Editor's Message

Practical infertility:
Challenges in Day to Day Life!

Although management of Infertility has become a specialized subject, all of us have to face the routine cases of Infertility in our day to day practice.

One in seven couples face this problem in their lifetime this is really a large section of society.

In view of this, the present FOGSI Focus is aimed at solving Practical Problems in Infertile Couples.

Experts from the fields are choosen from far & near, along with my co-editors: Dr. Manish Banker & Dr. Jaideep Malhotra-both infertile specialist themselves.

Specific topics were given to each contributor with instructions to give targeted tips for our members practicing at different parts of country.

I am sure after going through this booklet fellow members will be able to tackle their Infertility patients with confidence.

Our previous two "FOGSI FOCUS" one on PPH and other on PIH were well received. We are still getting positive feedbacks for both of them.

Please do not forget to fill up and send your feedback form in time. This will help us to improve in future.

We at Team 2007 are committed to serve FOGSI at best possible way.

Dr. Atul Munshi
munshiap@gmail.com

Co-editors' Message

Dear Colleagues,

It gives us great pleasure in brining out this issue of FOGSI FOCUS on Infertility. A lot of advances have been occurring in the field of infertility over the last decade. There has also been a tremendous increase in the awareness amongst patients coming for infertility treatment. This makes it absolutely necessary that all practicing gynecologists keep themselves upto date in trends and protocols related to infertility management.

Keeping this in mind, we have invited the stalwarts in this field to share their experience and knowledge. We have tried to cover the basic issues with simple carry home messages and treatment flowcharts along with some insights in to the recent advances.

We hope you will find this issue of immense benefit in your day to day practice.

We take this opportunity to thank the entire FOGSI team for entrusting us with this job and acknowledge & appreciate the help of all those who have contributed to FOGSI FOCUS.

We wish you a happy reading !

FOGSI FOCUS

Contents

Practical approach to an Infertile couple

Dr. Mirudhubashini Govindarajan
Coimbatore

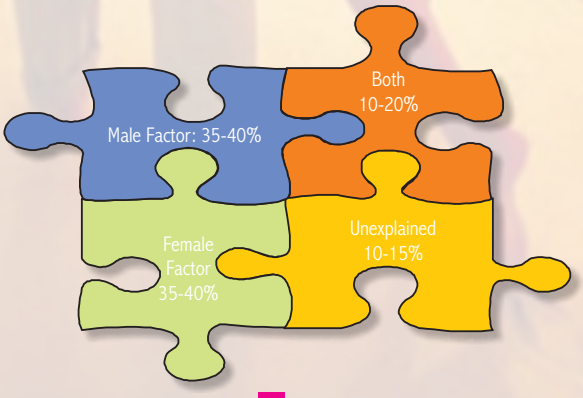
INTRODUCTION

Clinical definition of infertility is the inability to conceive after 12 months of adequate, unprotected intercourse.[1] Investigation and treatment is generally offered only after this 12 month period. However one should not defer evaluation of couple presenting earlier if there are clear cut problems such as advancing maternal age, oligoovulation, previous pelvic infection, surgery etc.

Incidence: Infertility affects approximately 10-15% of couple in the reproductive age group. Overall the male and female partners contribute evenly to infertility, with some degree of male factor implicated in over 40% of cases.

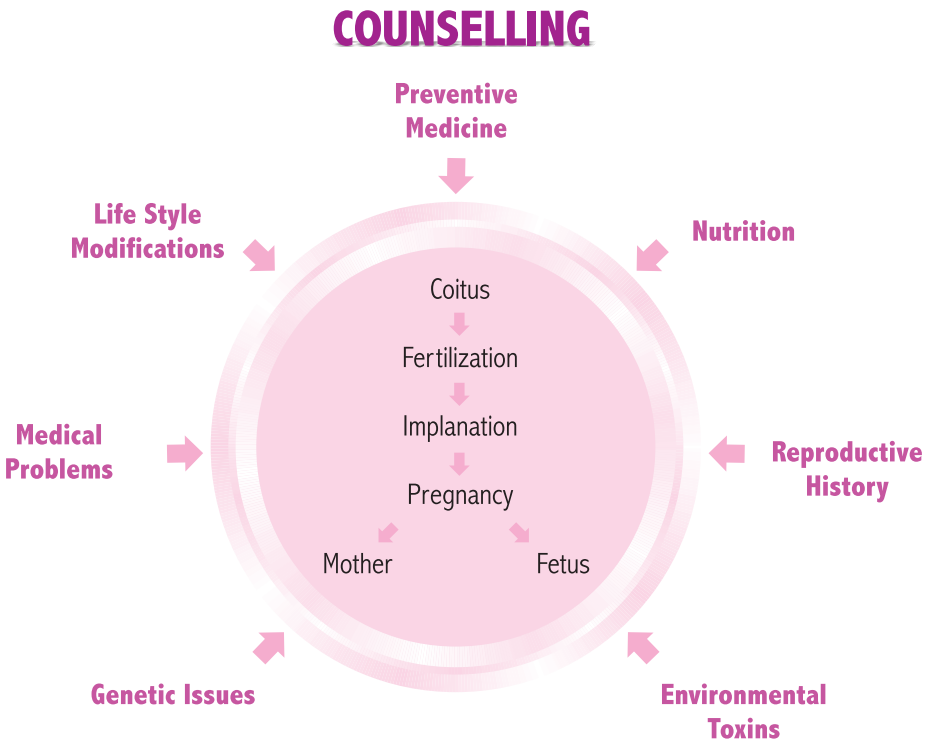
Causes of infertility

(a)	**Male Factor**	**35-40%**
(b)	**Female Factor**	**40%**
	Ovulatory dysfunction	20-40%
	Tubal	20-40%
	Advanced age	18-50%
	Luteal phase defects	<10%
	Uterine & cervical factors	10%
	Fibroids	2-3%
(C)	**Unexplained**	**10-15%**
(d)	**Combination**	**10-20%**



Initial consultation:

Both partners should be present during the visit to underscore the concept that infertility is a problem to be surmounted by the couple together. A thorough history and detailed physical examination of both partners is mandatory.



Emotional stress can contribute to and be aggravated by infertility and its management. Therefore adequate counseling should be an integral part of the management. Medical, paramedical or non medical members of the team may be the counselors and should deal with the couple with sympathy and understanding. Easy accessibility is also crucial.

A clear investigation and treatment protocol should be discussed. The proposed procedures and their potential side effects should be explained. Doubts and popular misconcepts should be dispelled. Cost, prognosis and time schedule should clearly be informed.

Couple should be assured regarding the future health of babies born out of infertility treatment. The couple should finally be assisted to take a decision regarding stopping the treatment or choosing alternatives, which might be necessitated by physical, mental or financial drain.

Basic investigations:

Some first line investigations with established correlation with pregnancy.[2]

1. Semen analysis

- At least 2 samples should be assessed in the same laboratory if the values are abnormal.

Normal values are:

- Sperm concentration > 20million/ml
- Motility > 50% motile (Grade a+b) or 25% with progressive motility (Grade a) within 60 minutes of ejaculation.
- Morphology > 30% normal forms.[3]
- Computerized semen analysis (CASA) is not superior to conventional semen analysis.[4]

2. Documentation of tubal patency by HSG or Laparoscopy.

- HSG is inexpensive outpatient procedure and has low complications rate.
- HSG has low sensitivity and high specificity making it a useful screening test for ruling out tubal obstruction. [2]
- When HSG shows bilateral tubal block chance of getting pregnant is only minimal.5
- If HSG is abnormal, diagnostic Laparoscopy should be the follow up procedure (Level of evidence grade B) [8]

3. Documentation of Ovulation

- Women with regular monthly menstrual cycles are likely to be ovulating.[6]
- There is no evidence that use of BBT charts and LH detection kits improves pregnancy outcome.[7]
- Women with regular menstrual cycle are can have a serum Progesterone in the mid-luteal phase (day21) to confirm ovulation. (Level of evidence grade B)[8]
- Women with prolonged irregular cycles should have Progesterone assay at a later day in the cycle depending on the cycle length.(GPP)[8]
- Transvaginal Sonography is the method of choice for women who are having ovulation induction.
- Women with possible fertility problems are no more likely than general population to have Thyroid disease and the routine measurement of Thyroid function should not be offered.(Level of evidence grade C)[8]
- Tests of ovarian reserve currently have limited sensitivity and specificity in predicting fertility.(Level of evidence grade C)[8]
- Women should not be offered an endometrial biopsy to evaluate the luteal phase as part of investigations of infertility because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates.(Level of evidence grade B)[8]

4. Screening for Chlamydia trachomatis

- Before undergoing uterine instrumentation women should be offered screening for Chlamydia trachomatis using an appropriately sensitive technique. (Level of evidence grade B)[8]
- Prophylactic antibiotics should be considered before uterine instrumentation, if screening has not been carried out. (GPP)[8]

Hysteroscopy is not a routine investigation for infertility as there is no evidence linking treatment of uterine anomalies with enhanced fertility.

