyperprolactinemia
6. Miscellaneous

According to two cell two gonadotrophin theory, both FSH and LH are required for folliculogenesis and final oocyte maturation. FSH stimulates the granulosa cells to increase expression of the cyctochrome P450 enzyme aromatase, while LH promotes the production of androgens from cholesterol and pregnenolone by stimulating 17 alpha hydroxylase activity in the theca cells These androgens then diffuse to the granulosa cells, where they are converted to estrogens by the activity of the aromatase enzyme. Adequate estrogen levels in the follicle are essential to facilitate FSH induction of LH receptors on the granulosa cells, allowing the follicle to respond to the ovulatory surge of LH levels. Thus, the LH surge is absolutely required for successful ovulation, oocyte maturation, fertilization, and implantation within the female reproductive tract.

HH patients who consult for infertility are investigated according to the usual protocol. Any structural abnormality of the reproductive tract should be ruled out by detailed transvaginal scan. Husband semen analysis and tubal patency should be confirmed before starting any treatment.

Mainstay of ovulation induction(OI) in HH patients is gonadotropin therapy. It can be done either by giving urinary preparations (hMG) or recombinant FSH along with recombinant LH or low dose hCG There is no role of oral agents or only FSH injections.

Optimal results can be achieved by administering both FSH and LH. It can be done either by giving urinary preparations (hMG) or recombinant FSH along with recombinant LH or low dose hCG.

Ovulation induction (OI) protocols

Patient is called on day 2 of the period (after giving estrogen & progesterone challenge). A baseline transvaginal scan is done. Usually we start from 150IU of hMG which is given daily for 5 days. Patients with higher BMI may require higher doses to start with. On day 6, TVS is done to see for any follicular growth and E2 levels are checked. Dose is increased by 33% every 5 days till adequate follicular growth is seen. Optimal response to gonadotropin therapy is considered if three criteria are met, i.e.(a) At least one follicle with a mean diameter of ≥ 17 mm (b) a pre-ovulatory serum E_2 level of ≥ 400 pmol/L(c) Midluteal phase progesterone level of ≥25 nmol/L(2)

Once these criteria are met, ovulation is triggered with hCG10,000 IU.

To avoid multifollicular development, FSH threshold should be identified and lowest effective dose should be used to start OI.

If recombinant preparations are to be used, 150 IU of rFSH is used along with 75/150U of rLH.

No studies have documented any benefit of recombinant preparations over urinary preparations in terms of safety, clinical efficacy and cost (3) .Carone D et al compared urinary gonadotropins (hMG, 150IU FSH + 150 LH) with recombinant gonadotropins (rFSH 150IU + rLH 75IU). Ovulation rate was 88% in urinary group as compared to 70% in recombinant group. But pregnancy rate was 55.6% in recombinant group as compared to 23.3% in urinary group(4). Further data is required to evaluate the efficacy of different types of gonadotropins.

Luteal phase support is deficient in these patients. It is necessary to give progesterone or low dose hCG(1500-2500IU every 3-4 days) to maintain the luteal phase support in these patients.

Defining the optimal LH dose

Various studies have been done to define the optimal dose of LH for ovulation induction in HH. Patients with LH < 1.2IU/ml are the ones who will be benefitted most from supplementing LH.

Shoham Z et al confirmed the validity of the 1.2 IU/L cut-off and the efficacy of 75 IU as the effective dose for LH supplementation for patients with profound LHdeficiency. Two-thirds of patients given lutropin alfa achieved follicular development compared with 20% of patients receiving placebo. A 1.5- fold increase in antral follicle number and a threefold increase in serum E_2 levels were detected in patients treated with lutropinalfa. The authors suggested that LH-related increase in E_2 levels may also facilitate endometrial support of implantation and pregnancy, particularly in older patients (over 35 years)(5).

Pretreatment with estrogen

Patients with HH who fail to achieve pregnancy with HMG are benefitted with pre treatment with estrogen with or without progesterone for 2-3 cycles. Also estrogen therapy given along with HMG therapy may improve the pregnancy rates(6). Further data is required to prove the mechanism of beneficial effect of estrogen.

Complications of ovulation induction in HH

1. **Multifetal gestation** - It is the most frequent complication of OI. Minimum effective dose of FSH should be stared in these patients. To avoid the this complication, criteria have been made for cycle cancellation(3). These include when ≥ 3 mature follicles (> 16-17 mm) or a large number of intermediate - sized follicles (10-15 mm) are observed or when the serum E_2 concentration exceeds 1000-1500 pg/mL.

2. **Ovarian hyperstimulation syndrome(OHSS)** - It is the most serious complication of OI. hCG is the main trigger for OHSS. OI dose should be individualized according to risk factors. Minimum effective dose of gonadotropins should be given for minimum duration to achieve therapeutic goal(7). 5000IU hCG can be given for trigger instead of 10,000IU.

Newer developments

Various adjuvant therapies e.g. Growth hormone(GH), pretreatment are being tried to increase the pregnancy rates in patients with HH.

Long acting FSH hormone (Corifollitropin alfa) may reduce the frequency of injections to once weekly with similar efficacy as conventional gonadotropins (8).

Kispeptin - GPR55 has been shown to stimulate the HPG axis. It can increase endogenous release of FSH and LS and has been shown to decrease exogenous gonadotropin requirement (9).

Further long term data is required to recommend routine use of these agents for ovulation induction in HH patients.

Bibliography

1. The Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril 2006;86(4):S148–S155.
2. Messinis IE. Ovulation induction: a mini review. Hum Reprod 2005;20:2688–2697
3. The practice Committee of the American Society for Reproductive Medicine. Gonadotropin preparations : past, present and future perspectives. Fertil Steril 2008;90(3):S13–S20
4. Carone D, Caropreso C, Chiappetta R. Efficacy of different gonadotropin combinations to support ovulation induction in WHO type I anovulation infertility : clinical evidences of human recombinant FSH/human recombinant LH in a 2:1 ratio and highly purified human menopausal gonadotropin stimulation protocols. J Endocrinol Invest. 2012 ;35(11):996-1002.
5. Shoham Z, Smith H, Yeko T, O'Brien F, Hemsey G, O'Dea L. Recombinant LH (lutropinalfa) for the treatment of hypogonadotrophic women with profound LH deficiency : a randomized, double-blind, placebo-controlled,

proof-of-efficacy study. Clin Endocrinol (Oxf) 2008;69:471-478.

6. Hayashi M, Tomobe K, Hoshimoto K, Ohkura T. Successful pregnancy following gonadotropin therapy in a patient with hypogonadotropic hypogonadism resulting from craniopharyngioma. Int J Clin Pract 2002;56:149-151.
7. Aboulghar M. Symposium : Update on prediction and management of OHSS. Prevention of OHSS. Reprod Biomed Online 2009;19:33-42
8. Fauser BC, Mannaerts BM, Devroey P, Leader A, Boime I, Baird DT. Advances in recombinant DNA technology : Corifollitropin alfa, a hybrid molecule with sustained follicle - stimulating activity and reduced injection frequency. Hum Reprod Update 2009;15:309-321
9. Roa J, Aguilar E, Dieguez C, Pinilla L, Tena - Sempere M. New frontiers in kisspeptin/GPR54 physiology as fundamental gatekeepers of reproductive function. Front Neuroendocrinol 2008;29:48–69

OVARIAN HYPER STIMULATION SYNDROME

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Introduction

The Knowledge of ovarian Hyper stimulation Syndrome (OHSS) is very important by the fact that it will be encountered by almost all who practice infertility . It may present with varying degrees of severity and in severe condition characterized by massive extra- vascular accumulation of exudates associated with depletion of intravascular volume leading to haemoconcentration & its complications and even death. Its importance is that it is a completely iatrogenic disease with an incompletely described physiology & if anticipated and treated properly can prevent from going into complications.

Incidence

OHSS is the result of ovulation induction. Usually it occurs 7-12 days after HCG administration. The incidence of OHSS in stimulated cycles in literature varies by 8.4-23% of mild hyper stimulation, 6-7 % of moderate hyper stimulation and 0.8 -2 % of severe hyper stimulation. [1]

Classification

Right from the first classification of OHSS by Rabau and colleagues in 1967[2] there have been different classifications for OHSS, but there has been no unanimity for the same.

One of the most followed classification of OHSS by Schenker and Weinstein is

Mild hyperstimulation

Grade 1 - Serum Estrogen > 150 ug/day and urinary excretion of pregnanediol > 10 mg/day

Grade 2 - Grade 1 with ovarian enlargement also there may be small cysts in ovary

Moderate hyperstimulation

Grade 3 - grade 2 with abdominal distention

Grade 4 - Grade 3 with nausea, vomiting and or diarrhea

Severe hyperstimulation

Grade 5 - Grade 4 with large ovarian cysts and ascites and /or hydrothorax

Grade 6 - Grade 5 with haemoconcentration with or without coagulation abnormalities.

Since mild OHSS will be there in about 15% of patients undergoing ovulation induction, a more practical classification correlating with treatment protocol and prognosis was put forward by Rizk and Aboulghar [3]

1. Moderate OHSS

Discomfort, pain, nausea, abdominal distension, no clinical evidence of ascites but ultrasonic evidence of ascites and enlarged ovaries, normal hematological and biological profiles.

2. Severe OHSS

Grade A

Dyspnoea, oliguria, nausea, vomiting, diarrhoea , abdominal pain .

Clinical evidence of ascites plus marked distension of abdomen or hydrothorax.

Ultrasound scan showing large ovaries and marked ascites

Normal biochemical profiles

Grade B

All symptoms of grade A plus, Massive tension ascites, markedly enlarged ovaries, severe dyspnoea and marked oliguria.

Biochemical changes in the form of increased haematocrit, elevated serum creatine & liver dysfunction.

Grade C

OHSS complicated by respiratory distress syndrome, renal shut down or Venous Thrombosis

Pathophysiology

Different factors have been put forward by different authors about the pathophysiology of OHSS. The theory by Rizk and colleagues[4] states that there is ovarian enlargement with significant degree of stromal oedema and multiple haemorrhagic follicular and theca luteal cysts resulting in extravasation of fluid into the peritoneal cavity.

Another more accepted theory is that there is enhanced capillary permeability which lead to acute body fluid shifts resulting in ascites and pleural effusion.[5] Increased production of prostagladins, histamine and the activation of the renin angiotensin enzyme system within the follicles have been postulated as the probable cause.

Prevention of OHSS

The importance of prevention of OHSS is that there is no definitive treatment for OHSS. [6] The prevention of OHSS involves identification of patients at risk and prediction of development of OHSS, and in cases of OHSS supportive therapy to prevent complications.

At Risk Patients

While undergoing ovulation induction, the following patients are at risk of developing OHSS [7]

- Patients with PCO
- Thin patients
- Young patients (< 35 years)
- Gonadotrophins usage for stimulation
- History of OHSS in previous cycle.
- GnRH Agonist Protocol

Prediction

Combined ultrasound and endocrine monitoring of follicular development helps in prediction of OHSS during ovarian stimulation[8,9]

a) Endocrine Monitoring

Plasma estradiol (E2) when elevated found to be the best predictor of hyperstimulation.

Hanning etal [10] found out OHSS occurred when E2 was > 4000 pg/ml and no OHSS occurred when E2 value was < 1000 pg/ml before giving HCG. But there is no consensus about the cut off value of estradiol. Some authors reported severe OHSS with peak follicular E2 value, well below 1500 pg/ml.[11] The practice committee of ASRM recommends cut off value of E2 as > 2500 pg/ml and caution when & serum Estradiol value rises rapidly during stimulation.[12]

b) Ultrasound follicular monitoring

Ultrasound monitoring of the number, size and pattern of distribution of follicles are important in prediction of OHSS[13]. The decrease in fraction of mature follicles and an increase in fraction of very small follicles is associated with increased risk of development of severe OHSS[14]. Also basal ovarian volume, if the ovaries are bulky with thick stroma, with large number of multiple small follicle we must be really anticipating OHSS .[15]

During stimulation not only mature follicles, but also small and intermediate follicles has to be monitored. This is because when HCG is given these follicles can also be contributing to OHSS pathology.

Prevention

1. Withholding HCG

This is done based on serum estradiol value, ultrasound features, evidence of OHSS, and slope of estradiol rise. But this has to be done at the expense of cancellation of the cycle.

2. Delaying HCG administration

This also called as 'coasting'[16] which involves withholding further gonadotrophin stimulation and delaying HCG administration until estradiol level Plateaus or decrease significantly, so that incidence and risk of OHSS is reduced. Available evidence suggest that coasting does not adversely affect IVF outcome unless it is prolonged > 3 days[17] This is also described as 'controlled drift period' by some authors.[18] Also Abdulla etal reported a higher successful oocyte recovery in patients receiving 10,000 U HCG than with 5000 U or 2000 U in IVF cycles [19]

3. GnRH - analogues to trigger ovulation

The initial flare up effect produced by agonist is utilized for ovulation, with decreased incidence of OHSS[20] The limitation of GnRHa is that it cannot be used in cycles where ovarian stimulation is done after pituitary down regulation is done using GnRHa.

4. Cryo preservation of Embryos and subsequent replacement

In IVF, this is possible with the advancement in the facilities for cryopreserving embryos and subsequent successful pregnancies by replacement of frozen - thawed embryos at a later cycle. There is aggravation of OHSS with increase in Beta HCG with pregnancy in hyper stimulation. So by cryo preserving & postponing embryo transfer the risk of OHSS is reduced drastically.

5. Luteal phase support with Progesterone

By avoiding the use of HCG and using only Progesterone for luteal phase support decrease the incidence of OHSS [21]

6. Step Up Protocol

Low dose step up protocol using gonadotrophins especially recombinant FSH is found to be producing reasonable ovulation & pregnancies in PCOs patients with history of OHSS , with less risk of developing OHSS. Here low dose recombinant FSH is started and dose increased in fractions of 37.5 U after giving the same dose for least 4-7 days and monitoring the response.