5. Advanced investigations

a. Male factor

- Sperm function tests like Hypo-osmotic swelling test,the Hemizona assay,the Mannose binding test,Sperm penetration assay,the Acrosome reaction test, Assessment of improved sperm motility potential with Pentoxyfilline co-culture etc.
- Endocrine assay in severe OATZ or Azoospermia.
- Karyotyping in severe OATZ or Azoospermia.
- Genetic testing in male partner for mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene and Y chromosome microdeletions.
- Testicular biopsy to assess spermatogenesis.

b. Female factor

- Sonohysterography has been shown to be superior to HSG in detecting uterine anomalies. 9
- Endocrine assay-Basal FSH and Estradiol (early follicular phase) levels serve as an excellent indicator of ovarian reserve.
- Karyotyping in Premature ovarian failure.
- Colour Doppler for growing follicles, functional integrity of Corpus luteum and developing endometrium.
- Clomiphene citrate challenge test to ascertain ovarian response.
- GnRH challenge test in anovulation due to hypothalamic pituitary failure.
- Endometrial function-Endometrial expression of HOXA-10 gene and Beta -3 integrin levels in endometrium.

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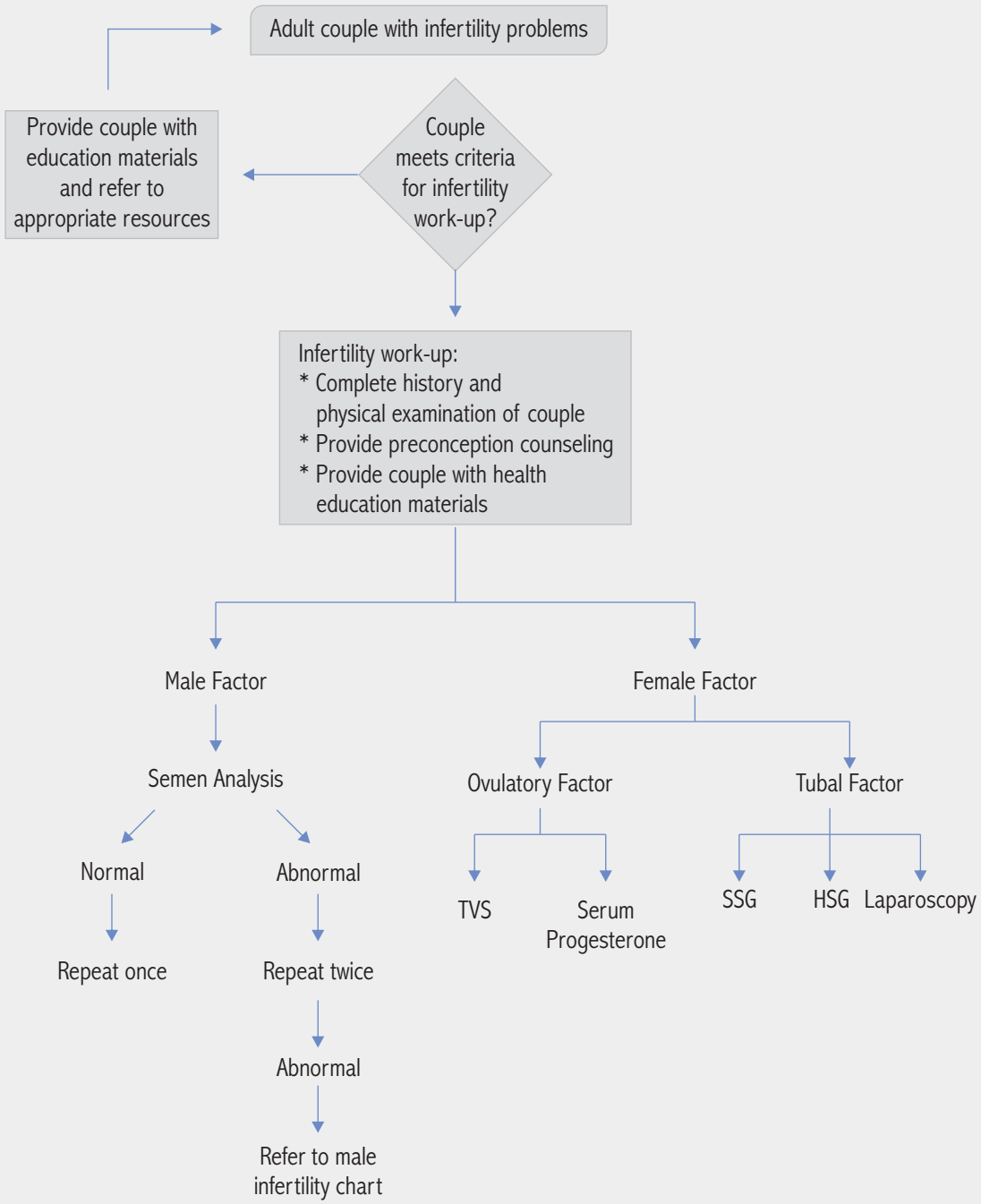
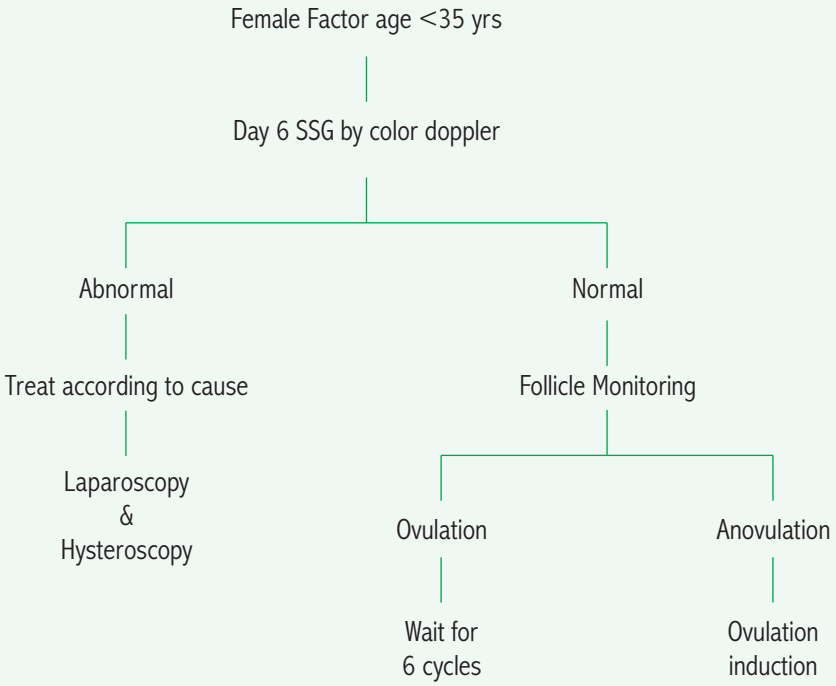
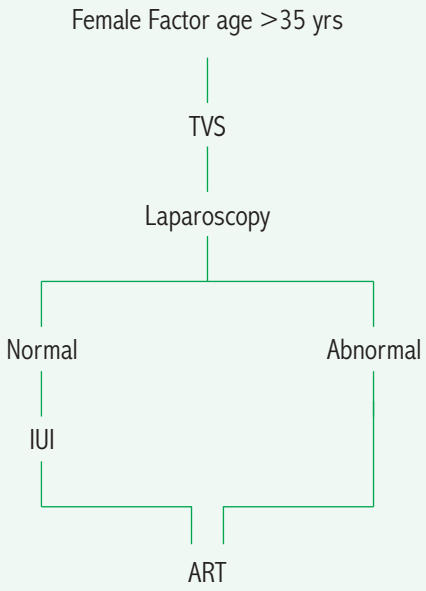
Dr. Mirudhubashini Govindarajan
Phone: +91 422 221 3411 / 220 0033
E-mail ivf@vsnl.com / ivfcbe@gmail.com

BASIC INFERTILITY WORK-UP



BASIC INFERTILITY MANAGEMENT





Dr. Jaideep Malhotra
Agra

Transvaginal Sonography for Ovulation Monitoring

INTRODUCTION

Transvaginal ultrasound (TVS) has greatly improved the evaluation of the ovary and understanding of the normal ovarian cycle and follicular development one of the first steps in the diagnosis and evaluation of the infertile women is to determine if her ovarian function and ovulatory status in normal as ovulatory dysfunction accounts for almost 30% causes of female in fertility.(1)

The first clue to a woman's ovulatory status is her menstrual cycle history. A regularly menstruating woman is usually ovulatory; patients with irregular menses or with anenorrhea may be anovulatory or may be in consistently ovulating. There are multiple methods for evaluating ovulation in women.(2)

ROLE OF ULTRASOUND

Ultrasound (TVS) is now widely, rather only modality to evaluate non-invasively, the menstrual cycle and provides information (anatomic and physiologic) an ovarian morphology, endometrial thickness and co-existing pelvic masses.

Ovarian follicles as small as 1-2 mm can be seen by TVS throughout the menstrual cycle these are antral follicles and a good basal antial follicle count (10-20 on day 2 of M.C.) indicates good ovarian reserve. Antral follicle count an day 2 is important to predict the ovarian response to ovulation induction drugs.

A baseline day 2 / 3 scan is important in a follicle or ovulation monitoring cycle to see for:

1. Endometrial shedding.
2. Ovarian cysts (Persistent C.L. cysts)
3. Any other ovarian pathology (PCO / Dermoid / Endometrioma)
4. Ovarian follicle count (Antral follicle count)
5. Ovarian volume and reserve estimation.

Only after a normal day 2 or day 3 scan should an ovulation induction protocol be worked out for an individual women.

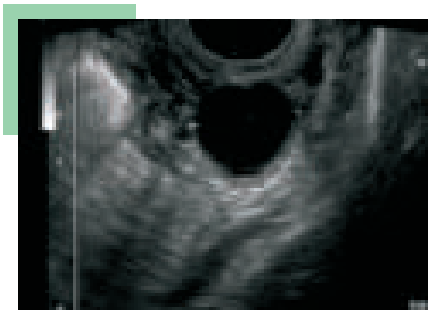
Follicle Monitoring

After a day 2/3 first scan then the ovulation monitoring should be done by TVS daily from day 7 onwards to see for

1. Serial follicular growth
2. Follicular content clearity.
3. Visualisation of cumulus
4. Measurement of follicle
5. Double contour sign
6. Evidence of ovulation
7. Presence of free fluid in pouch of douglas
8. Endometrial growth co-relation (ovarian endometrial synchrony)

Spontaneous Cycle

In a spontaneous cycle on day 7 there are usually several follicle of 4-8 mm size. Out of these in a spontaneous cycle one or two growth (dominant follicle) these dominant follicles are identified grow at the rate of 1-2 mm. per day



Mature Follicle

to a maximum size varying 15 mm to 23 mm (an average preovulatory follicle is 20 mm in size). This triggers the LH singe from pitutary via a complex hormonal feed back mechanism. Following the LH surge the mature oocyte (egg (M2) is surrounded by granulosa cells which form a corona radiata, stats to separate from the follicular wall (double contour sign on TVS) and finally this is expelled out of the follicle (ovulation) (collapse of follicle, crenated follicular edges, free fluid in pouch of douglas and internal echos in the follicle).

Ultrasound Signs of Imminent Ovulation

1. Identification of cummlus mass (1 mm)
2. Detachment of inner wall
   (a) Double contour
   (b) Infolding of wall
3. An average size of 20 mm.

Signs of Ovulation

1. Irregular follicle walls
2. Collapse of follicle
3. Fluid in cul-de-sac.

Corpus Luteum

1. Fresh C.L. : 15-25 mm hypoechoic with internal echoes.
2. Thick echogenic irregular rim.
3. Neovascularisation on periphery by color doppler.

STIMULATED OVARIAN CYCLE

A female infertile patient may be stimulated with any of the various protocols available.

It is very essential for the sonologist to know which protocol is being followed and what response is expected from that patient. Common ovulation inducing drugs used are :

1. Clomiphene citrate.
2. Tamoxifen or the newer letrazol.
3. Gonadotrophins (FSH, FSH + LH, Recombinant FSH)
4. HCG trigger (5000 or 10,000 units)
5. GnRh analogue down regulation protocols.
6. GnRh antagonist protocols.
7. Additional drugs like Bromocriptin, Estrogens etc.

The ovulation inducing drugs like clomiphere act via Hypothalamic Pitutary axis by inducing and increasing gonadotrophins act directly on the ovaries. These drugs are used singly or in combination.

These drugs are usually started in early follicular phase and they usually will target all the antral follicles and lead to multiple follicular growth. There will be many growing together and growing erratically. The LH surge in stimulated cycles is usually 1 to 2 days earlier than spontaneous cycles.

It is also sometimes difficult to measure individual follicles in a stimulated ovary because many follicles together many not appear spherical follicles. 3-D imaging might be of some help in accurate assessment of number of stimulated follicles and their follicular fluid volumes.

The suggested protocol to trigger ovulation by HCG injection is as follows :

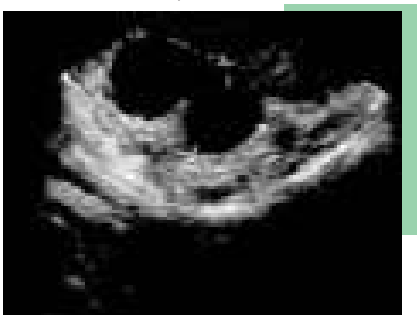
1. Spontaneous cycle	Average follicular size 20 mm
2. Clomiphene / Letrazole cycle	at $\geq$ 18 mm
3. COH by Gonadotrophins	at $\leq$ 16 mm

A proper timing of HCG injection is very essential for oocyte maturation and for preventing luterised unruptured follicle syndrome.

How to Measure a Follicle

The internal diameter of the follicle should be measured in three planes and the mean value calculated. Accurate measurements are very important as the guide the clinician for HCG trigger. Timing of HCG is again very important as the guide the clinician for HCG trigger. Timing of HCG is again very important for getting a mature M2 fertilizable oocyte out of the follicle. In controlled ovarian hypostimulation accurate measurements are even more important as despite of close monitoring 15-30% patients will still have a spontaneous LH surge.

It should be remembered that whenever gonadotrophins are used, HCG is administered when the dominant follicle is 17 mm average and then the patient is advised intercourse or IUI is done. Even if and when a LH surge occurs it should be augmented with HCG as the surge in super ovulated cycles is often attenuated.(3)



Measurement of Follicle : Longitudinal or oblong follicle need two measurement

Applications of Ultrasound in Ovulation Monitoring

Ultrasound, TVS, follicle monitoring is absolute essential in the management of an infertile couple.

1. Timing of post-coital test.
2. Timing of hCG trigger.
3. Timing of intercourse.
4. Timing of IUI
5. Timing of oocyte recovery in ART cycles.
6. Diagnosis of endometrial receptivity.
7. Diagnosis of luteal phase changes.
8. Timing of endometrial biopsy.
9. To predict ovarian reserve and ovarian response.
10. For counseling patients as to their ovarian status.

Role of Ultrasound & Color Doppler

Ultrasound (T.V.S.) offers a simple, reliable, reproducible, quick & non invasive method for assessing the female pelvis.