7. Laparoscopic ovarian drilling / wedge resection

This when done prior to ovarian stimulation especially in patients with polycystic , bulky ovaries, decrease the incidence of OHSS. The advantage of these procedures done laparoscopically is that it reduces chances of adhesions. [22]

8. Intravenous albumin

Prophylactic IV administration of 25% albumin at the time of oocyte retrieval is recommended by some authors to reduce OHSS. Studies of its efficacy have mixed results.

9. Follicular aspiration

The meticulous follicular aspiration has shown to reduce corpus luteum Progesterone Production, but not found to prevent OHSS in ART cycles.

10. Correction of circulatory and electrolyte imbalance

By strict monitoring of electrolytes and haematocrit values and correction of electrolyte imbalance and giving plasma expanders reduce the progression and complications of OHSS.

11. Paracentesis

Aspiration of ascetic fluid either by transvaginally or transabdominally under ultrasound guidance reduces the complications of OHSS. It is found to decrease pain, improved pulmonary function and renal function. Many studies have showed that average hospital stay and period with severe symptoms and disturbed electrolyte balance was much shorter when aspiration of ascitic fluid was performed even with early evidence of ascites than in those who underwent conservative treatment.

The transvaginal, ultrasound guided aspiration is better preferred because of better drainage of ascitic fluid , less chance of injury and is a simple procedure which can be done even without anesthesia. Serial paracentesis with replacement of plasma proteins may be needed.

12. VEGF Antagonist

The existence of a vasoactive molecule released in response to hCG is believed to be the main feature associated with the increased vascular permeability that occurs with development of OHSS, and vascular endothelial growth factor (VEGF) is the main candidate as the hCG mediator. Cabergoline - 0.5mg /day for 10 days has found to decrease the incidence of OHSS. Recently few studies of quinagolide hydrochloride (Norprolac) 75mgBD for 15 days have found to decrease OHSS

Conclusion

OHSS can result in significant morbidity and even life threatening complications in severe forms. With proper identification of patients at risk, and monitoring the patients, we can decrease the incidence and progress of OHSS.

References

1. Shenker J G, Weinstein D. Ovarian Hyper stimulation syndrome, a current survey Fertility Sterility 1978, 30: 255-68
2. Rabau. E Serr D. M. etal. Human menopausal gonadotrophin for anovulation & sterility Am J Obst Gynecol 1967, 98: 92-8
3. Text book of assisted Reproductive Techniques by Gardner, Weissman 9, 132-34
4. Rizk B, Aboulghar MA, The role of vascular endothelial growth factor and interleukins in the pathogenesis severe OHSS Human Reproduction update 1997; 3: 255-66
5. Aboulghar MA, Mansoor R. T. etal, Ovarian hyper stimulation syndrome, modern concepts in Pathophysiology and management Middle east Fertility Society J 1996; 1:3-16
6. Navot D etal, OHSS in novell reproductive technologies, prevention and treatment Fertil. steril 58.: 249, 1992
7. Mac Dougal M. J etal, A controlled study comparing patients with and without PCO undergoing IVF . Human Reprod 8: 233, 1993
8. Rizk B OHSS, In Studd. Progress in obsterics & Gynaecology 1993; 11: 311-49
9. Abdulla H.I , Rizk B –OHSS in Assisted Reproductive Technology,Oxford 1999;37-39
10. Haning R.V.etal.Plasma Estradiol is superior to ultrasound & urinary Estriol as a predictor of OHSS during induction of ovulation. Fertil steril 1983; 40:31-6
11. Schwartz M.etal. The use of human menopausal and chorionic gonadotrophins for induction of ovulation. Am J Obst Gynecol 1980; 138:801
12. Practice committee of ASRM of OHSS Fertil ster 2003: 30; 5; 1309-11
13. Tal. J etal. Ultrasonographic and clinical correlates of menotrophin versus sequential clomiphene citrate, menotrophin Fertil sterl 1985, 4: 342-9
14. Delvign etal. OHSS in invitro fertilization, a Belgian multicenter study. Hum Repro 1993; 8-1361-71
15. Danninger B etal. Prediction of OHSS of baseline ovarian volume prior to stimulation Hum Repro. 1996; 11: 1597-9
16. Rabinovici J etal. Rescue of menotropin cycles prone to develop ovarian hyperstimulation Br. J. obst Gynecol 1987

:94:1098-102

17. Ulugu, Bacbceci etal. The significance of coasting duration during ovarian stimulation for conception in assisted fertilization cycles Hum Reprod 2002;17:310-3

18. Urman B etal. Management of overstimulated gonadotrophins cycles with controlled drift period. Human. Reprod. 1992;7:213-17

19. Adbulla H, ahmoye M etal. The effect of the dose of Human Chorionic gonadotrophins and type of gonadotrophins stimulation Fertil Steril1987:48:958-63

20. Emperaire J. C. Ruffie A Triggering ovulation with endogenous lubeinizing hormone may prevent OHSS. Fert sterl 1991; 56:506-10

21. Rizk B, Smitz J Ovarian hyperstimulation syndrome after superovulation for IVF Hum. Reprd 1992;7: 320-7

22. Antoni J Duleba etal Success of laproscopic ovarian wedge resection Fertil Steril 2003 ; 79: 4: 1008 -14

OVARIAN STIMULATION IN POOR RESPONDERS.

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Despite the advances in Assisted Reproductive Technology (ART), the management of poor responders is still a dilemma. The prevalence of poor responders varies from 9%- 24%(1). The European Society for Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM) have developed the minimal criteria to define poor responders, which include any 2 of the following 3 features (2):

a) Advanced maternal age (⩾ 40 years) or any other risk factor for poor ovarian response.

b) A previous poor ovarian response (⩽ 3 oocytes with a conventional stimulation protocol).

c) Abnormal ovarian reserve tests.

The predictors of poor ovarian response include (3) :

- Advanced age
- Baseline serum FSH > 15 mIU /ml ,
- Serum LH < 3mIU/ml,
- Baseline FSH/ LH ratio > 3,
- Serum estradiol levels > 80pg/ml,
- Rise in S. FSH levels following the Clomiphene Challenge Test,
- Estradiol levels < 15 pg/ml following GnRha stimulation test
- Low Gonadotropin Surge Attenuating /Inhibiting factor (GnSA/IF).

Ovarian stimulation with clomiphene or gonadotropins and Intrauterine insemination (IUI) can be tried in women above 40 yrs, but very low live birth rate of only 1.4% - 3.9% has been reported in various studies. IVF is the most efficient treatment in these women(4) .

When the ovarian response is poor, **increasing the gonadotropin dosage** is an option to improve the response, to reduce cancellation rates of stimulated cycles and to improve pregnancy rates with limited effectiveness, though not much difference has been noted when the dose is increased beyond 450 IU/day(5).

Ovarian Stimulation protocols include the use of

GnRh agonist

I. Long protocol : The underlying mechanism of GnRH agonist is to inhibit the production of pituitary gonadotropins and thus prevent a premature LH surge. The GnRH agonist is started on Day 21 of the luteal phase in the previous cycles.

II. **Flare protocol** - 1 mgm GnRh agonist is started on day 2 of the cycle and is continued till the last day of stimulation. It is associated with an initial FSH flare to augment the effect of the gonadotropins along with blunting of LH, though no benefit on the cycle outcome has been observed. In comparison with luteal phase GnRh agonist, follicular phase GnRh agonist is associated with a rise in the androgen and progesterone levels which lowers the pregnancy rates(6)

III. **Microdose flare protocol** - In this protocol GnRh agonist is started in a dose of 20-40 ug twice daily on Day 2 or 3 of the menstrual cycle along with gonadotropins after 2 days. It leads to increase in the follicular recruitment due to endogenous gonadotropin release and subsequently also prevents the LH surge(7).

IV. **Stop protocol** - Continuation of the luteal phase agonist after the initiation of gonadotropins is associated with decreased COH response in case of poor responders. Faber et al., in a prospective randomized study have demonstrated a n ongoing pregnancy rate of 24% per transfer in patients where the GnRh agonist was discontinued on the initiation of menstruation with only 1 patient exhibiting a premature LH surge (8).

V. **Luteal phase FSH + GnRh agonist protocol** - The initial phase of follicular recruitment is hormone independent and starts in the luteal phase of the previous cycle. In a prospective randomized study, recombinant FSH and GnRh agonist were initiated on day 21 of the previous cycle leading to an increase in mature oocytes and clinical pregnancy rates but was not statistically significant (9).

VI. **Mini dose luteal phase GnRh agonist protocol** - decreases the extent of endogenous gonadotropin suppression, leading to a reduced gonadotropin dose for stimulation, with good E2 levels, oocytes and embryos (10).

GnRh antagonist : GnRH antagonist is administered daily in a small dose of 0.25ug subcutaneously daily when the follicle reaches a size of 14mm or as a fixed single dose of 3mg subcutaneously. It is associated with decreased gonadotropin requirement, less duration of stimulation and cost as compared to the use of long protocol of GnRh analogue.

Two randomized controlled trials comparing microdose- flare protocol of GnRh agonist to GnRh antagonist protocol and long GnRh agonist protocol to fixed GnRh antagonist protocol and found no statistical difference in the pregnancy rates between the agonists and antagonists. Prapas et al., in their study reported high cancellation rates in the antagonist group but no difference in the pregnancy rates between the two groups (11)

Clomiphene citrate / Aromatase inhibitor + GnRh antagonist protocol : When administered for 5 days along with the gonadotropins they enhance the endogenous follicular phase gonadotropins release in the cycle and also the response of gonadotropins. GnRh antagonist is initiated when the leading follicle diameter is 14 mm. On comparison with long protocol, lower cancellation rates and higher implantation rates have been found(12).

Natural cycle IVF : Due to lower pregnancy rates and higher gonadotropin requirement, natural cycle IVF was developed, where no gonadotropin stimulation is required and HcG is given when the oocyte reaches16-18mm. In a large retrospective study of 294 poor responders, natural cycle IVF was performed with decreased cost leading to pregnancy rate of 17.1% per embryo transfer and 29.7% in women of less than 35 years of age(13).

Adjuncts to Ovarian Stimulation in poor responders

A variety of adjuncts have been used to enhance the ovarian response with varying success rates. They include :

L-Arginine - Oral L-Arginine increases the nitric oxide (NO) levels in the blood. NO acts as a vasodilator, decreases the resistance to blood flow in the perifollicular arteries, increases the permeability of follicular epithelium to plasma proteins and thus increasing the susceptibility to FSH and GH which in turn increases the IGF-1. IGF-I helps in follicular maturation and differentiation of granulosa cells. The improved intrafollicular milieu in L-arginine treated patients, thus improves the follicular growth, and in turn the oocyte quality and fertilization (14).

Growth Hormone (GH) - It increases the IGF -1which in turn increases ovarian steroidogenesis and amplifies the response of the granulosa cells to gonadotropins. A Cochrane Review analysis has demonstrated a statistically significant difference in poor responders favouring the use of GH. (15)

Androgen and androgen modulating agents : Androgens stimulate the early stages of follicular growth and increase the pre antral and antral follicular count. Androgen augments follicle stimulating hormone receptor expression in granulosa cells, thus enhancing FSH sensitivity. The various androgens or androgen modulating agents are (16):

a) **Pre treatment with Transdermal testosterone** - Recent randomized trials with pretreatment have found the use of transdermal androgens to be inconclusive.

b) **Dehydroepiandrosterone supplementation (DHEAS) -** DHEAS is a precursor of ovarian steroidogenesis and also augments IGF-1 secretion. Though the findings in literature merit further consideration, well defined large scale confirmatory studies are needed.

c) **Addition of Aromatase Inhibitors -** Aromatase Inhibitors block the conversion of androgens to estrogens thus increasing the androgenic mileu. Various RCTs conducted show that the treatment is inconclusive.

d) **Pretreatment or addition of Recombinant LH (rLH), Recombinant hcG (rHCG)during ovarian stimulation** - The rationale behind using rLH or rHCG is that LH is essential in maintaining adequate intraovarian androgens and also helps in follicular growth. hCG provides LH like activity in the later stages of the follicular development. Currently, there is still insufficient data to recommend its use.

The Cochrane Database of Systemic Reviews 2010, reports that there is insufficient evidence to support the routine use of any particular intervention either for pituitary down regulation, ovarian stimulation or adjuvant therapy in the management of poor responders to controlled ovarian stimulation in IVF(17).

There is no universally accepted protocol in case of poor responders, but protocols should be individualized depending on the response during previous stimulation and the existing ovarian reserve in order to increase cost effectiveness. Despite the enormous progress, oocyte donation is a successful alternative in the treatment of poor responders who fail to conceive or fail to produce good quality eggs when they undergo COH. As per the SART cors online data 2012(18), in cases of diminished ovarian reserve, success rate of around 56.8% is seen with donated oocytes and fresh embryo self transfer. In our own experience we achieved a success rate of around 52.1% in cases of oocyte donation and self transfer in poor responders, in whom the success rates with their own eggs was only 14.5%(19).

References

1) Surrey ES, Schoolcraft WB. Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. Fertility Sterility 2000; 4: 667-676.

2) Ferraretti AP, La Marca A, Fauser BC et al., ESHRE consensus on the definition of poor response to ovarian stimulation for in vitro fertilization : the Bologna criteria. Human Reproduction 2011;26:1616-24.

3) Kamini A Rao. Poor responders - Prediction and management. Recent advances in Infertility management. 2001:159-166.

4) Amir Wiser, Einat Shalom, Shauna L et al., Ovarian stimulation and intrauterine insemination in women aged 40 years or more.Reproductive Biomedicine Online 2012; 24: 170-173.

5) Chung Hoon Kim. Strategies for Poor Responders in IVF cycles. Reproductive System & Sexual Disorders 2011;S5:1-4.

6) Gelety TJ, Pearlstone AC, Surrey ES. Short term endocrine response to gonadotropin releasing hormone ag nist initiated in the early follicular, midluteal, or late luteal phase in normal cycling women. Fertility Sterility 1995;64:1074-1080.

7) William S, Eris S. Ovarian hyperstimulation for poor responders. Ovarian Stimulation . 2011;77-86.

8) Faber BM, Mayer J, Cox B et al., Cessation of gonadotropin releasing hormone agonist therapy combined with high dose gonadotropin stimulation yields favorable pregnancy results in low responders. Fertility Sterility 1998;69:826-830.