Ultrasound Technique for Uterine Biophysical Profile

To perform the UBP special care should be taken. The following guidelines are recommended : (Apple baum 96)(1)

1. To determine the presence of a 5-line appearance, information from both the transabdominal and transvaginal studies may be useful. For example, although a 5-line appearance may be noted transabdominally, it may not always be possible to see it endovaginally due to uterine position (and vice versa). In this case, a 5-line appearance is considered to be present and endometrial vascular penetration may be estimated when performing the endovaginal study.
2. Perform the Doppler study slowly. The flow of blood in the endometrium is of low velocity, it may take time for the ultrasound machine to register the presence of blood flow and create the image. If one sweeps through the endometrium too quickly, flow may not be seen. Additionally endometrial blood flow has a mercurial personality - it

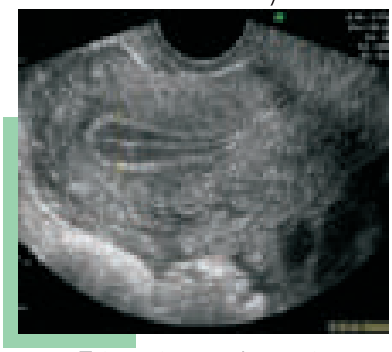
may appear as if it comes and goes. It may also appear in some areas and not others. Do not observe hastily.

3. Endeavor to make the endometrium as specular a reflector as possible. Use the techniques of manual manipulation of the anatomy and probe pressure to achieve this.
4. Scan endovaginally both coronally and sagittally. There may be a difference in how well the blood flow is imaged.
5. When measuring the endometrium in the A-P dimension, try to obtain the value when no contraction affecting it is present. Contractions may affect this value. Also when possible, obtain the measurement in a standard plan such as when both the endometrial and cervical canals continuous.

The Uterine Biophysical Profile

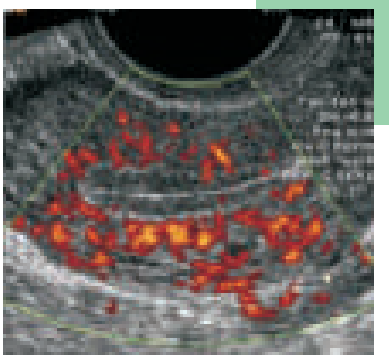
In our experience,(1) certain sonographic qualities of the uterus are noted during the normal mid-cycle. These include :

1. Endometrial thickness in greatest AP dimension of 7 mm or greater (full-thickness measurement).



Triple line endometrium

2. A layered ("5 line") appearance to the endometrium.
3. Blood flow within zone 3 using color Doppler technique.
4. Myometrial contractions causing a wave like motion of the endometrium.
5. Uterine artery blood flow, as measured by PI, less than 3.0.
6. Homogeneous myometrial echogenicity.
7. Myometrial blood flow seen on gray-scale examination (internal to the arcuate vessels).



Vascularisation of Endometrium

The uterine scoring system for reproduction ("USSR") comprises evaluation of the following parameters :

1. Endometrial thickness (full-thickness measured from the myometrial-endometrial junction to the endometrial-myometrial junction).
2. Endometrial layering (i.e., a 5-line appearance).
3. Myometrial contractions seen as endometrial motion.
4. Myometrial echogenicity.
5. Uterine artery Doppler flow evaluation.
6. Endometrial blood flow.
7. Gray-scale myometrial blood flow.

Each parameter is scored as follows :

1. Endometrial thickness
   a. < 7 mm = 0
   b. 7-9 mm = 2
   c. 10-14 mm = 3
   d. > 14 mm = 1
2. Endometrial layering
   a. no layering = 0
   b. hazy 5-line appearance = 1
   c. distinct 5-line appearance = 3

3. Myometrial contractions (seen as wave-like endometrial motion high-speed playback from videotape)

a. 3 contractions in 2 minutes (real-time)=0
b. 3 contractions in 2 minutes (real-time)=3

4. Myometrial echogenicity

a. coarse/inhomogeneous echogenicity = 1
b. relatively homogeneous echogenicity = 2

5. Uterine artery Doppler flow
   a. PI-3.0 = 0
   b. PI-2.99 = 0
   c. PI-2.49 = 1
   d. PI < 2 = 2

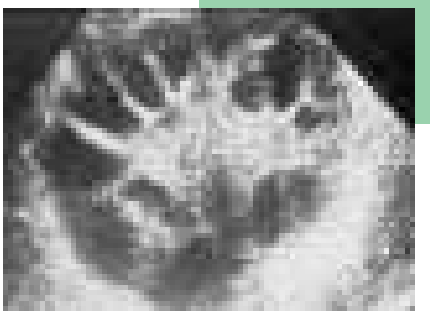
6. Endometrial blood flow within Zone 3
   a. absent = 0
   b. present, but sparse = 2
   c. present multifocally = 5

7. Myometrial blood flow internal to the arcuate vessels seen on gray-scale examination
   a. absent = 0
   b. present = 2

The values assume a technically adequate ultrasound examination with no abnormalities of uterine shape or development, no other gross uterine abnormalities (e.g. significant masses) and a normal ovairan cycle (e.g. without evidence of ovarian-ultrine dyscoordination). A male factor component to the infertility is not present.

Aberrant Follicular Growth

1. No increase in follicular size indicate anovulation.
2. Rupture of follicles when they are still small in size (14-16 mm) seen in some women who have luteal phase defect due to improper folliculogenesis.
3. Slower than normal follicular growth.
4. Multifollicular ovary where several follicles reach 12-14 mm diameter and only occasionally ovulate (due to hypothalamic dysfunction).
5. Polycystic ovaries typical cogwheel picture.
6. Multicystic ovaries.
7. Ovarian functional cysts.
8. Persistant corpus luteum haemorrhagic cysts.



Polycystic Ovary

CONCLUSIONS

The ovary is an extremely dynamic organs and changes in size, texture and vascularity with the menstrual cycle ultrasound (TVS) assessment of the ovaries and other pelvic structures is a vital adjunct or rather a vital first step investigation in the management of a tub fertile female.

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Dr. Jaideep Malhotra
Phone: 98970 33335
Email: jaideepmalhotraagra@gmail.com

Dr. P. G. Paul
Cochin

Dilemma in managing Tubal factor

Tubal disease is responsible for 25-35% of female infertility 1 It may involve the proximal, distal, or the entire tube, and may be transient (obstruction), or permanent (occlusion) 2. The most common predisposing factors are pelvic inflammatory disease, previous pelvic surgery, endometriosis, pelvic tuberculosis and appendicitis. Management of tubal infertility was exclusively surgical before the era of ART. Now the infertility specialist is in a dilemma of choosing the right approach. This article aims to give an evidence based management of tubal factor infertility.

MANAGEMENT

Management of tubal factor for infertility depends on the type and degree of tubal dysfunction. Various approaches are available. The treatment of choice is also determined by other factors such as the age and the ovarian reserve of the patient, presence or absence of a male factor, and socioeconomic considerations. In addition to less invasive techniques such as transcervical tubal cannulation and selective salpingography, and various surgical approaches, in-vitro fertilization and embryo transfer (IVF-ET) is a viable alternative for all types of tubal dysfunction.

Proximal tubal occlusion

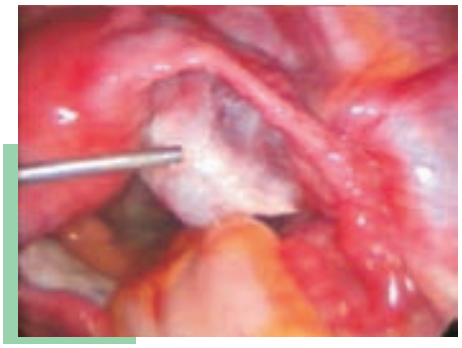
Proximal tubal obstruction and occlusion account for 10-25% of tubal factor. Proximal Tubal obstruction can be due to chronic salpingitis, salpingitis isthmica nodosa (SIN),intratubal endometriosis,amorphous material (e.g,mucus plugs), or spasm. Treatment for proximal tubal occlusion include transcervical tubal cannulation, tubocornual anastomosis, and IVF-ET.