9) Kucuk T, Sozen E. Luteal start of exogenous FSH in poor responder women. J Assist Reprod Genet 2007;24:635-638.

10) Olivennes F, Righini C, fanchin R etal., A protocol using a low dose of gonadotropin - releasing hormone agonist might be the best protocol for patients with high follicle stimulating hormone concentrations on day 3.Human reproduction 1996; 11: 1169-1172.

11) Yannis Prapas, Stamatios P, Yannis P etal., GnRH antagonist versus long GnRh agonist protocol in poor IVF responders : a randomized clinical trial. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2013; 166: 43-46

12) D'Amato G, Caroppo E, Pasquadibiscegli A et al., A novel protocol of ovulation induction with delayed gonadotropin releasing hormone antagonist administration combined with high dose recombinant follicle stimulating hormone and clomiphene citrate for poor responders and women over 35 years. Fertility Sterility 2004;81: 1572-1577.

13) Schimberni M, Morgia F, Colabianchi J etal., Natural cycle in invitro fertilization in poor responder patients : a surveyof 500 consecutive cycles. Fertility Sterility 2008; 7: 1765.

14) Cesare B, Michela S, Nicoletta M etal., Adjuvant L-arginine treatment for in-vitro fertilization in poor responder patients. Human reproduction 1999; 14 (7): 1690-1697.

15) Duffy JMN, Ahmad G, Mohiyiddeen L etal., Growth Hormone in invitro fertilization. Cochrane Database of Systemic Reviews. 2010.

16) Bosdou KJ, Venetis CA, Kolibainakis EM et al., the use of androgens or androgen modulating agents in poor responders undergoing in vitro fertilizatin : a systemic review and meta-analysis. Human Reproduction Update 2012; 18(2): 127-145.

17) Pandian Z, Aucott L, Bhattacharya S et al., Interventions for poor resonders to controlled ovarian hyperstimulation (COH) in in vitro fertilization. Cochrane database of Systemic Reviews 2010; Jan 20 (1): CD004379.

18) Sart cors online 2012. www.sart.org

19) Duru Shah. Gynaecworld Unpublished Data 2007-2013.

ADJUNCTS FOR OVARIAN STIMULATION

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Several drugs, shown to be safe for other uses, have proven to be highly effective adjuncts for ovarian stimulations. Numerous studies have proven efficacy of various drugs used as adjuvant for ovarian stimulation.

TABLE I

Weight loss and lifestyle modification:Anovualtory infertile women with polycystic ovary syndrome are more resistant to clomiphene treatment. These patients are typically obese and obesity further contributes to insulin resistance and anovulation. In obese anovualtory infertile women with polycystic ovary syndrome, weight loss alone (5% or more) decreases hyperinsulinemia and hyperandrogenimism and often restores ovulatory cycles. In a study by Clark et al. 60 of 67 obese anovolutory women (90%) who lost an average of 10kg/m^2 in a diet and exercise program resumed spontaneous ovulation and 52 (78%) ultimately achieved pregnancy, 18 (27%) without other interventions(1).

Metformin

Insulin resistance and hyperinsulinemia are now recognized as a common feature of polycystic ovary syndrome and an important contributing cause of the hyperandogenism and chronic anovulation that characterize the disorder. Recognition of the pathopshiological role of insulin resistance in the polycystic ovary syndrome has stimulated intense interest in the insulin-sensitizing agents for the treatment of the disorder.

Metformin is an oral hypoglycemic agent in the biguanide class that acts primarily by reducing hepatic gluconeogenesis, but also decreases intestinal absorption of glucose and increases peripheral glucose uptake and utilization.

The biguanide metformin (dimethylbiguanide) is an oral hypoglycemic agent widely used in the management of noninsulin-dependent diabetes mellitus. It is an insulin sensitizer that reduces insulin resistance and insulin secretion. It acts primarily by reducing hepatic gluconeogenesis, but also decreases intestinal absorption of glucose and increases peripheral glucose uptake and utilization.

In diabetics it lowers blood sugar levels, but in non-diabetics, they lower only insulin levels. Over the last few years there has been increased interest in the use of metformin(at dose of 1500-2500 mg/day) to increase ovulatory frequency, particularly in women described as having PCOS.

In a Cochrane systematic review, metformin was a concluded to be an effective treatment for anovulation in first-line treatment, and with some evidence of benefit in parameters of the metabolic syndrome. Ovulation rates were higher when combined with clomiphene(76% vs 46% when used alone). Finally, the authors recommended that it should be used as an adjuvant to general lifestyle improvements, and not as a replacement for increased exercise and improved diet (2).

However, some recent studies have questioned usefulness of metformin PCOS patients. In a meta-analysis of randomized trials in PCOS patients undergoing OI or IVF/Embryo transfer, co-administration of metformin did not significantly improve ovulation or pregnancy rates, but was associated with the reduction in the risk of OHSS(3).Metformin appears to have benefits in women with PCOS throughout ovulation induction treatments and particularly during IVF cycles by reducing OHSS.

Side effects of merformin include diarrhoea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headaches. These side-effects can be severe to limit the dose administered or require discontinuation of the treatment. Lactic acidosis can be a rare but fatal complication of metformin treatment. These side-effects tend to be dose-dependent and diminish with time, hence it is best to begin with a low daily dose and increase gradually at weekly intervals as tolerance allows.

Because most women with polycystic ovary syndrome are insulin-resistant and metformin treatment can restore ovulatory cycles in many, hence considered an important adjuvant for ovarian stimulation.

Dopamine agonists

Elevated prolactive level with or without galactorrhoea indicates abnormal GnRH pulse secretion. This causes ovulatory dysfunction, luteal phase defect or amenorrhoea. Bromocriptine for treatment of hyperprolactinemia, is usually started as 1.25 mg daily at bedtime to effectively suppress the normal nocturnal increase in prolactin secretion. A low initial dose also helps to minimize the frequency and severity of gastrointestinal and cardiovascular side-effects related to dopamine receptor stimulation (4).

Cabergoline treatment usually begins with a dose of 0.25mg twice weekly, increasing gradually thereafter about every four weeks until the effective dose is established. Most women achieve normal prolactin levels with 0.5-1mg weekly; doses greater than 2mg weekly are rarely required. Cabergoline has proven effective in 70-85% of hyperprolactinemic women who are resistant to or cannot tolerate bromocriptine treatment (5). Cabergoline and other dopamine agonists decrease expression of the receptor for vascular endothelial growth factor and therefore the actions of vascular endothelial growth factor in causing OHSS (6).

Overall, dopamine agonists' treatment normalizes and maintains normal prolactin levels in approximately 60-85% of hyperprolactinemic women. Cyclic mensis are restored in 70-90%, usually within 6-8 weeks after treatment begins, and ovulatory cycles return in 50-75% of treated women with or without tumors (5).

Side effects of dopamine agonists are common but generally well tolerated and most severe during the first two weeks of therapy. Because bromocriptine stimulates both D1 and D2 dopamine receptors most will experience mild adrenergic;

side-effects like nausea, dizziness, vomiting, nasal stuffiness and orthostatic hypotension. Side effects of Cabergoline are similar but less frequent and severe, most likely due to the drugs higher affinity for D2 receptors.

Hypothyroidism

Prevalence of hypothyroidism is 2-4% in women in the reproductive age group. Hypothyroidism can affect fertility due to anovulatory cycles, luteal phase defects, hyperprolactinemia, and sex hormone imbalance. Simple, oral hypothyroidism treatment for 3 months to 1 year can be of great benefit to conceive in otherwise asymptomatic infertile women. Chung et al in their study have shown that the miscarriage rate was significantly lower in the LT4 treatment group than in the control group. Embryo implantation rate and live birth rate were significantly higher in the LT4 treatment group. In the control group, both thyroid peroxidase antibody and thyroglobulin antibody levels were significantly higher in the miscarried subgroup than in the delivered subgroup(7).

Glucocorticoids

Adjuvant treatment with glucocorticoids may suppress preexisting or induced elevated androgen levels. Use of Prednisolone 5mg-10mg daily or Dexamethasone 0.5-2mg daily as either continuous or more limited follicular phase treatment regimen (cycle days 5-14) have been described. Many studies have found that the combined treatment with clomiphene and glucocorticoid can successfully induce ovulation in patients who fail to respond to clomiphene alone.

The mechanism of glucocorticoid action remains unclear, but appears to involve more than simple androgen suppression. Although the major increase of androgens during ovarian stimulation results from FSH stimulation, suppression of adrenal production of androgen by dexamethasone may contribute to maximizing uterine receptivity by lowering the total androgen levels and altering the ratio of cortisol (F) to cortisone in follicular fluid (FF).Thus, maximizing uterine receptivity(8).

In the largest randomized trial involving more than 200 clomiphene-resistant anovulatory infertile women, over 80% of those receiving combined treatment with clomiphene (200mg daily cycle days 5-9) and dexamethasone (2mg, cycle days 5-14) ovulated, campared to 20% of controls treated with clomiphene and placebo; the cumulative pregnancy rate in women receiving dexamethasone (40%) was 10-fold higher than in those who received placebo (4%)(9).

Studies have shown that the rate of ovulation increased four to five fold and the rate of pregnancy per cycle increased to 8-10 folds. Also in a large randomized trial of dexamethasone during stimulation for IVF, a dramatic decrease of cancelled cycle from 12.4%-2.8% was noted, and the implantation rates and the pregnancy rates were higher, despite inclusion of those poor prognosis women going to egg retrieval(10).

Side effects with the glucocorticoids are minimal, but it should be used with caution in patients with peptic ulcer disease, infections and diabetes.

Low Dose Aspirin

The low aspirin is thought to increase blood flow by changing the balance of vasoconstricting thromboxane relative to vasodilating prostacyclin. Ovarian blood flow has been reported to correlate with ovarian response and uterine blood flow has been implicated in implantation, which is a highly vascular phenomenon. It is not known how long ovarian blood flow must be increased to potentially influence ovarian response. The most important time for maximal blood flow may be between hCG and egg retrieval, during which meiosis resumes.

Rubinstein et al., in 1999 in this journal (11), published a large, well designed trial that found increases of ovarian response, pregnancy outcome, and ovarian and uterine blood flow with 100mg of aspirin compared with placebo in a population residing in a large metropolis. The aspirin was begun with the onset of midluteal agonist and was continued through early pregnancy.

Vaginal sildenafil Citrate

Endometrial growth is thought to depend on uterine artery blood flow and the importance of endometrial development in successful IUI/IVF outcome has been reported. Nitric oxide (NO) relaxes vascular smooth muscle through a cGMP-mediated pathway and NO synthase isoforms have been identified in the uterus. Sildenafil Citrate, a type 5-specific phosphodiesterase inhibitor, augments the vasodilatory effects of NO by preventing the degradation of cGMP. Sildenafil is prescribed in dose of 25 mg four times a day.

Takasaki et al in their pilot study showed that sildenafil improved endometrial thickness and Radial artery-resistance index in 92% patients in study group as against 10% in control group who received no treatment(12).

G-CSF (Granulocyte colony-stimulating factor):Chronically thin endometrium resistant to standard treatments affects a small number of patients undergoing IVF. This problem, nevertheless, is of considerable importance because endometrium below 7 mm in thickness is widely considered sub-optimal for transfer and associated with reduced pregnancy chances.

G-CSF is a glycoprotein growth factor present in endometrium, macrophages and in other immunocytes. How G-CSF works is still unknown. A growth spurt in endometrial thickness can be observed within 48 hours of G-CSF administration.

In a study by Gleicher et al, G-CSF (Nupogen™) 300mcg/ml was administered per intrauterine catheter by slow infusion before noon on the day of hCG administration. If the endometrium had not reached at least a 7-mm within 48h, a second infusion was given following oocytes retrieval. They have reported an ongoing pregnancy rate of 19.1% (13).

Estradiol Valerate

Clomiphene citrate(CC) is an orally active non-steroidal estrogen agonist/antagonist that is widely used as the first line ovulation induction drug. But CC has a negative effect on the cervical mucus and its anti-estrogenic activity can cause thinning of endometrium. Presently, one of the most effective ways to improve endometrium thinning caused by CC treatment is to add an exogenous estrogens treatment during the course of CC stimulation. Exogenous estrogens treatment increased endometrial thickness, improved pregnancy rate, and reduced miscarriage rates(14). Estradiol valerate is given in a dose of 2mg-18 mg/day.Exogenous estrogen exerts its positive effect on endometrium by binding to estrogen receptors in endometrium and facilitates endometrium development. It is known that the exogenous estrogen can antagonize the negative effects of CC on endometrial glandular-stromal tissue(15).

H Growth Hormone

Abir et al, have demonstrated the expression of hGH receptor in human ovaries from fetuses as well as and of GH in human fetal ovaries. The hGH receptors mRNA is also expressed in human oocytes and through preimplantation embryonic development (16).

2002 Cochrane Review assessing efficacy of adjuvant hGH in women undergoing COS reported that no significant difference was noted in the number of follicles and oocytes or gonadotropin usage and hence concluded that adjuvant use of hGH needed further study. However several recent studies have increased the interest in the use of adjuvant hGH (17). Tesari K et al in their randomized placebo-controlled study reported a significantly higher plasma and intrafollicular E_2 levels, clinical pregnancy and live birth rates in hGH group. However no improvement in the number of oocytes retrieved was observed. In conclusion, limited data availability and considerable extra cost, there is no conclusive rate of

hGH in poor responders and use of hGh requires further studies (18).

Testosterone Supplementation

Kim et al in an RCT of 110 poor responders have shown potentially beneficial effects of testosterone gel application. Transdermal testosterone gel, 12.5mg, was applied daily for 21 days in the preceding cycle. They concluded that, it significantly increased the number of oocytes retrieved, mature oocytes, fertilized oocytes and good quality embryos in the study group. Implantation rates and clinical pregnancy rates were also significantly higher in testosterone treated group (19).

Human Chorionic Gonadotropin

Due to inconsistency of the spontaneous LH surge in ovarian stimulation human chorionic gonadotropins has been routinely used and is approved as an LH surrogate to induce ovulation. When preovulatory follicles are present, administration of hCG is followed by granulose cell luteinization, a switch from estradiol to progesterone systhesis resumption of meiosis and oocytes maturation, and subsequent follicular rupture 36-40 hours later. It is administered in a dose of 5000-10000 IU of urinary hCG or 250 IU of recombinant hCG.

Leuprolide Acetate (LA)

More than 20 years ago, LA was found to effectively block premature ovulation, which otherwise resulted in the cancellation of about 20% of IVF cycles. This benefit was so clear it should be used routinely for IVF (20).

The concept that a bolus of gonadotrophin releasing hormone agonist (GnRHa) can replace human chorionic gonadotrophin (HCG) as a trigger of final oocytes maturation was introduced several years ago. Recent developments in the area strengthen this premise. GnRHa trigger offers important advantages, including virtually complete prevention of ovarian hyper-stimulation syndrome (OHSS) (21).

TECHNIQUE OF IUI

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IUI is the placement of high density, good, motile, processed sperms directly into the uterine cavity to enhance their encounter with the oocyte at the time of ovulation in order to achieve pregnancy. It is simple, easy, least invasive and cost effective as compared to IVF. Today,it is the commonest method used to treat infertility worldwide.

IUI is one of the oldest techniques used to treat infertility. The first report was that of John Hunter in 1770 who advised a man with hypospadias to collect his semen in syringe and inject his wife with it and had a pregnancy. 1

Artificial insemination was also practiced amongst Arabs. More than 600 years ago, an Arab Sheikh had inseminated the mares of his enemy with inferior stallions' semen.

In 1765, Jacobi of Germany successfully performed artificial insemination with fish eggs. In 1789, Lazzaro Spallanzani, an Italian biologist shut a dog and his female counterpart who was in heat in separate rooms. He collected the dog's semen and inseminated her. She produced 3 haelthy pups later.

Modern methods of insemination were initially used in cattle by dairy farmers to improve milk production.

Science has come a long way to where we are at present. Revival of interest in IUI happened after IVF was born. With better understanding of sperm physiology, sperm preparation media

and techniques improved and hence IUI became the first line treatment for infertility.

Sperm Collection

The couple should be instructed not to refrain from intercourse right in the beginning of the IUI cycle. Many a times, they do so in order to produce a concentrated specimen on day of IUI which is absolutely incorrect.

Prolonged period of abstinence leads to increased ROS in the sample thereby increasing DNA fragmentation, dead sperms and debris. 2

Recently, studies have shown that abstinence of 2 days produced the highest pregnancy rate. This higherconception rate occured despite a decrease in total number of motile sperms. SEMEN PROCESSING:-

After the sample is collected, it is analyzed and processed in order to rid the sperm of prostagladin, seminal vesicalsecretions, dead sperm and removal of the debris.

Technique of IUI

In an infertility unit that has a heavy load of patients, or otherwise too, it is a good practice to inform the andrology lab and receptionist regarding the details of the patient and the procedure on the day of trigger.

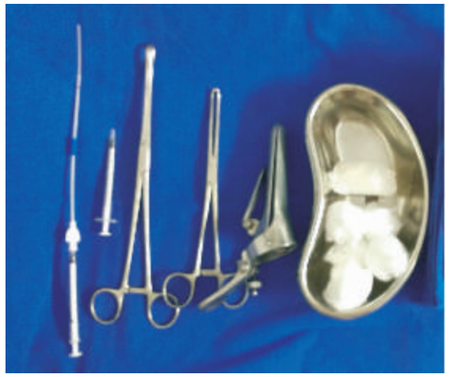
Semen sample should be collected 1 hour prior to the intended IUI to give time for semen processing.

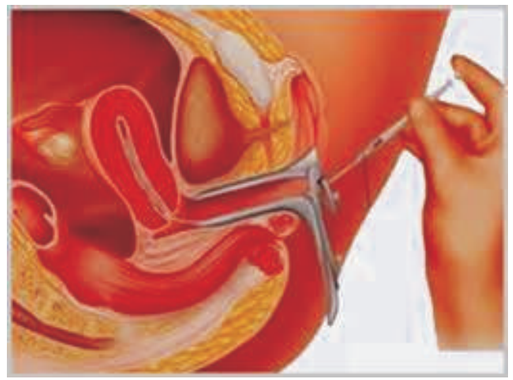
Consent of wife and husband should be obtained.

Setting up of IUI trolley

The IUI trolley should have the following:-

1. Cusco's pelvic speculum
2. Powder free surgical gloves- 1 pair
3. 1 cc sterile syringe
4. Allis forceps/ tenaculum
5. Gauge
6. Sponge holder
7. Saline
8. IUI cannula





Steps

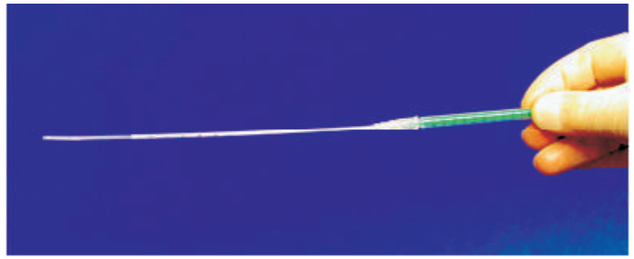
1. Verification of the sample identity is a must. Assessment of count and motility of the processed sample should be done. The andrology lab and insemination room should be preferably close to each other and IUI should be done as soon as possible after processing. In case of long wait, exhaustion of energy sources in the washing media may occur hampering the motility of the spermatozoa.

   Additionally, since the sperms are capacitated, the fertilization potential of the sperm decreases as time passes.

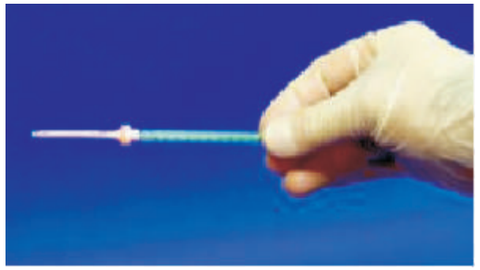
2. Hands must be scrubbed.
3. Put the patient in lithotomy or modified lithotomy or dorsal portion. Good illumination is a must.
4. Do pervaginum examination to see the position of uterus.
5. The position of the uterus, the uterocervical lengthand angle must be observedand made note of during the follicle monitoring. In case of a previous h/o a difficult IUI, it maybe useful to do a mock IUI under U/S control.
6. Clean vulva with saline.
7. Drape the patient.
8. Insert the Cusco's speculum.
9. Examine the cervix. You may clear the mucus on exocervix with sterile gauge if it is obstructing the view of external os.
10. Routine use of tenaculum is not required in all cases. Use of tenaculum may or may not affect the pregnancy outcome. Recently, it has been reported that the use of tenaculum increases the pregnancy rates.
11. Attach 1 ml syringe withmedium to the IUI cannula and sprinkle in the cervical canal. It is also prudent to check for the passage by advancing it just beyond the internal os as a mock trial of being able to negotiate the canal while actually doing the IUI. If we succeed, proceed to next step.
12. Take another 1ml syringe. Fill air in it upto 0.3ml to accommodate for the volume of the cannula. This is very important step as failure to do so might result in the semen being trapped in the cannula itself. It would not be pushed into the uterus. 0.2-0.3ml is the volume of the cannula- so that much air is required to push it through the cannula and into the cervix
13. Adjust the stopper to the length of 1cm less than UCL. (The insemination should take place over 60-80 seconds. It should not be sudden or jerky.) Next, load the processed semen into it. Thare should be no air bubbles in the cannula.
14. Insert the cannula through the external os into the canal and then into the uterine cavity. Stop short of the fundus.
15. An atraumatic, gentle technique is mandatory in order that the endometrium is not disturbed. This negates the chance of a pregnancy. Be sure not to touch the tIp of the cannula.
16. Push the plunger gently over 60-80seconds smoothly in order to release the sample once the mid cavity of the uterus is reached. Keep the catheter there for 60 more seconds., Withdraw the catheter gently, raise the foot end of the table or put a pillow beneath the patient's pelvis.
17. Ask the patient to rest there for 10-15 minutes. Limited data is available on the importance of rest. A randomized trial reports higher pregnancy rates in rested patients compared to those who were immediately mobile post IUI- PR 25% (Hb/55) vs 4/40 (10%). 4.Though psychologically it definitely helps the patient.

Catheters for IUI

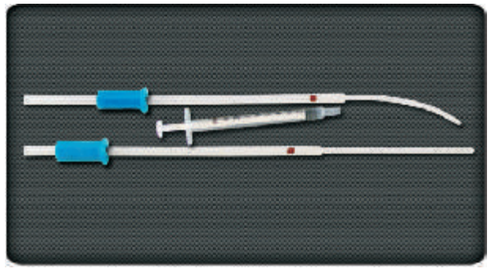
There are many types of catheters available - both soft and firm but there is insufficient evidence to suggest the superiority of one over the other. 3



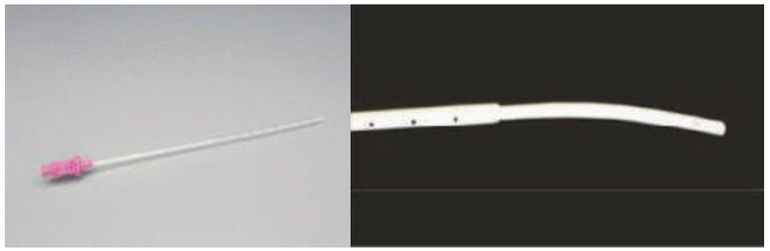
Maklers Catheter



Frydmans Catheter



Tomcat Catheter



Wallace Soft Catheter

Soft Catheters

a. Wallace ET catheter

- Polytheylene
- Open ended
- 18-23cm long inner catheter
- Diameter = 1.6cm
- Outer teflon introducer

b. Wallace artificialinsemination catheter

- Soft flexible double lumen
- Inner catheter 18cm long with round tip
- Outer sheath with memory.

c. Cook

- Soft flexible double lumen

d. Gynetics

- Soft flexible double lumen
- 20.6cm long with round tip.

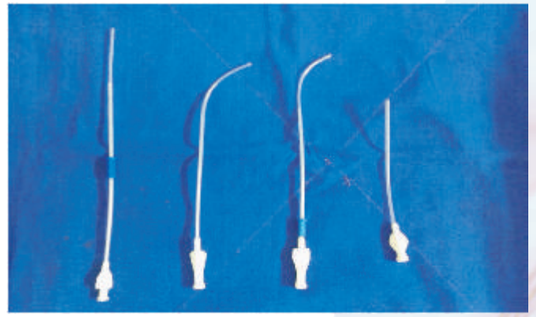
Firm Catheters

a. Tomcat

- Firm, single lumen
- 11.4cm 3.5 Fr lumen

b. Makler IUI cannula

- Has a broad base which serves to block the cervix to prevent reflux of semen.



Instructions

Post procedure counselling is very important. The patient may be instructed to have intercourse on that night. There is no requirement of rest. She may go to work and resume her day to day activities.

Sometimes, there is a feeling of wetness after the IUI. Patient should be counselled that it is due to loosened cervical mucus and the media that you have sprinkled in the cervical canal.

Any cramping or discomfort in the lower abdomen would subside in a few minutes.

Light spotting or bleeding may occur from the site of Allis bite.

Difficulties faced during IUI Procedure

1. Difficulty in negotiating the cervical canal: This may due to
   a. Fibrosis leading to stenosis of cervical canal.
   b. Creation of a false passage.

c. Retroverted uterus.

d. Acutely antiverted uterus.

It is a good idea to negotiate the cannula through the intended passage before loading the processed semen in it.

How to deal with it?

1st Use of tenaculum/Allis forceps in order to straighten the utero cervical angle and align them to allow the passage of the IUI catheter/cannula.

FAILS

2nd Use of a metal catheter. Patient may be asked to fill her bladder to straighten the uterocervical angle in an acutely antiverted uterus.

These steps make it possible to do the IUI in most of the cases.

FAILS

3rd You may perform the procedure under USG guidance

FAILS

4th Rarely, the patient may require general anasthesia.

IUI cannulas with wire inside them are available. The wire gives them rigidity which are otherwise soft and floppy. They can be moulded into the desired shape that follow the passage comfortably.

Complications of the Technique of IUI

Complications of IUI techniqueare few and not life threatening.

1. Genital Infection - It is the most unwanted complication of IUI. It occurs in < 0.5%of patient .

Infection may come from

a. Infected semen

b. Non sterile technique of semen collection.

c. Contamination of tip of IUI cannula by accidently touching it with hand or on vaginal walls.

d. Reactivation of a previous chronic infection, most common organism is E.coli and tuberculosis is some cases.

e. Not taking aseptic appropriate precautions while doing the procedure.

2. Lower Abdominal Discomfort

This is due to uterine cramps. It is reported in 5% of patients due to

a. Introduction of IUI cannula.

b. Mild scratching of endometrium may cause secretion of protaglandins.

c. Seminal fluid prostagladins may cause cramps.

It does not indicate infection.

3. Spotting

- From Allis bite
- From mild abrasion of the passage while negogiating the cannula.

Bleading during IUI decreases the chances of pregnancy.

4. Vasovagal Attack

Some patients have low pain threshold and may have hypotension and faint during the procedure.

Patient should not be fasting and the temperature of the room should be cool to ensure comfort to the patient. Few sips of water may be offered.

5. Lab Error

Resulting in mixing up of semen sample can have disastrous consequences. Ensure to have a well labelled container and double check the identity of the patient before proceeding for IUI.

6. Anaphylactic Reactions

They are very rare. They are due to various agents like bovineserum albuin present in the media.

7. **Donor Insemination**

Proper consent of the couple is a must to save any legal complications later.

The technique of IUI is simple , has a short learning curve, and can be mastered easily to get good results.