Transcervical tubal cannulation for the reversal of proximal tubal occlusion can be performed under fluoroscopic, falloposcopic, sonographic, or hysteroscopic guidance[3,4]. Tubal recanalisation by hysteroscopic control offers a number of advantages over other techniques. First the guidance of the tubal catheter in to the tubal ostia is simple because it is done under direct vision. Second, since it is done along with a laparoscopy the presence of distal tubal disease can be diagnosed and treated simultaneously. So it offers a one-step evaluation and treatment in infertile patient with proximal obstruction. While 85% of occlusions can be overcome in this way, there is a 30% reocclusion rate, and tubal perforation occurs in 3-11% of cases 5. Hysteroscopic transcervical tubal cannulation gives an average ongoing pregnancy rate of 30-40%6. Laparotomy with microsurgical tubocornual anastomosis (TCA)gives pregnancy rates from 38 to 56%7 . In selected patients, without tubal pathology, hysteroscopic transcervical tubal cannulation, may be effective, & less invasive and less costly[8].

PROXIMAL TUBAL OCCLUSION

* Accounts for 10 to 25 % of tubal factor
* Causes - salpingitis, SIN, intratubal endometriosis & amorphous plug
* Therapeutic approach-Transcervical tubal cannulation,tubocornual anastomosis & IVF-ET
* Transcervical approach-Fluoroscopy, falloposcopy, sonographic or hysteroscopic guidance
* Hysteroscopic approach-one-step evaluation and treatment,85 % occlusion can be corrected
* Pregnancy rate 30 to 40%

Hysteroscopic cannulation
Guidewire with outer cannula



Guide wire is seen in the isthmic portion of the tube

Distal tubal occlusion

Distal tubal disease represents approximately 85% of all cases of tubal infertility. In addition to IVF, surgical interventions, such as salpingostomy and fimbrioplasty, are available for the treatment of distal tubal occlusion. Fimbrioplasty gives 60% pregnancy rate compared 30% for salpingostomy[9]. Success rate of laparoscopic surgery for distal tubal disease are directly related to the severity of the preexisting tubal disease. Incidence of ectopic pregnancy also increases with the severity of tubal disease[10]. Following salpingostomy by laparoscopy, an intrauterine pregnancy rate of 44% has been reported in patients demonstrating normal mucosa. No pregnancy occurred in patients with no folds or with a honeycomb appearance[11]. So it is important to evaluate the degree of tubal damage. Salpingoscopy is a useful tool to evaluate the tubal mucosa and to predict the pregnancy outcome[10].

DISTAL TUBAL OCCLUSION

* Accounts for 85 % of all cases of tubal infertility
* Treatment -Salpingostomy , fimbrioplasty or IVF
* Fimbrioplasty gives pregnancy rate of 60 % compared to salpingostomy (30%)
* Success rate depends on the severity of preexisting tubal disease
* Salpingoscopy is useful tool to evaluate tubal mucosa & to predict the pregnancy outcome

Hydrosalpinges and ART

Meta-analyses have shown that women with hydrosalpinx have about half the pregnancy, implantation, and delivery rates, and up to twice the incidence of spontaneous abortion after IVF-ET[12,13]. Treatment options for hydrosalpinx include drainage, salpingostomy, proximal tubal ligation, and salpingectomy. Laparoscopic salpingectomy should be considered for all women with hydrosalpinges due to undergo IVF-ET[14].

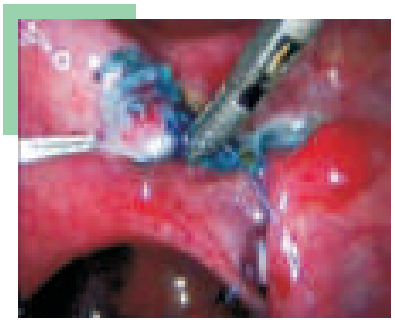
Adhesions

Patients with adnexal adhesions that are extensive, thick, or vascular are less likely to benefit from surgery. The limited evidence suggests that laparoscopic lysis of adhesions is first line of treatment for mild disease while patients with severe disease should instead undergo IVF-ET[15].

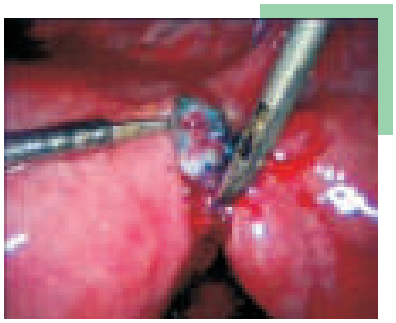
Tubal reanastomosis

Microsurgical tubal anastamosis is the gold standard for reversal of sterilization. It gives an intrauterine pregnancy rate of 60-80% and very low ectopic pregnancy rate of 1-6%[16]. Success rate mainly depends on the type of sterilization; Falope rings and clips give a higher success rate than Pomeroy's and other techniques[17]. Two other prognostic factors associated with success of the procedure were tubal length and type of anastomosis. The results obtained by laparoscopic microsurgical anastomosis look promising with good intrauterine pregnancy rates of 60-80% and a very low ectopic pregnancy rate of 1-6%.

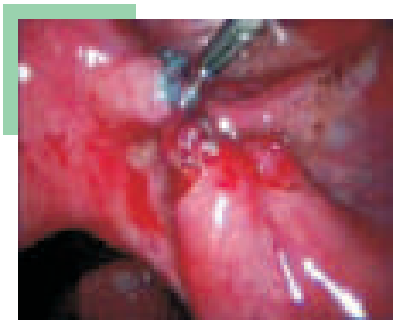
Sterilization reversal in younger patients has a high success rate and allows for multiple subsequent pregnancies[17]. IVF-ET success rates decrease with advancing age from almost 50% in patients less than 30 years of age to 28% in patients between age 35 and 38years, and 9% or less in patients over 41 years[15]. A Scandinavian study reported a 33% term pregnancy rate in women over 40 years following sterilization reversal[18]. So, tubal anastomosis must be offered to patients with good length of healthy tube available for anastomosis.



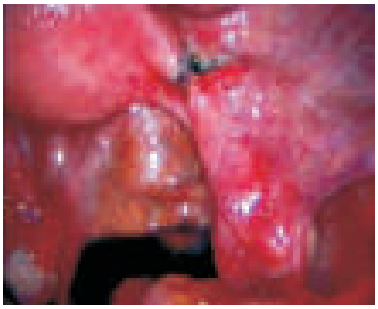
6 o' clock suture is taken from outside inside on the distal stump and inside outside on the proximal stump



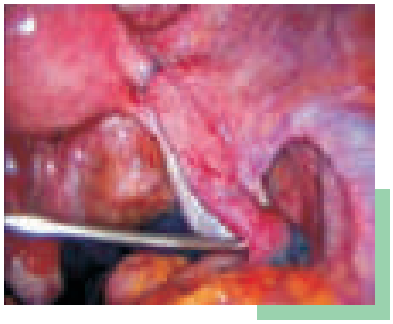
9 o' clock suture is taken from inside outside on the proximal stump, 12 o' clock suture already taken



3 o' clock suture is taken inside outside on the proximal stump



all four sutures completed



second layer (seromasularis) competed and chromopertubation

CONCLUSION

Based on the available evidence, the following recommendations can be made[15].

CONCLUSION

* Mild to moderate tubal disease in young women- An initial surgical approach, at the time of diagnostic laparoscopy
* IVF-ET if pregnancy does not occur within 1 year following surgery
* Older patients and those with severe tubal disease -directly to IVF-ET
* Patients with severe tubal disease & hydrosalpinx -prophylactic salpingectomy to maximize the chances with IVF-ET.
* Choice surgery, IVF-ET, or both needs to be individualized to the patient as it depends on the presence of coexisting infertility factors, local IVF success rates, and cost