References

1. OMBELET W, VAN ROBAYS J History of human artificial inseminationF, V & V IN OBGYN, 2010, MONOGRAPH : 1
2. Sanchez-Martín P[1], Sánchez-Martin F, González-Martínez M, Gosálvez J. Increased pregnancy after reduced male abstinence. SystBiolReprod Med. 2013 Oct;59(5):256-60
3. van der Poel N, Farquhar C, Abou - Setta AM, et al. Soft versus firm catheters for intrauterine insemination. Cochrane Database Syst Rev 2010; :CD006225.
4. Saleh A, Tan SL, Biljan MM, Tulandi T.A randomized study of the effect of 10 minutes of bed rest after intrauterine insemination. FertilSteril. 2000;74(3):509

LUTEAL SUPPORT IN IUI

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Abstract

Progesterone and estradiol are required for successful pregnancy, both to prepare the uterus for embryo implantation and to stabilize the endometrium during pregnancy. The supplementation of the luteal phase with exogenous progesterone is necessary to optimize cycle outcomes. Administration of intravaginal progesterone preparations is equally efficacious and better tolerated by patients compare to intramuscular preparations. HCG if used as a luteal support increases rate of ovarian hyperstimulation syndrome to many fold.

Here, we review the evidence for route, efficacy, dose and timing of different progesterone preparations in IUI cycles.

Introduction

The term used to describe the administration of medications aimed at supporting implantation process in luteal phase is Leuteal Phase Support (LPS). The prevalence of luteal phase insufficiency in natural cycles with infertility was demonstrated to be about 8.1% in normal ovulatory patients[1]. In normal menstrual cycles, progesterone is secreted in a pulsatile fashion every 1-4 hours ranging between 4 and 20 ng/ml during peak production, which is usually 4 days after ovulation.

Any method to detect ovulation is not 100% accurate, the date of ovulation is calculated by basal body temperature chart (70% accurate), detection of LH surge (85%) or sonography (96%). A study comparing correlation between ovulation and endometrial histology for endometrial dating, suggested a lag of more than 2 days between chronological and histological dating shows the endometrium is out of phase. The out of phase endometrium is correlated with poor implantation rate. There are several drawbacks of detection of luteal phase defect by this method. The endometrium is out of phase in 49% of fertile female, and 43% infertile female.

Endometrial thickness and endometrial volume on sonography is also not useful to detect the luteal phase defect. The pulsatile nature of the progesterone hormone secretion makes single serum progesterone measurement on day 21 an inadequate method to detect luteal phase defect.

There are two schools of thought about luteal phase support. It can be given prophylactic to all patients or only those with inadequate luteal phase.

Considering the inadequacy of the method to detect the exact time of ovulation, luteal phase defect and the effect of stimulation on luteal phase, advocates of the second school of thought administer luteal phase support to all patients undergoing ovulation induction and IUI.

Role of Progesterone in luteal phase

1. Progesterone induces a secretory transformation of the endometrium in the luteal phase[2] and by that it improves endometrial receptivity of adequate estrogen priming[3]. Thus, improves implantation rate.

2. Progesterone promotes local vasodilatation by inducting nitric oxide synthesis in decidua, which improves endometrial growth and secretory changes[4].

3. Progesterone has uterine-relaxing properties.

Optimum Route of progesterone administration

Progesterone is available in different formulations include oral, vaginal, rectal and intramuscular.

Oral : Micronized progesterone by oral route is not preferred as

1. It is subjected to first-pass hepatic metabolism having low bioavailability (only 10%)[5,6]

2. Erratic absorption

3. Serum levels of progesterone return to baseline in 6 hours

4. Having advantage of acceptability only

To overcome this problem, Dydrogesterone, a biologically active metabolite of progesterone having good oral bioavailability, was introduced[7,8]. It was claimed to have similar pregnancy rates with micronized vaginal progesterone after IVF[9].

Contrary, many studies showed exogenous vaginal micronized progesterone is significantly more effective than oral dydrogesterone in creating an “in phase” secretory endometrium[10,11].

Intamuscular : The most common form of progesterone that has been used for luteal phase support has been progesterone oil administered as intramuscular injections (IMP)[12,13]. IMP gives rise to higher plasma concentrations, with levels being maintained for a longer duration[14]. While reasonably effective, IMP are painful for the patients, inconvenient to administer, needs another person to help with administration, associated with severe side effects, such as infections, abscesses, allergic rashes to even pulmonary complications[15,16,17,18]. On the bases of presented evidence, IMP is not recommended as a “first choice” luteal phase support method in stimulated IUI cycles.

9. Chakravarty BM, Shirazee HH, Dam P, et al. Oral dydrogesterone versus intravaginal micronised progesterone as luteal phase support in assisted reproductive technology (ART) cycles: results of a randomised study. J Steroid Biochem Mol Biol 2005; 5: 416-420

10. Fatemi HM, Bourgain C, Donoso P, et al. Effect of oral administration of dydrogesterone versus vaginal administration of natural micronized progesterone on the secretory trasformation of endometrium and luteal endocrine profile in patients with premature ovarian failure: a proof of concept. Hum Reprod 2007; 22: 1260-1263

11. Pellicer A, Matallin P, Miro F, et al. Progesterone versus dehydrogesterone as replacement therapy in women with premature ovarian failure. Hum Reprod 1989; 4:777-781

12. Zarutskie PW, Phillips JA. A meta-analysis of the route of administration of luteal phase support in assisted reproductive technology: vaginal versus intramuscular progesterone. Fertil Steril 2009; 92: 163-169

13. Tavaniotou A, Smitz J, Bourgain C, et al. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod Update 2000;6: 139-148

14. Posaci C, Smitz J, Camus M, Osmanagaoglu K, Devroey P. Progesterone for the luteal support of assisted reproductive technologies: clinical options. Hum Reprod 2000; 15: Suppl 1: 129-148

15. Propst AM, Hill JA, Ginsburg ES, et al. A randomized study comparing Crinone 8% and intramuscular progesterone supplementation in in vitro fertilization- embryo transfer cycles. Fertil Steril 2001; 76: 1144-1149

16. Bouckaert Y, Tobert F, Englert y, De Backer D, De Vuyst P. Delbaere A. Acute eosinophilic pneumonia associated with intramuscular admnistration of progesterone as luteal phase support after IVF: case report. Hum Reprod. 2004; 19: 1806-1810

17. Veysman B, Vlahos I, Oshva L. Pneumonitis and eosinophilia after in vitro fertilization treatment. Ann Emerg Med. 2006; 47: 472-475

18. Phy JL, Weiss WT, Weiler CR, Damario MA. Hypersensitivity to progesterone-in-oil after in vitro fertilization and embryo transfer. Fertil Steril 2003; 80: 1272-1275

19. Cicinelli E, Schonauer LM, Galantino P, et al. Mechanism of uterine specificity of vaginal progesterone. Hum Reprod 2000; 15 Suppl 1: 159-165

20. De Ziegler D, Seidler L, Scharer E, et al. Non-oral administration of progesterone: experiences and possibilities of the transvaginal route. Schweiz Rundsch Med Prax 1995; 84: 127-133

21. Simunic V, Tomic V, Tomic J, et al. Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal phase support. Fertil Steril 2007; 87: 83-87

22. Bulletti C, de ziegler D, Flamigni C, et al. Targeted drug delivery in gynecology: the first uterine pass effect. Hum Reprod. 1997; 12: 1073-1079

23. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct trasport of progesterone from vagina to uterus. Obstet Gynecol. 2000; 95: 403-406

24. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmoush L, Sauer MV. Pharmacolinetics and endometrial tissue levels of progesterone after administration by intramuschular and vaginal routes: a comparative study. Fertil Steril. 1994; 62(3): 485-490

25. Schoolcraft WB, Hesla JS, Gee MJ. Experience with progesterone gel for luteal support in highly successful IVF programme. Hum Reprod. 2000; 15: 1284- 1288

26. Polyzos M, Messini C, Papanikolaou E, et al. Vaginal progesterone gel for luteal phase support on IVF/ ICSI cycles: a meta-analysis. Fertil Steril. 2010; 94: 2083- 2087

27. Gibbons WE, Toner JP, Hamacher P, Kolm P. Experience with novel vaginal progesterone preparation in a donor oocyte program. Fertil Steril. 1998; 69: 96-101

28. Jobanputra K, Toner JP, Denoncourt R, Gibbons WE. Crinone 8% (90 mg) given once daily for progesterone replacement therapy in donor egg cycles. Fertil Steril. 1999; 72: 980-984

29. Dal Prato L, Bianchi L, Cattoli M, Tarozzi N, Flamigni C, Borini A. Vaginal gel versus intramuscular progesterone for luteal phase supplementation: a prospective randomized trial. Reprod Biomed Online. 2008; 16: 361- 367

30. Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein MD. Comparison of Crinone 8% intravaginal gel and intramuscular progesterone supplementation for in vitro fertilization/embryo transfer in women under age 40: interim analysis of a prospective randomized trial. Fertil Steril. 2008; 89: 485-487

31. Kahraman S, Karagozogly SH, Karlikaya G. The efficiency of progestone vaginal gel versus intramuscular progesterone for luteal phase supplementation in gonadotropin-releasing hormone antagonist cycles : a prospective clinical trial. Fertil Steril. 2010; 94: 761-763

32. Mochtar M, Van Wely M, Van der Veen F. Timing luteal phase support in GnRH agonist down-regulated IVF/ embryo trasfer cycyles. Hum Reprod. 2006; 21(4): 905-908

33. Williams SC, Oehninger S, Gibbons WE, Van Cleave WC, Muasher SJ. Delaying the initiation of progesterone supplementation results is decreased pregnancy rates after in vitro fertilization: a randomized, prospective study. Fertil Steril. 2001; 76(6): 1140- 1143

34. Andersen NA, Popovic-Todorovic B, Schmidt KT, et al. Progesterone supplementation during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial. Hum Reprod. 2002; 17: 357-361

35. Aboulghar MA, Amin Y, Al-Inany H, et al. Prospective randomized study comparing luteal phase support for ICSI patients up to the first ultrasound compare with an additional three weeks. Hum Reprod. 2008; 3(4): 857-862

DIFFICULTIES IN IUI TECHNIQUE

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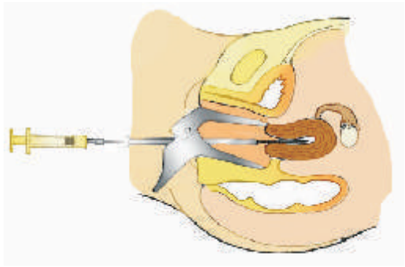
IUI has become a popular method because of its simplicity, low operation cost and ambulatory character. But it should not be taken as panacea of infertility treatment as there are lot of disagreement about the results. There are lot of controversies about the use of IUI in natural or stimulated cycle, no. of inseminations, lab. methods of sperm preparations and IUI techniques.

Basic rationale is to reduce the effects of factors such as vaginal acidity and cervical mucus hostility and to benefit from the deposition a bolus of concentrated motile morphological normal sperms as close as possible to the oocytes.



Most clinicians consider intrauterine insemination to be a simple procedure of inserting the IUI catheter inside the uterine cavity and pushing the prepared semen sample. But insemination is a blind technique, and if not done meticulously it can cause failure of IUI.

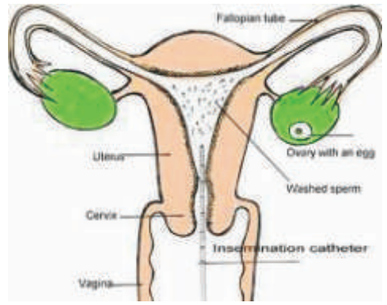
IUI technique is neither lengthy or complicated. Although 80% of inseminations areeasy butsuboptimal technique has the potential tocompromise the success rate of IUI in different ways:

(i) The endometrium may be disrupted

(ii) Inducing uterine contractions

(iii) The products of local tissue-reaction to injury may be hostile to spermatozoa

Steps of insemination in IUI



- Before insemination, the name on the specimen and the name of the patient being treated must be checked by (i) the physician; (ii) the patient; and (iii) by at least one of the witnesses employed by the physician or clinic
- Aseptic technique to avoid genital infection
- Partially filled urinary bladder
- Dorsal position sometimes with hip and knee flexed, and hip slightly abducted
- Gently and atraumatically expose external os with Cusco'sspeculum,avoid gel
- Clean excessive vaginal secretion and cervical os with normal saline,avoid antiseptic solution
- Keep cervix centrally in vagina by speculum manipulation and eexternal os in transverse axis of vagina
- The IUI catheter is gently introduced into the cervix. Once past the internal cervical os, the catheter is advanced to a depth of at least 4 cm but no more than 6 cm to avoid trauma to the endometrium. Next, the specimen (0.4–0.5 ml) is slowly ejected from the syringe (this should take no less than 30 sec)
- Patient remains on the table for 15 minutes and then goes home or returns to work

Signs of difficult insemination

- Greater resistance during catheter negotiation
- Harder catheter needed
- Cervical dilatation needed
- Blood in catheter

Difficulties can be classified as

1. Negotiating the catheter into the uterine cavity
2. Regurgitation of the inseminate
3. Trauma
4. Anaphylaxis which is very rare

Negotiating the catheter into the uterine cavity

Causes :

- Stenosed cervix
- External os flushed with vagina
- Pinpoint external os
- Acutely anteverted, retroverted, anteflexed or retroflexed uterus
- Distorted uterine cavity e.g. fibroid or uterine or cervical polyp

How to overcome these difficulties

- Position the patient properly
- Manipulate the cervix with the Cusco's speculum
- Guide the catheter tip with a long artery forceps through the internal os
- Hold the anterior lip of the cervix with an Allis tissue forceps or vulsellum and put gentle traction tostraighten out utero-cervical angulation. Try not to clamp the Allis, to avoid pain and uterine muscle contraction. If there is ttransient discomfort to the patient, ask her to cough
- If persistent cervical stenosis or sharp cervico uterine angles are encountered, a rigid catheter or catheter with a stylet can be used
- Inability to pass the catheter requires cervical dilatation
- There is one paper which says that using misoprostol 2 hours before vaginally helps not only in insemination but also increases pregnancy rate
- Bleeding from the cervical canal may be seen in difficult negotiations. It may be advisable to negotiate the cannula before loading it with the sperm preparation. In this way the contamination of the inseminate with blood can be prevented. Mild spotting or bleeding after an IUI has been reported to be associated with a lower pregnancy rate as pH of seminal fluid or intrauterine contents changes
- When it is not possible to introduce a catheter into the uterus for IUI, 'high' intracervical insemination may be performed instead of traumatizing more to endometrium and cervical canal

Anatomy of cervix to take into consideration during insemination

IO to left of EO (80%)IO to right of EO (10%)IO in straight line with EO (10%)

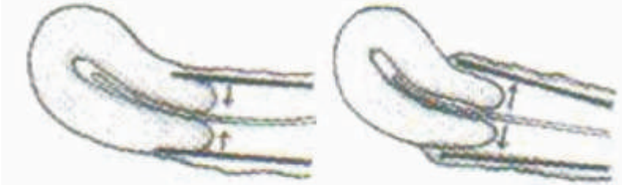
Regurgitation of the inseminate

Causes :

- IUI catheter getting kinked
- Internal cervical os is open

How to overcome

- Ensure IUI catheter is well placed in uterine cavity
- Inseminate a small semen volume slowly
- Use a cervical guard to prevent regurgitation
- Slowly withdraw the IUI catheter to prevent the suction effect
- Check the IUI cannula is not blocked
- Press the blades of the Cusco's speculum on the portio-vaginalis of the cervix



Trauma

Causes

- cervical erosion, cervical polyp, cervical tear

How to avoid

- Avoid handling cervix if cervical erosion is present
- Cervical polyp can be removed at later date to avoid bleeding during the procedure

How to avoid difficult IUI

1. Trial or Mock IUI enables the clinician to assess the degree of difficulty by

- Assessment of depth and shape of uterus
- Selection of optimal catheter type
- Mapping the easiest and least traumatic entryinto uterine cavity
- Identify cervical stenosis

2. Using ultrasound guidance before or during IUI

- Diagnosing acute anteversion or retroversion during folliculometry
- Measuring the utero-cervical angle with ultrasound before IUI and moulding the catheter accordingly

3. Hysteroscopy and cervical dilatation

before next IUI preferably on D5 of cycle with mapping of canal and direction on paper. We use at our center clock position to document it.

e.g. 3 O'clock 5 O'clock

Concluson

Although intrauterine insemination is a simple procedure, difficulties are often faced during the procedure. Pregnancy rates will be improved if proper technique is applied, by apprehending and overcoming the difficult procedures. It's very true like Murphy's law, If anything can go wrong, it will go wrong.

Bibliography

1. 'Insemination technique and insemination complications', Richard P. Dickey, Peter R. Brisden, Roman Pyrzak, pp. 109–116, in Manual of Intrauterine Insemination and Ovulation Induction, Cambridge University Press, 2010

2. 'IUI techniques and difficulties faced during insemination', Madhavi Panpalia, Firuza Pajesh Parikh, pp. 272–288, in Intrauterine Insemination, Jaypee Bothers Medical Publishers, 2012

3. 'Efficacy of passive uterine straightening during intrauterine insemination on pregnancy rates and ease of technique',S. Ayas, A. Gurbuz, R. Ayaz, M.R. Asoglu, Journal of Obstetrics, 2012 (Wiley Online Library)

4. 'Ultrasound-guided artificial insemination : a randomized controlled trial', Olga Ramón, Roberto Matorrasetal., in HumanReproduction, Vol.1, No.1, pp. 1–5, 2009

5. 'Sperm suspension is a highly ultrasonically visible material:a novel model to study uterine activity',R. T. Mansour, Hesham G. Al-Inanyetal.,HumanReproduction, Vol. 22, No.7, pp. 1942–1945, 2007

6. Brown et al 2001, Barraso et al 2001

7. Kerin JF, Quinn P. Supracervical placement of spermatozoa : utility of intrauterine and tubal insemination. In : Soules MR (Ed).Controversies in reproductive endocrinology and infertility New York : Elsevier;1989

DETERMINANTS OF SUCCESS IN IUI

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The success rate of IUI varies in different study groups and on an average the success rate is 8-22% per cycle in various studies. Success rates in IUI depend on various factors:

Patient Profile

1. Age : Female age is inversely proportional to the IUI success, significantly declining after the age of 37 yrs[1]

2. Cause and type of infertility : Success is more in ladies with secondary infertility than those having primary infertility. Maximum success seen in couples with mild male factor and unexplained infertility.[2]

Clinical Parameters

3. Ovulation induction protocol : Though of unproven use in male factor infertility, better chance of conception is seen in cases of unexplained infertility and mild to moderate endometriosis. Among the medications used for ovulation induction in non male factor infertility best chance of conception is with gonadotropins compared to oral agents.

Ultrasound and Doppler

4. Number of preovulatory follicles : when 2-3 in number success is better than single follicle.

5. Endometrial response: endometrial thickness < 6mm and more than14mm have poor prognosis for pregnancy

Timing of IUI

6. When ovulation is triggered by exogenous hCG, IUI is best performed 34-40 hours later. NO difference noted in success when the IUI was done after ovulation.

Site of Insemination

7. Pregnancy rate with IUI more than twice that of cervical insemination.

Technique

8. Should be as atraumatic as possible

IUI Catheter

9. Catheter choice does not seem to have a detrimental effect on success rates of IUI.[4]

Male Factors

10. Age

11. Post wash semen parameters : One of the most important predictors of success. Chances of conception with IUI is better when total motile sperm count (TMSC) is more than 10 million. Patients with TMSC < 1 million have poor results with IUI and should be counselled for ICSI.

12. Sperm processing methods : swim-up and density gradient centrifugation offer a greater chance for success than conventional sperm washing. NO difference was seen between swim up and density gradient method in recent Cochrane analysis [3]

Duration of Infertility

13. Better prognosis is seen in patients with shorter duration of infertility.

Number of IUI Cycles

14. Most pregnancies occur in first two IUI cycles. Although lower pregnancy rates were noted no statistically significant association was noted. The total number of IUI cycles should not exceed six

Number of Inseminations per Cycle

15. Many studies have proved that single IUI is better and no extra benefit is seen with performing a double IUI

Laboratory Factors

16. Standardized equipments
17. Good air quality
18. Non-toxic disposables and environment

References

1. Merviel P, Heraud MH ,et al Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature. Fertility Sterility 2010;93:79-87

2. Khalil MR, Rasmussen PE, Erb K et al. Homologous IUI. An evaluation of prognostic factors based on review of 2473 cycles. Hum REprod 1999;14:698-703.

3. Boomsma HV, Heineman MJ, Cohlen BJ et al. Semen preparation techniques for IUI. Cochrane Database Syst Rev 2007;17(4):CD004507

4. Ahmed MA,Ragana TM, Hesham G, et al. IUI catheters for assisted reproduction: a systematic review and meta-analysis. Human REprod 2006;21:1961-7.

COMPLICATIONS OF IUI

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Though IUI is a safe procedure,with few complications. The complications may be divided as:

Due to ovarian stimulation

IUI is usually combined with controlled ovarian stimulation (COH) as natural cycle IUI is rarely done. COH can be associated with certain complications.

Immediate

- **Ovarian hyperstimulation syndrome (OHSS)** : is an iatrogenic and most dreaded complication of ovarian stimulation with incidence ranging from 3-27%. Usually seen in gonadotropin cycles but rarely can occur after clomiphene citrate use. So follicular monitoring is a must in gonadotropin stimulated cycles. Strict criteria for cycle cancellation should be employed and hCG trigger should be withheld in case of more than 4 dominant follicles > 16mm.size. In certain cases, after counselling couple can be offered conversion to IVF cycle with use of GnRH antagonist.

- **Multiple pregnancies** : IUI adds significantly to burden of multiple births resulting from use of assisted conception techniques. Women at high risk of multiple gestation are less than 30 yrs age, with 6 or more preovulatory follicles and peak serum E2 > 1000 pg/ml.

Delayed

- **Ovarian cancer risk** : Earlier studies have suggested a 3 - fold increased risk but this has not been replicated in recent reports[2]. Some studies have reported an increased risk of borderline ovarian tumours with use of clomiphene citrate.[3]

Complications due to procedure : rare

- Pelvic Infection ; not common (1.8 per 1000 cases)[3]. Sources of infection are resident flora, airborne bacteria in collection room and contamination due to faulty technique like cannula tip touching vagina or non sterile preparation techniques.
- **Trauma and Bleeding** : due to injury to internal os or endometrium by cannula or cervical lip by allis forceps
- Pain (Cramping) ; seen in 5% patients and associated with lower pregnancy rates. In case of difficult IUI or faulty preparation.
- Non infective Salpingitis ; rare
- Allergic Reactions ; Due to semen or allergy to any of the ingredients of wash media
- Anti sperm Antibody ; Deposition of large number of sperms directly into uterine cavity may induce ASA in cervical mucus or serum.
- Vasomotor symptoms

Other Complications

- Ectopic Pregnancies : 5 times higher than in general population.
- Abortion : 20-30 %, attributable to higher age and increased incidence of multiple pregnancy

Failure of IUI treatment

References

1. Schenker IG, Weinsyein D. Ovarian over stimulation syndrome :m a current survey. Fertility Steril 1978;30:179-83
2. Ayhan A, Salman MC, Celik H, et al. Association between fertility drugs and gynaecological cancers, breast cancer andchildhood cancers. ActaObstetGynecolScand 2004;83:1104-11.
3. Brinton LA, MOghissi KS, Sciccia B, et al. Ovulation induction and cancer risk. FertilSteril 2005;83:261-74.
4. Sacks PC, Simon JA. Infectious complications of intrauterine insemination, a case report and review of literature. Int J Fertil 1991;36:331-8.

SEMEN BANKING

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Semen banking is one of the most important parts of an ART clinic. It means storage of spermatozoa for future use. The desire to have your own genetic offspring has been a goal which is fulfilled with the help of semen banking especially for cancer patient about to undergo surgery or chemo radiotherapy.

Sperm is usually stored by cryopreservation. Cryopreservation is a technique in which the gametes are stored at subzero temperatureswhich can later be thawed for further use[1]. Spermatozoa is one of the earliest gametes in which glycerol was used as cryoprotectant.

The history of semen banking dated back to 1776 when Spallanzani made an observation of recovery of sperm after freezing.In 1949 Polge made the discovery of glycerol as cryoprotectant and it was Sherman in 1963 who reported the birth of child after using sperm stored in liquid nitrogen[2].

Indication of Semen Banking

1. In case of donor insemination after fulfilling the ICMR criteria and the male is fully screenedand the quarantine period is over, the sample can be used for donor insemination in couples with azoospermia or in patients with severe male factor infertility who have failed to achieve pregnancy with ART.
2. Preserving male fertility in males with cancer prior to their chemotherapy treatment[3].
3. In case sperms have been collected by TESE/PESA, after the procedure of ICSI has been done, the remaining spermatozoa can be stored for future use.
4. In case of patients undergoing ART procedure with anhistory of ejaculatory failure, or history of inability to give sample on the day of the procedure like IVF /IUI
5. In case of nonmalignant chronic disease like diabetes and autoimmune diseases in which certain immunomodulators are used, sperms can be frozen.
6. In case of patients undergoing vasectomy .

Criteria for Donor Sperm to be Used in Artificial Insemination with Donor Sperm (AID)

The person donating spermsshould be screened for infectious diseases and the semen sample should have the following:

1. Volume > 2 ml
2. Motility > 50%
3. Count > 50 million/ml
4. Normal morphology > 4%.

Semen Sample Collection

1. **MASTURBATION :** Can be used in case of postpubertal boys and adult males after an abstinence of 3-4 days. In case of patients with cancer, shorter period of abstinence and at times no abstinence is advised.(asrm 2013)[3].
2. **VIBRATOR :** It is helpful in males who are unable to produce sample by masturbation.
3. **ELECTROEJACULATION :** In cases of patients having erectile dysfunction and ejaculatory failure who are unable to produce sample with the help of vibrator.
4. **SURGICAL TECHNIQUES - TESE/PESA :** This is useful in case of severe OAT or azoospermic males in which after using the sperm for ICSI the excess is stored for future usage.Also in case of cancer patients, it is observed that either the count is very low or the quality is very bad or there are no sperms in the ejaculate. In these patients, specimen is taken from the testis and sperms are stored in liquid nitrogen. Also for prepubertal boys, sperms can be preserved by TESE.

Tecniques of Sperm Freezing

Sperms can be stored by two methods slow : freezing and rapid freezing

Comparison between these two Methods

	SLOW FREEZING	RAPID FREEZING
TIME REQUIRED	> 3 HOURS	10 MINUTES
INSTRUMENTS	Expensive	Inexpensive
CPA Concentration	Low	High
ICE CRYSTAL	Yes	No
DIRECT CONTACT WITH LIQUID NITROGEN	No	Depends on the carrier used
MECHANICAL DAMAGE	More	Less
CHEMICAL DAMAGE	Less	More

Cryoprotectants Used

Cryoprotectants have low molecular weight and are highly permeable chemicals. They are added in the medium to prevent the injuries caused by thermal shock. They can be of two types: permeable and non-permeable. Glycerol is most commonly used cryoprotectant for sperm freezing. It acts on the cell membrane and stabilizes the lipid bilayer, decreases the freezing point of the substrate, reduces the amount of salts and prevents ice crystal formation[7].

Slow Freezing

It can be done manually and automatically

Manual : The sample & cryoprotectants are at room temperature. They are mixed in the ratio of 2:1 dilution (CPA:SPERM). Leave the mixture at room temperature for 10 minutes. Label the straw/cryovial with identification of patients. Load the specimen in the respective straw /vial. The cooling is started from room temperature to 5^0C at the rate 5 to 1^0C/minute.Sample is then frozen from 5^0C to -80^0C at a rate of 1-10^0C/min and then plunged into liquid nitrogen at -196^0C[4].

In case of automated freezing, freezer uses software which helps in cooling from 20^0C to-80^0C. After completion of freezing, the vials are put into liquid nitrogen at -196^0C[5].

It has been observed that slow cooling leads to extensive mechanical damage to the sperms with less recovery of sperms after thawing and so rapid freezing came into vogue.