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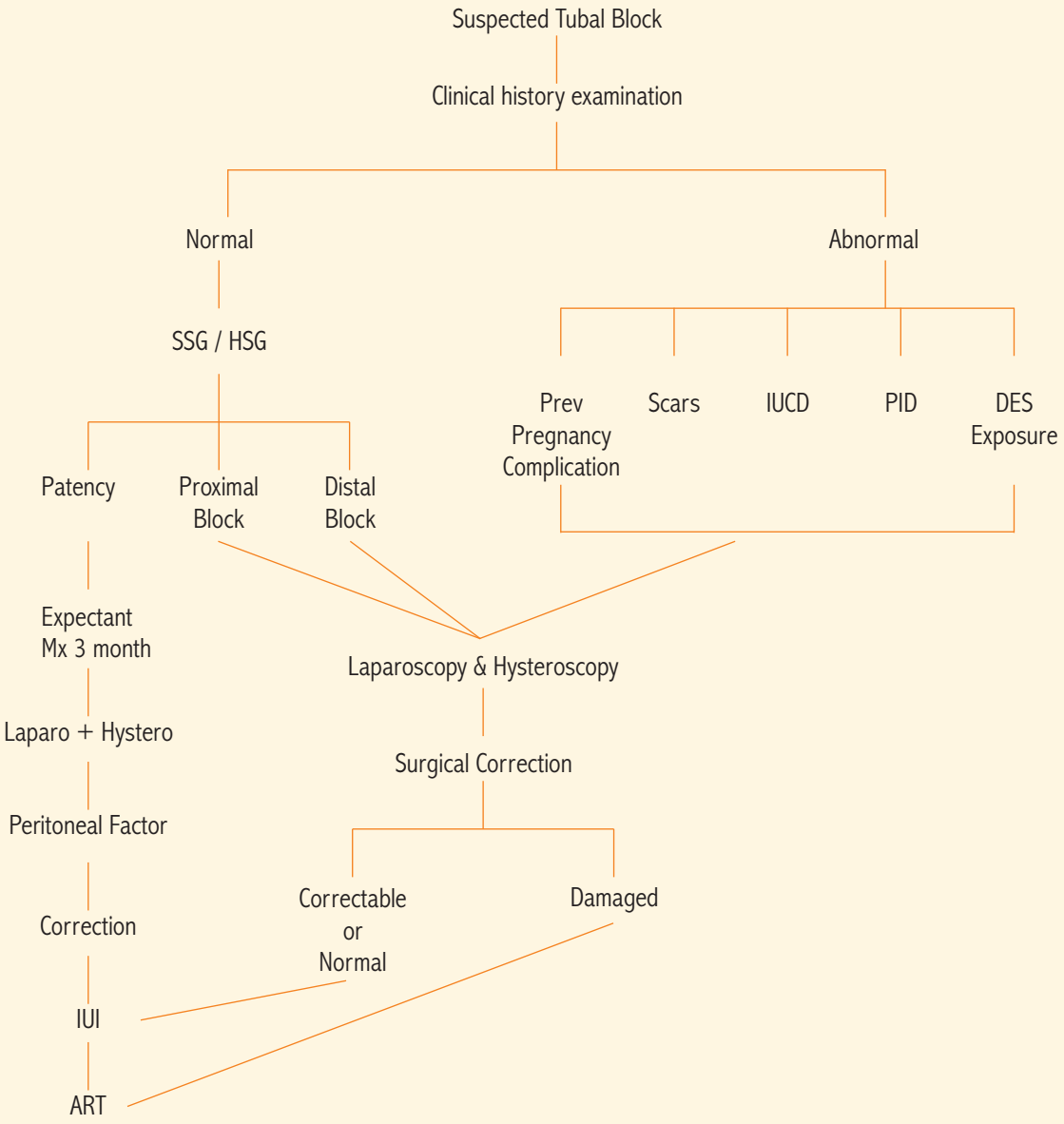
Dr. P. G. Paul
Phone: 9895151797
Email: paulpg@vsnl.com

Approach to Tubal Factor



Ovulatory infertility

Dr. Manish Banker
Dr. Pravin Patel
Ahmedabad

INTRODUCTION :

Ovulatory disorders can be identified in 18 to 25 % of couples presenting with infertility[1]. Most of these women have oligomenorrhea, arbitrarily defined as menstruation that occurs at intervals of 35 days to six months. While ovulation may occasionally occur, spontaneous conception is unlikely.
The World Health Organization (WHO) classifies ovulatory disorders into three groups

WHO class 1 (hypogonadotropic hypogonadal anovulation) 5% to 10% ;
WHO class 2 (normogonadotropic normoestrogenic anovulation) 70% to 85%; and
WHO class 3 (hypergonadotropic hypoestrogenic anovulation) 10% to 30%.

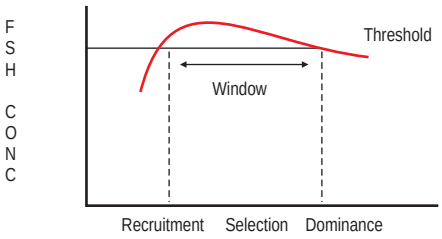
Induction of ovulation in anovulatory women is aimed at inducing monofollicular development. Controlled ovarian stimulation denotes use of drugs to induce multifollicular ovulation in normally ovulating women as a part of their infertility treatment.

PHYSIOLOGY :

When inducing ovulation with drugs, a couple of important things need to be considered.

FSH Threshold : This is the minimum amount of FSH required to induce monofollicular ovulation in an anovulatory woman.

FSH window : This the duration for which FSH is above the threshold. Longer the window period, higher the number of follicles recruited.



LH threshold: This denotes the minimum amount of LH required for adequate folliculogenesis

LH ceiling: LH higher than this leads to follicular atresia

OVULATION INDUCTION DRUGS

- Gonadotrophins
  - FSH
  - LH
  - HMG
  - HCG
  - Purified FSH/LH
  - Recombinant HCG
  - GnRh Agonists
  - GnRh Antagonists
- Non Gonadotrophins
  - Clomiphene
  - Tamoxifen
  - Letrozole

Adjuvants
Bromocriptin, Cabergolin
Dexamethasone, Metformin
Estrogens, Dichlroinositol
Nacfil, Barkitt

Clomiphene Citrate: Clomiphene citrate has been the most widely used treatment for fertility enhancement for the past 40 years. Clomiphene occupies estrogen receptors in the

hypothalamus and pituitary, thereby blocking the negative feedback action of estradiol. Thus, the main mechanism appears to be a rise in serum FSH concentrations by around 50 %, resulting in stimulation of follicle growth and follicular estradiol production. However, other mechanisms, such as induced changes in the insulin-like growth factor system and SHBG levels, may also contribute[2].

The primary indication for clomiphene citrate is infertility secondary to oligoovulation or anovulation in normogonadotropic, normoprolactinemic, euthyroid women (WHO class 2). These women produce gonadotropin and estrogen (as evidenced by spontaneous menses or withdrawal bleeding in response to a progesterone challenge) and are therefore able to respond to clomiphene. This group includes women with PCOS.

How to use Clomiphene Citrate

Initiation of therapy, duration and dosage

Clomiphene therapy for ovulation induction is typically started on the fifth day of a cycle, following either spontaneous or induced bleeding. However, the results of therapy, in terms of ovulation, pregnancy, or spontaneous miscarriage, are comparable when clomiphene is begun as early as day two [3].

Clomiphene is initially begun empirically at a dose of 50 mg daily for five days; If ovulation does not occur in the first cycle of treatment, the dose is increased to 100 mg. Thereafter, dosage is increased by increments of 50 mg to a maximum daily dose of 250 mg (although 100 mg is the maximum dose approved by the FDA; the ACOG does not encourage the use of more than 150 mg [4]) until ovulation is achieved, at which point the woman should attempt to conceive for four to six cycles.

Most conceptions initiated by clomiphene citrate occur within the first six ovulatory cycles,

CLOMIPHENE CITRATE:

* Use the lowest effective dose. Increasing a satisfactory dose does not increase the pregnancy rate
* Anti estrogenic actions are not dose dependant. Occurs in recurrent cycles in the same woman
* 75 % of pregnancies occur in the first 3 ovulatory cycles. Very few pregnancies occur after 7 cycles.

approximately 50 % occur at the 50 mg dose and another 20 to 25 % at 100 mg and 10 % at 150 mg [5,6]. There is no benefit to increasing the clomiphene dose in subsequent cycles once ovulation occurs.

There have been some papers linking the occurrence of ovarian neoplasms to long term use of clomiphene citrate. Since most conceptions with clomiphene occur within 6 ovulatory cycles and there is a possibility of ovarian neoplasms, RCOG recommends its usage for 6 ovulatory cycles only.

RESULTS: A literature review including data from over 5000 patients with a variety of indications for clomiphene therapy reported an ovulation rate of 73 % and a pregnancy rate of 36 % [7]. Of patients who became pregnant, the miscarriage rate was approximately 20 % and the multiple pregnancy rate was 8 to 13 %. The discrepancy between the ovulation and pregnancy rates may be partly explained by the peripheral anti-estrogenic effects of clomiphene on cervical mucus (impairing fertilization) and the endometrium (impairing implantation) or by hypersecretion of LH. After six months of treatment, the pregnancy rate per cycle falls substantially despite regular ovulation [8].