Rapid Freezing

In this method of freezing we take the semen sample and check for the count. If the count is normal, then raw sample is taken and if the count is low, sample is mixed with media and then centrifuged at 1500rpm for 10 minutes.; the supernatant is discarded and fresh media is added to reconstitute the sample . Dropwise cryoprotectant is added to the test tube containing semen ,with constant shaking in between so that all the sperms are coated well at room temperature. The semen is placed in vials or straws , which are sealed and labeled. Then the sample is kept at 4^0C for 20 minutes and then4 cm above the liquid nitrogen vapors for another 10-20 minutes and finally plunging in liquid nitrogen at -196^0C[6].

Freezing of Testicular Tissue : After obtaining the sample from TESE/PESA, the sample is kept in a petri dish and washed with medium. Then with the help of forceps/tuberculin syringe theseminiferoustubules are teased and sperms are obtained. The count is checked and after using the sample for ICSI, the rest of the sample is centrifuged at 1500 rpm for 5 minutes after adding media. The supernatant is discarded andfresh media is added to reconstitute the sample. The rest of the procedure is like rapid freezing.

Thawing

Most common thaw method is to first bring the straw/vial at room temperature for 10 minutes and then keep at 37^0C for another 10 minutes. The semen is then washed, centrifuged and is then ready to use.

Cryoperservation of Spermatazoa in Zona Pellucida

Another way of preserving spermatozoa is sperm cryopreservation in ZONA pellucida. It is especially useful in cases of samples collected from TESE/PESA. The recovery of motile spermatozoa is good with this method[8].

How to Perform this Method : Donor oocyte is emptied with the help of micropipette and then is placed in glycerol solution. After preparing sperms from TESE, the sperms are injected in the zona pellucida. This way sperms are cryopreserved.The motility is better preserved by this method.

Different Types of Semen Sample Carrier in Liquid Nitrogen

Straws (high Security Straw)

- Best Contact Ratio between Semen and Wall.
- No Cross Infection in Liquid Nitrogen
- Hermetic Free
- Clear Flexible Tubes
- Available in Different Colours

Cryovial

- Polypropylene Made with Screw Cap
- Easy to Fill
- Store Large Amount in One Go(1.5ml)

	Straw	Cryovial
Capacity	Less	More
Cross Infection	Less	More
Contamination	Less	More
Cooling Area	More	Less
Cryoinujury	Less	More
Explosion After Thawing	No	Yes
Safety	More	Less

Samples can be stored in two forms

1. Liquid nitrogen
2. Liquid nitrogen vapors

	Liquid Nitrogen	Nitrogen Vapours
Contanimation	More	Less
Safety	More The Cryovials are Immersed in Liquid Nitrogen	Less The Cryovials are Placed Over Liquid Nitrogen at a Predetermined Height for Specific time period.

Effect of Cryopreservation on Spermatazoa

After thawing in cryopreservation, around 50% of motility remains[9]. In spite of advances in sperm freezing techniques, there is still damage to the spermatozoa, especially the loss of motility[10].This has been related to the osmotic stress sustained during cryopreservation.

In case of testicular samples, there are contradictory results. De croo observed a low implantation rate with the use of cryopreserved testicular sperm[11].

Prevention of Cross Infection in Semen Banks

1. Screen the patients meticulously for HIV, HbsAg, HCV, VDRL and isolate samples in cryocans till the quarantine period.
2. Use of straws CBS(CryoBioSystems)which are hermetically sealed.
3. Use of liquid nitrogen vapours.
4. If the patient is known to carry an infective condition, then store the samples in different containers.
5. Samples must be handled and stored with proper care so asto prevent spillage of the specimen.
6. Double checking of reports by doctors as well as embryologists to prevent error.

ICMR Guidelines for Sperm Donor

1. The individual must be free of HIV and hepatitis B and C infections, hypertension, diabetes, sexually transmitted diseases, and identifiablecommon genetic disorders such as thalassemia.
2. The age of the donor must not be below 21 or above 45 years.
3. An analysis must be carried out on the semen of the individual, preferably using a semen analyzer, and the semen must be found to be normal according to WHO method manual for semen analysis, if intended to beused for ART.
4. The blood group and the Rh status of the individual must be determinedand placed on record.
5. Other relevant information in respect of the donor, such as height, weight, age, educational qualifications, profession, colour of the skin and theeyes, record of major diseases including any psychiatric disorder, andthe family background in respect of history of any familial disorder, must be recorded in an appropriate proforma.

Conclusion

With the advent of cryopreservation, the desire to have our own genetic child becomes possible for many males including those having cancers. Today, sperm cryopreservation is one of the most widely used techniques for storage of sperm. With the help of newer straws and the use of liquid nitrogen vapours, the chance of contamination has decreased. Until the advent of stem cell therapy, cryopreservation of sperm is the only documented options for male cancer survivors for fulfilling their desire of harbouring their own offspring.

References

1. Parker AS. Preservation of human spermatozoa at low temperatures. Brit MJ.1945;2:212-13.
2. Sherman JK, Burge RG. Observations on preservations of human spermatozoa at low temperatures. Proc Soc Exp Bio Med.1953;82:686-88.
3. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy : a committee opinion. Fertil Steril. 2013;100:1214-23.
4. Thachil JV, Jewett MA. Preservation techniques for human semen. FertilSteril.1981;35:546-8.
5. Holt WV.Basic aspects of frozen storage of semen. Anim reprod Sci.2000;62:3-22.
6. Sherman JK. Cryopreservation of human semen. In : Keel BA, Webster BW(Eds). Handbook of the laboratory diagnosis and treatment of infertility. USA:CRS Press;1990.
7. Hammit DG, Walker DL, Willamson RA. Concentration of glycerol required for optimal survival and in vitrofertilization capacity of frozen sperm is dependant on cryopreservation medium. Fertil Steril.1988;49:680-87.
8. Hseih YY, Tsai HD, Chang CC,Lo HY. Cryopreservation of human spermatozoa within human or mouse empty zona pellucida. Fertil Steril. 2000.73(4);694-98.
9. Bunge RG, Keetel WC, Sherman JL. Fertilization capacity of frozen human spermatozoa. Nature.1953;172:767-68.
10. Schuffner A, Morshedi M, Oehinger S. Cryopreservation of fractionated, highly motile human spermatozoa : effect on membrane phoshatidylserine externalization and lipid peroxidation. Hum Repod.2001;16:2148-53.
11. Croo ID, Van Der Elst J, Everaert K et al. Fertilization, pregnancy and embryo implantation rates after ICSI with fresh frozenthawed testicular spermatozoa. Hum Repod.1998;13(7):1893-7.

ETHICAL ASPECTS OF DONOR INSEMINATION

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Infertility in the past was always looked down upon as a stigma. Today with advancement of modern medicine, assisted reproduction has become a blessing to the millions of infertile couples.

ART has developed leaps and bounds from the birth of the first IVF baby Louise Brown in 1978. World's second and India's first IVF baby, Kanupriya was born in 1978, just three months later. India is becoming a technological, scientific hub as well as a hub for infertility treatment options available around the world. Low cost of treatment as compared to the West and easy availability of surrogates or gamete donors has caused a surge of 'reproductive tourism' in India. In recent years with infertility being on a rise, there has been an unregulated spurt in IVF clinics and specialists, claiming to have the best technology and results.

With budding of every new technology there has always been associated ethical and legal issues. ART has turned into a minefield of such constantly erupting issues. The need for uniform ethical guidelines is universally recognized and this issue has now gained a critical urgency. The guidelines need to be updated constantly with the speed of changes in the field.

A welcoming step in this direction has been the formulation of the Assisted Reproductive Technologies Bill, 2010 drafted by the Ministry of Health and Family Welfare and the ICMR. It provides for the accreditation, supervision and a regulation of ART clinics in India.

Code of Practice

1. This Code of Practice deals with all aspects of the treatment provided and the research done at registered clinics.
2. Any information about clients and donors must be kept confidential, except with the consent of the person to whom the information relates, or in a medical emergency, or a court order.
3. All relevant information must be given to the patient before a treatment is given.
4. No treatment should be given without the written consent of the couple
5. A standard consent form recommended by the accreditation authority should be used by all ART clinics.
6. Specific consent must be obtained from couples who have their gametes or embryos frozen, in regard to what should be done with them if he/she dies, or becomes incapable of varying or revoking his or her consent.
7. People seeking registered treatment must be given a suitable opportunity to receive proper counseling about the various implications of the treatment.

Third party reproduction - gamete - sperm donation

Sperm donation may be the only solution to procreate in couples with absent sperms or enabling them to have a offspring without genetic link. It may also be applied to avoid the transmission of genetic conditions to the offspring.

Sperm donors need to be between 21 to 45 years and should not donate to more than 6 to 10 families to prevent consanguinity. The semen sample has to be preserved for six months before it is used. One sample of semen supplied by an ART bank shall be used by the assisted reproductive technology clinic only once on only one recipient.

For a oocyte donor the age should be between 21 to 35 years and she can donate oocytes for a maximum of six times in her life time with at least 3 months gap between each donation (ASRM guidelines).

We have two types of donors - altruistic and paid. Probably it is apt to reasonably compensate the donor for the effort taken. Adequate counseling for the donor and recipient is essential

Ethical aspects involved with gamete donation

Anonymity - Several different rights are at stake :

(i) The right of autonomy and privacy of the parents

(ii) The right of privacy of the donor

(iii) The right of the child to know his/her origins

Here the identity of the donor may be released to the offspring when they have reached maturity.

Known donation - A known donor is known to the recipient at the moment of conception or treatment. Donation by friends has generated additional problems like possible future conflicts due to changing views on the rights and obligations toward the child. Trans-generation donation should be avoided because of the difficulty of defining the status of the child within the family.

Screening is necessary in order to protect the recipient and the future child. Medical and psychological evaluation of the general abilities and intellectual capacity of the donor candidates is necessary.

The process of information giving, with counseling concerning the implications of donating or receiving gametes, is essential to enable the donor or recipient to give his informed consent.

Rights and duties of donors

All information about the donors shall be kept confidential and the identity of the recipient shall not be made known to

the donor. A semen donor does not have any parental rights over the child which may be conceived from his gamete. Information about gamete donation shall not be disclosed to anyone other than the central database of the Department of Health Research, except with the consent of the person or persons to whom the information relates, or by an order of a court of competent jurisdiction. The donor has the right to decide what information may be passed on and to whom, except in the case of an order of a court of competent jurisdiction. A child may, upon reaching the age of 18, can ask for any information, excluding personal identification, relating to the donor. No assisted reproductive technology procedure shall be conducted on or in relation to any gamete of a donor unless such donor has obtained the consent in writing of his or her spouse.

The parents of a minor child have the right to access information about the donor, other than the name, identity or address of the donor, or the surrogate mother, when and to the extent necessary for the welfare of the child.

here is also growing concern that those born from donated sperm (AID) over the last generation know nothing about their inherited DNA. Should the children be told of their origin? This is advocated once the children are 18 years, but 90% of parents who have benefited from gamete donation apparently do not tell. This indicates a need for further thought about parental feeling and privacy when it comes to gamete donation?

Intra-familial sperm donation

Many times couples in need of third party assisted reproduction sometimes prefer the help of a family member over an unrelated donors. Intra- familial medically assisted reproduction (IMAR) could be either intra- or inter-generational and could contribute either sperm or oocytes or be a surrogate. At every step the clinician must see that the relationship must not be consanguineous

In terms of genetic classification their relation may be first degree (brother, sister, parent, child), second degree (aunt, uncle, niece, nephew) or third degree(cousins). Genetic material that is donated:

- Sperm donation the possible donors include brothers, cousins and the prospective father's father

One possible reason for intra-familial ART is that it allows them to preserve a genetic link between the infertile partner and any children thus conceived. The second possible reason is the psychological advantage of knowing where the gametes come from. At times easy availability of relatives for collaboration can reduce the waiting time and also reduce costs as no payment for the gametes or the uterus should be considered.

But one must agree that the helping act (the donation) may considerably affect this partner's life. It is also associated with consanguinity or incest may generate negative societal reactions.

Risks for the donors include psychosocial risks, may be put under more or less subtle familial pressure to collaborate, even to the point of coercion. Clearly, this may cause grave conflicts, guilt- feelings, stress and emotional disturbances with long-lasting adverse effects. The risk is greater with (first-degree) intergenerational collaboration than with intra-generational collaboration. The child also faces the risk of psychosocial stress by growing up in the unconventional familial environment thus created. Relationships may be confusing for the child. In case of brother-to-brother sperm donation, for example, a social uncle will be the genetic father while the rearingfather is actually a genetic uncle. The risk of identity problems of the child may increase in case of role confusion on the part of a collaborator wanting to take up part of the parental responsibilities. There is also an increased genetic risk in case of consanguinity and aged people as may increase this further, in cases of intergenerational gamete donation with an elderly father who donates sperm to his son.

Both combined and separate counseling of recipients and collaborator is crucially important, as this may facilitate decision-making and contribute to self-selection, thereby reducing psychosocial risks.

Medically assisted reproduction using third parties is widely accepted in many countries and this includes India also. In India the ICMR guidelines suggest that third party reproduction should involve individuals unknown by the recipients.

Welfare of children born after sperm donation

Addresses the risks associated with medically assisted conception and its implications on the mental and physical health of the child.

In all these cases the child will have identical legal rights as a legitimate child born through sexual intercourse. The birth certificate of a child born through ART shall contain the name or names of the parent or parents. The child born to a foreigner by sperm donation will not get Indian citizenship though he or she is born in India. A child may, upon reaching the age of 18, ask for any information, excluding personal identification, relating to the donor or surrogate mother. The legal guardian of a minor child has the right to get any information (excluding name, address and other personal identification details) regarding his/ her genetic parent/s when required in view of welfare of the child. Personal identification of the genetic parent or parents may be released only in cases of life threatening medical conditions, which require physical testing or samples of the genetic parent or parents. Such personal identification will not be released without the prior informed consent of the genetic parent or parents.

Depending on the specific kind of risk, children should be followed and evaluated by apaediatrician, geneticist and/or psychologist

General duties of assisted reproductive technology clinics

a. Should ensure that patients are medically tested and are eligible to avail the assisted reproductive technology.

b. Ensure that donors of the gametes are medically tested for sexually transmitted diseases and all communicable diseases which may endanger the health of the parent/s, surrogate mother or child born.

c. Should offer professional counseling to patients or individuals about the rationale and implications for the suggested treatment, alternate options, success rate, cost of the procedure, advantages, disadvantages, limitations, side effects, health risks, etc. The counseling should help the patient/s in taking a decision that is best for them and should not compel them in selecting an option.

d. Patients should be explained about the rights of a child born through ART

e. A written consent must be obtained from all the parties seeking ART to all possible stages of such treatment or procedures including the freezing of embryos generated from sperm donation

f. In case of embryo cryopreservation specific instructions and consent should be taken in writing from all the parties seeking ART in respect of what should be done with the gametes or embryos in case of death or incapacity of any of the parties.

g. A specific consent should be taken in writing from all the parties to whom the assisted reproductive technology relates before using any human reproductive material to create an embryo or use an in vitro embryo for any purpose. The consent of any of the parties obtained under this section may be withdrawn at any time before the embryos or the gametes are transferred to the concerned woman's uterus.

h. ART clinic should ensure that information about clients, donors is kept confidential and that information about ART treatment shall not be disclosed to anyone other than a central database to be maintained by the Department of Health Research, except with the consent of the person or persons to whom the information relates, or in a medical

emergency at the request of the person or persons or the closest available relative of such person or persons to whom the information relates, or by an order of a court of competent jurisdiction.

i. When the central facilities are made available, information on the progress of the patient such as biochemical and clinical pregnancy can be made available online within 7 days of getting the information, withholding the patient identity.

j. ART (sperm) bank should maintain all the records for at least ten years, after which the records shall be transferred to a central database of the Department of Health Research, Government of India. Where an ART bank closes before the expiry of the ten year period, the records shall be immediately transferred to the central database of the Department of Health Research, Government of India.

k. The ART (sperm) bank shall keep a record of all the gametes received, stored and supplied, and details of the use of the gametes of each donor. If not otherwise ordered by a court of competent jurisdiction, all ART banks shall ensure that all information about clients and donors is kept confidential and that information about gamete donation shall not be disclosed to anyone other than the central database of the Department of Health Research.

l. Should design a system to look into the patient complaints and the necessary action taken should be recorded.

m. Should issue discharge certificate to the infertile couple / individual stating details of the ART procedure(s) performed on the couple / individual.

n. It shall be the responsibility of an assisted reproductive technology clinic to obtain, from ART (sperm) bank(s), all relevant information, other than the name, personal identity and address, of possible gamete donors, and assist the couple or individual desirous of the donation, to choose the donor.

o. ART clinic should obtain donor gametes from ART banks that have ensured that the donor has been medically tested for sexually transmitted and communicable diseases which may endanger the health of the parents, or any one of them, or child.

p. Either of the parties seeking assisted reproductive technology treatment or procedures shall be entitled to specific information in respect of donor of gametes including, but not restricted to, height, weight, ethnicity, skin colour, educational qualifications, medical history of the donor, provided that the identity, name and address of the donor is not made known.

Duties of assisted reproductive technology clinics using gametes - sperms

The following practices are strictly prohibited

1. Performing any treatment or procedure of ART without the consent in writing of all the parties seeking ART
2. Treating woman with gametes derived from the gametes of more than one man or woman
3. Mixing of semen from two individuals before use
4. Using medically unanalyzed semen sample
5. Offering to provide a child of pre-determined sex through ART
6. Prescribing / administering anything which would ensure or increase the probability of getting embryo of one particular sex
7. Identification of the sex of an in vitro derived embryo (except to diagnose, prevent or treat a sex-linked disorder or disease)
8. Separating or enriching X or Y bearing spermatozoa
9. Using sperm donated by a relative or known friend of either of the parties seeking assisted reproductive technology treatment or procedures.
10. Performing ART on a woman below 21 years of age

Registration and accreditation of clinics

The Assisted reproductive technology (ART) clinic should be registered with the Registration authority. The application should contain the particulars of all applicant and details of the techniques and procedures of assisted reproductive technology practiced at such clinic. Assisted reproductive technology clinics registered under this Act shall be deemed to have satisfied the provisions of the PC & PNDT Act, 1994, and shall not be required to seek a separate registration under the said Act. The clinic must ensure that all the procedures offered by the clinic are according to the norms of the scientific practice and should have ethical clearance.

Maintain records

To maintain records in an appropriate proforma (to be prescribed by the authority)

The information about the donor (including a copy of the donor's DNA fingerprint if available, but excluding information on the name and address – that is, the individual's personal identity) should be released by the ART clinic after appropriate identification, only to the offspring and only if asked by him/her after he/she reaches the age of 18 years, or as and when specified and required for legal purposes, and never to the parents (excepting when directed by a court of law).

When commercial DNA fingerprinting becomes available, to keep on its record, if the ART clinic desires and couple agrees, DNA fingerprints of the donor, the child and the couple should be done.

To maintain appropriate, detailed record of all donor oocytes, sperm or embryos used, the manner of their use. These records must be maintained for at least ten years after which the records must be transferred to a central depository to be maintained by the ICMR. If the ART clinic/centre is wound up during this period, the records must be transferred to the central repository in the ICMR.

Conclusion

Gametes should be considered as potentially hazardous biological materials and should be handled with maximum precautions. Handling should be done in sterile conditions using a vertical laminar air - flow with personal safety precautions.

A carefully specified procedure for obtaining informed consent is vital for the ethical implementation for all procedures involving human gametes. In order to preserve the interests of the infertile population, all treatment and research activities must be performed with strict attention to ethical standards. Informed consent, along with counseling and maintaining confidentiality form a mainstay for all procedures performed in the embryology lab and ART clinic.

IUI IN AN URBAN INDIAN SETTING - AN EXPERIENCE

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Urbanization and its effects on lifestyle have a significant impact on the way fertility management is practiced. Intrauterine insemination is an important fertility therapy, in the armamentarium of a fertility specialist. In our country acceptance of IUI by the couple also requires counseling as there are false notions & the procedure being not natural.

Pre IUI counseling is also necessary to give the patients realistic expectations regarding the success rates. This helps to prevent depression and disappointment following a cycle failure.

Counseling for donor IUI is especially essential. feelings of detachment from the child can occur, especially in the husbands, and these need to be addressed and solved before the actual procedure.

However over the years we have seen that the acceptance has become more common.

In our Set up at The Cradle IVF center IUI is undertaken for following indications:

Male Factor

- Mild to Moderate oligoasthenospermia (50%)
- Ovarian Factor-Anovulation (25-30%)
- Unexplained and Cervical Factor (15%)
- Sexual Dysfunction (10%)
- **Azoospermia** - for IUI with donor sperm (around 2-3%)

It is interesting to note that we have found significant increase in male factor infertility is especially in the IT sector. One can conjecture as to the cause whether it could be long working hours, continuous exposure to Wi-Fi Zone, Mobile radiations, Radiofrequency, sedentary life style.

Erectile dysfunction is also on the rise and the probable reasons could be obesity, hypertension and stress in everyday life. Older age and late night working hours could also play a part.

Similarly female Dysfunction requiring General Anesthesia for IUI is on the rise and the causes in IT industry could be similar to the causes above in the males.

Ovulation induction and IUI

We use Clomiphene Induction alone predominantly in Patients with Male Factor Infertility or Subtle tubal factor while Superovulation IUI is considered in patients with anovulation, unexplained Infertility. Nowadays use of Enclomiphene is on the rise and has produced good and consistent result without the need for addition of estrogens to develop the endometrium as it has less anti estrogenic activity. In Superovulation IUI we prefer to add HMG during the post clomiphene phase reducing the dose of HMG required, preventing the risk of OHSS and Mutiple Gestation. Adjuvant therapy in the form of Myoinositol or Metformin is selected depending on the patient's clinical scenario.

Double IUI in particular cycle has not significantly shown a drastic increase in Pregnancy rates compared to combination of IUI and Times intercourse.

Double IUI is used specifically in situation where Ovulation trigger has failed to bring about ovulation in a specified period.

We Plan IUI on the day of Ovulation either just pre-ovulatory or post ovulatory whichever is closer to ovulation and have found similar outcomes. Technically we prefer to use preovulatory in Male factor and post ovulatory in Patients with normal Semen Parameters, Use of Ultrasound in IUI is needed in Patients with Acutely verted uteri and in previously known difficult negotiation of the cervix. It improves the patient satisfaction rate and reduces the patient discomfort especially the post IUI cramping which occurs in such situations. Special Difficult catheters like the ones used in Embryo transfer also Simplify such negotiations and we use them in almost 10% of our patients.

Medicolegal aspects: consents of the couple are essential before the procedure is conducted. The ICMR guidelines have specific formats for both husband and donor IUI which we follow on a regular basis. These consents also specify the legal status of the child born through this process.

Success rates

At our Cradle IVF center, we do around 130-140 IUI per month, with a Success rate of around 11-12%.

In male Factor Infertility it is around 8%and maximum in Cervical and Mechanical Dysfunction at 16-18%.

We can say the IUI success rates vary between 10-15%.

To Summarize IUI treatment must be individualized depending on clinical scenarios and the Couple's understanding especially the number of IUI cycles a Couple needs to undertake.

Non-Medical Factors like Financial Situation, Husband's Travel, Social Stress, Marital Disharmony modify the way we conduct treatment and taking them into consideration while treating the couple is of utmost Importance.

SETTING UP OF AN IUI LABORATORY

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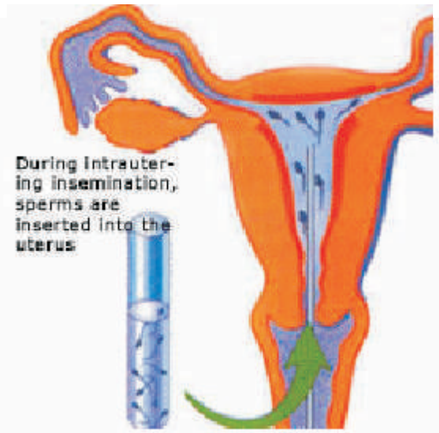
Introduction

An IUI lab set up is cost effective and can gives optimum results. IUI laboratory is an ART laboratory with small dimensions.



Registration and Accreditation

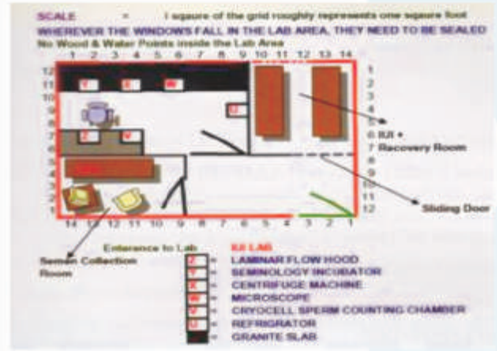
According to ICMR(Indian Council of Medical Research),registration is mandatory under appropriate licencing authority.

Laboratory Design

Sterility is an uncompromising issue so strict asepsis should be maintained.

1) Adequate storage space should be there for storage of

a) Liquid nitrogen tank for freeze semen sample

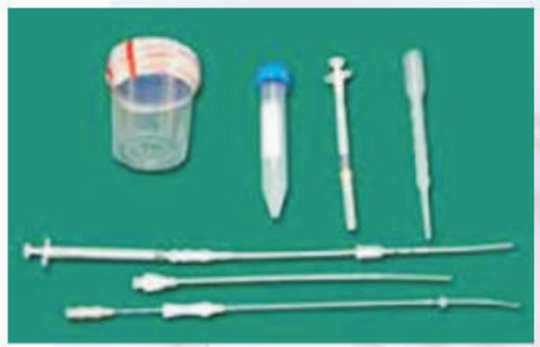


b) Disposables, like Semen container (Gamma sterile)

- 6 ml Test tube (Gamma Sterile)
- 14 conical tube, 1 ml serological pipette (Gama sterile)
- IUI Cannula
- BD syringes and Liquid Nitrogen

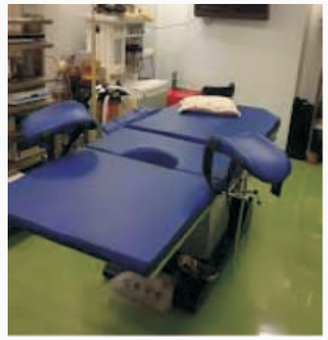
c) Equipment for Insemination

- Speculum
- Tenaculum
- Sponge holder
- Ant. Wall retractor - sound
- Gauge
- Powder free gloves



2) Sample Collection room - It should be clean and should have proper ventilation and toilet. Also have suitable aids to help in collection.

3) Procedure room - it should have all the facilities required for gynaecological examination and procedure such as bench space, water for washing hands and dust and smoke free environment.



Equipments

Centrifuge - It should have a timer and rotor whose speed can be controlled.

- It should be auto lock on the lid to avoid accident during processing.
- It should have a Alarm, to indicate the end of processing.

Incubator - Incubator with digital display of temperature and Co_2 gas control is essential. Incubators should have stainless steel interiors and provide uniform heating.

- It should have inner size 12" X 12"
- It supplied with perforated shelves & workable on 220 volts.

Laminar Flow Hood - It ensures a clean air inside the lab.

- It can be either Vertical or Horizontal. Laminars used should have stainless steel top which is durable and easy to clean and maintain.
- Size 4'X 2'X 2 Workspace 4'X 2 '
- Air velocity across workspace 90 + 20 feet/minute
- Illuminated by tube light (Fluorescent)
- Should have UV light for sterilization
- It should have pressure indicator.

Microscope - Trinocular microscope preferably phase contrast is required to test the semen.

- It should have objective 5 X, 10X, 20 X, 40X & 100X, with anti fungal treatment
- It should have camera port.
- Should have 360 degree Rota table Trinocular head.

Sperm Counting Chamber - Non disposableMakler chamber is preferred.

Media

Various media are available in market which varies from salt solutions

- Single Layer density gradient, Double layer Density gradient
- HTF (Human Tubal Fluid)/ Flushing Media
- Cryo Preservation media

Record Keeping

Record of all procedures, semen analysis details, type of method used for semen preparation, consent of the couple should be maintained thoroughly.