The probability of multifetal pregnancy is increased: twins have been reported in 6.9 to

9 % of pregnancies, triplets in 0.3 to 0.5 %, quadruplets in 0.3 %, and quintuplets in 0.13 % [9]. The risk may be reduced by ultrasound monitoring and withholding hCG, IUI, or intercourse if more than two follicles >15 mm diameter are seen.

Fecundity with Clomiphene treatment

Group	Fecundity (%)
Anovulatory women who respond to treatment	15
Anovulatory women who respond to treatment and have no other infertility factors	22
Women with unexplained infertility	3.4 to 8.1
Women with unexplained infertility treated with clomiphene and IUI	8.5 to 9.5

Adapted from Use of clomiphene citrate in women. Fertil Steril 2003; 80:1302.

Adverse Effects: Commonest are hot flashes (10-20%), uncomplicated ovarian enlargement (14%), multiple gestation (primarily twins, <10 %). True OHSS is rare. Less frequent side effects include abdominal distention and pain, nausea/vomiting, breast discomfort, visual symptoms, mood swings, and headaches.

Adjuvants: Women who do not become pregnant using clomiphene are often offered treatment with alternative approaches before referring them for resource intensive interventions.

Modified regimens - High-dose clomiphene citrate (200 to 250 mg daily) may be given for 8-10 days in women refractory to standard doses. This extended regimen of clomiphene is particularly well suited for woman who cannot receive exogenous gonadotropins, but the overall experience is limited and the dose exceeds current FDA recommendations.

HUMAN CHORIONIC GONADOTROPIN - An absent or inadequate midcycle LH surge may result in a failure to ovulate or a short luteal phase, despite clomiphene-induced follicular development. In this situation, exogenous hCG (single dose 5,000 - 10,000 IU) may be added to the regimen. It is given when transvaginal ultrasonography (TVS) shows that the leading follicle has reached 18 to 20 mm in diameter [10]. Ovulation occurs approximately 36 to 44 hours after the injection.

Bromocriptine is indicated for ovulation induction in women with hyperprolactinemia or galactorrhea. It has also been tried in women with no galactorrhea and normal prolactin who have failed clomiphene therapy.

LIFESTYLE MODIFICATIONS : Obese anovulatory women with polycystic ovary syndrome (PCOS) and hyperinsulinemia are sometimes unresponsive to clomiphene treatment. Weight loss (5 to 10 %) alone or in combination with exercise is associated with reduced hyperinsulinemia and hyperandrogenism and a high rate of resumption of ovulation in these women.

Metformin - Many women with PCOS and ovulatory infertility are insulin resistant. In these women, elevated insulin secretion may directly stimulate ovarian androgen secretion and result in anovulation. Reducing insulin secretion with an insulin sensitizing agent such as metformin may lower ovarian androgen secretion, increase the rate of spontaneous ovulation.

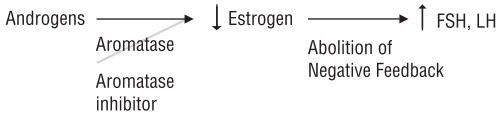
Dexamethasone or oral contraceptives - Anovulatory women in WHO group 2 appear to

have reduced ovulation and pregnancy rates when they are treated with clomiphene. Some studies suggest that treatment with clomiphene plus dexamethasone or pretreatment with oral contraceptives improves pregnancy rates in these women.

Ovarian drilling - Laparoscopic ovarian drilling may be considered in women with PCOS who fail to ovulate despite an adequate trial of clomiphene citrate.

Aromatase inhibitors :

Aromatase inhibitors have been tried as ovulation inducing agents since 2001, when the first report appeared. Aromatase Inhibitors block the enzyme aromatase which is responsible for the conversion of androgens to estrogens. This leads to decreased estrogen synthesis, releasing the pituitary from negative feedback leading to increase in gonadotropins. This action is, however short lasting. As folliculogenesis progresses, there is increased androgen production [LH mediated - substrate overload] and increased aromatase activity [due to FSH]. Both of these lead to gradually increasing estrogen production [competitive inhibition] negating the action of letrozole. As a result, aromatase inhibitors generally lead to fewer follicles as compared to clomiphene.



Administration: Letrozole is available as 2.5 mg tablets. It is administered in 2 ways : (a) 2.5 mg per day for 5 days beginning from day 2 - 5 of the cycle, similar to clomiphene; (b) 20 mg as a single dose on day 3.

Uses and Advantages: Numerous reports have appeared over the last few years highlighting the use and advantages of letrozole compared to clomiphene. Some of the findings are summarized below :

1. Oral administration of letrozole is effective for induction of ovulation in anovulatory infertility [75%] and for increased follicular recruitment in ovulatory infertility.
2. Letrozole appears to avoid the unfavourable effects on the endometrium frequently seen with clomiphene
3. Letrozole improves response to FSH as evidenced by lower FSH dose and higher number of follicles

Side Effects :

1. Estrogen deprivation
   * Hot flushes, hair thinning
2. Anorexia, nausea, vomiting
3. Musculoskeletal pain, arthralgia, headache
4. Rash, peripheral edema
5. Somnolence

There are some yet unanswered questions regarding letrozole use : ideal dose, duration of treatment and dose-effect relationship. Data on long term safety and congenital malformation is also yet to come.

GONADOTROPINS :

Two types of gonadotropins are used for ovulation induction :

1. HMG : contains equal amount of FSH and LH
2. FSH : contains only FSH

Both the gonadotropins are available in 3 different forms : urinary, Highly Purified and recombinant [for FSH]. These 3 types differ in their purity which ranges from 5 % for urinary to > 95 % for HP to 99 % for recombinant.

Indications :

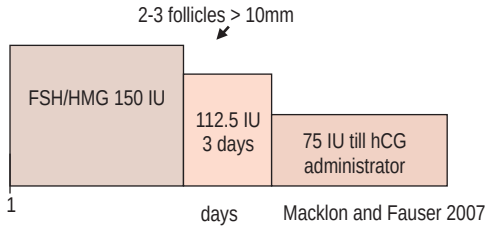
The indications of gonadotropin use are :

1. Hypogonadotropic hypogonadism : These women are deficient in FSH and LH and are hence hypoestrogenic. Clomiphene citrate will not work in them and gonadotropins are be the drug of choice for ovulation induction.

2. Clomiphene failure :
   a. Anovulation with maximum dose
   b. Ovulation but failure of pregnancy:? anti estrogenic actions
3. Superovulation in ART : with or without clomiphene.

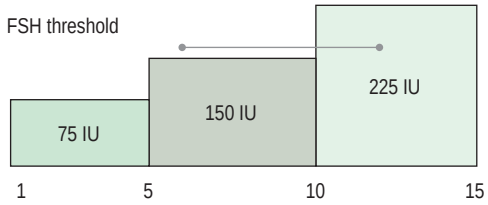
Usage: When used for ovulation induction in anovulation, the aim of treatment is to achieve monofollicular ovulation. Gonadotropins are given in gradually increasing dose to find and just exceed the threshold.

a. Step down Protocol :



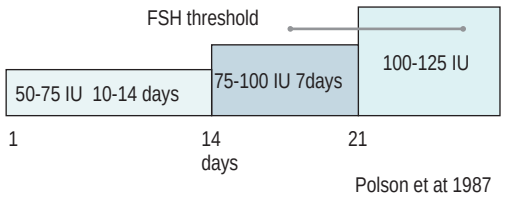
This protocol mimics the natural cycle. Gonadotropns are given in a high dose of 150 IU per day for the first few days till follicles are recruited [10mm]. The dose is then stepped down to 75 IU till the day of HCG administration. The advantage of this protocol is that it requires fewer days of stimulation and lower dose of gonadotropins. It is however difficult to titrate the dose and the risk of hyperstimulation is higher.

b. Standard Step UP Protocol:



Gonadotropins are started at a dose of 75 IU per day and increased by 75 IU every 5 days till adequate follicular recruitment occurs. This becomes very risky many times as the threshold may be exceeded by a large amount and multiple follicles are recruited.

c. Chronic Low Dose Step Up Protocol:



This is a low dose regimen based on threshold concept and that gradual rise will limit the number of follicles forming. Stimulation is initiated at a very low dose of 50-75 IU per day and continued for 10-14 days. If adequate follicular recruitment has not occurred, dose is stepped up in increments not exceeding 33 % [25 to 50 IU] every 5 to 7 days. This makes it a very safe protocol but requires a lot of patience as it can go on for 2-3 weeks.

SUPEROVULATION :

Gonadotropins are used in combination with clomiphene [or letrozole] to induce multi follicular ovulation in ART. The actions of both the drugs are complimentary and combining clomiphene [or letrozole] with gonadotropins reduces the requirement of gonadotropins and hence the cost of treatment. There is no single standard protocol for this combination and numerous combinations are being used [cc 50 mg day 3 to 7 + HMG 75 IU day 4,6,8 ; clomiphene 50 mg day 3 - 7, HMG 75 Day 8,9 10 ... etc]. These protocols are difficult to titrate as 2 drugs with different mechanisms are being combined.

COMPLICATIONS :

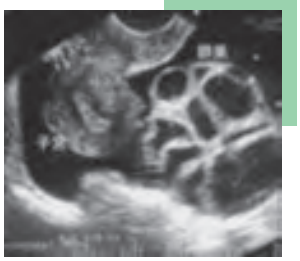
The 2 most dreaded complications of ovulation induction are :

1. Multiple Pregnancy:

Far more multiple pregnancies occur following ovulation induction than following IVF-ICSI. This is because even though ovarian hyperstimulation is carried out in IVF-ICSI, multiple pregnancies can be

controlled by restricting the number of embryos transferred to 2 or 3. In ovulation induction, however, there is no way to restrict multiple pregnancy once the ovaries are stimulated. This makes it mandatory that proper monitoring and dose titration is carried out.

2. Ovarian Hyper Stimulation Syndrome [OHSS] :



OHSS is a completely iatrogenic and often fatal complication of ovarian stimulation seen in approx. 2 to 5 % of women undergoing ovarian stimulation. It is due to a shift in fluids from the intravascular to the extravascular compartment resulting from increased vascular permeability as a result of increased Vascular Endothelial Growth Factor [VEGF] following massive luteinisation in the large number of follicles stimulated. The only means of completely preventing this condition is to avoid ovulation by giving GnRH antagonist and withholding HCG.

CONCLUSIONS: Ovulation induction is an art. There are many drugs and innumerable protocols that can be used. One should be very careful in choosing the right protocol for every patient. One should start with a few simple protocols and change or use more stronger protocols once the experience increases.

PREVENTION OF OHSS

* Decease the dose of HCG or use GnRh-a as an ovulation trigger
* Avoid HCG
* Give daily GnRh antagonist for 3 - 4 days till follicular atresia sets in to prevent ovulation
* Convert to IVF and cryopreserve all embryos

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Dr. Manish Banker
Cell: 98240 26659
Email : mivfg@yahoo.com, drbanker@pulse-hospital.com

Dr. Pravin Patel

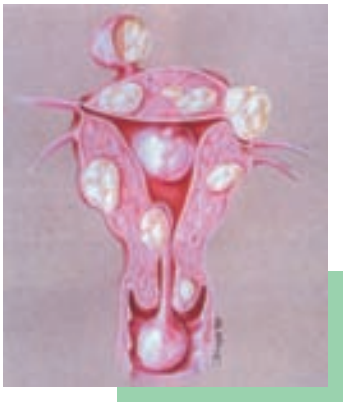
Fibroids & Infertility:
is there a relationship

Dr. Pranay Shah
Mumbai
Dr. Narendra Malhotra
Agra

Fibroids of the uterus are the most common solid pelvic tumors found in women and are estimated to occur in 20-50% of women with increased frequency during the late reproductive years (Verkauf 1992)[1]. It is well recognized that uterine fibroids may cause menorrhagia, dysmenorrhoea, and pelvic pressure. The impact of fibroids on reproduction is more controversial and the benefit of myomectomy for these patients is not clear.

The incidence of myomas in infertile women without any obvious cause of infertility is estimated to be between 1-2.4% (Buttram and Reiter, 1981)[2].

Fibroids may impair fertility through several mechanisms including distortion of the uterine cavity, obstruction of the tubal ostia, and alterations in the endometrium affecting embryo implantation and growth. Fibroids that distort the endometrial cavity impair fertility by creation of an abnormal site for placental implantation, increased risk of spontaneous abortions, preterm labor and delivery. Fig.shows various fibroids which will definitely cause infertility and/or abortions



However, because the incidence of fibroids increases with age, fertility declines with age, and many women with fibroids conceive spontaneously, it is difficult to assess the direct impact of fibroids on fertility. Ideally, to prove a relationship between fibroids and infertility, prospective randomized studies should be performed comparing women desiring pregnancy with and without myomas. One publication (Bulletti, 1999)3 compares spontaneous conception in infertile women with and without myomas in whom male factor and tubal factor infertility have been excluded. The authors found a significant difference ($P< 0.002$) in pregnancy rates between infertile women with and without myomas (11 versus 25%). It is the only prospective RCT to date. If it is to be believed, infertility women with myomas have better pregnancy rates after myomectomy (42%) than infertile women without myomas (25%), who in turn have better pregnancy rates than infertile women with untreated myomas (11%).

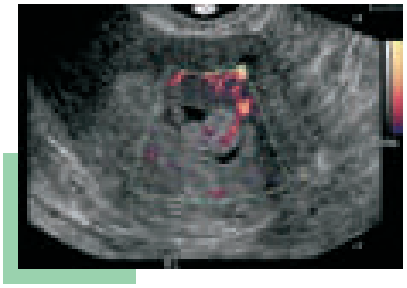
Fibroids and IVF

Another way to approach the issue is to assess the influence of fibroids on implantation rates. IVF provides a good model to assess this influence. Several studies have compared the results of IVF in women with untreated fibroids and without fibroids. Table 1 gives the pregnancy rates in women with fibroids distorting the cavity (9%), in women with fibroids not distorting the cavity (33.5%) and in a control group of women without fibroids (40%). It seems reasonable to conclude that

submucous and intramural fibroids distorting the uterine cavity impair implantation and pregnancy rates in women undergoing IVF. Figure shows the fibroids distorting cavity and these must be removed before any ART procedure is undertaken

The effect of medium and large intramural fibroids on fertility is less clear. A retrospective study showed that IVF live births were not improved by myomectomy. IVF "ongoing" pregnancy rates were 16.9% after myomectomy, 20.8% with fibroids diagnosed but not removed and 19% in "nonfibroid" controls. However, there was a 50% spontaneous abortion rate with fibroids compared to 34% after myomectomy in this study, possibly suggesting compromised pregnancy outcome in the presence of fibroids (Seoud , 1992)[4]. In a study evaluating the contribution of intramural fibroids on pregnancy rates, the pregnancy rate was significantly decreased only when intramural fibroids were 4 cm or larger. This group recommends removal of larger fibroids before IVF. (Oliveira et al, 2004)[5]

Myomectomy and fertility outcome in infertile patients: The favourable pregnancy rates obtained after myomectomy lead us to believe that myomas influence fertility. For submucous fibroids, transhysteroscopic removal using the resectoscope is the standard approach. Pregnancy rates in infertile women vary from 16.7 to 76.9%, with a mean value of 75%. (Donnez et al6, 1990; Valle, 19917; Vercellini et al 19998; Fernandez et al 20019).

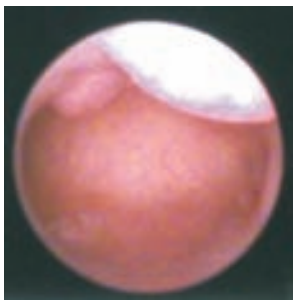


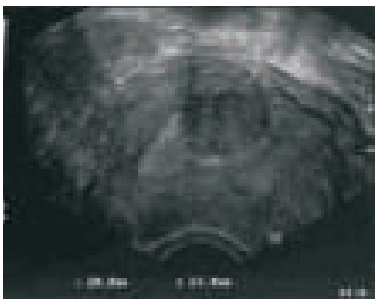
For intramural and subserous myomas, laparoscopic and abdominal removal can be considered. The pregnancy rates are similar with both techniques. Are there any indications that one of these two techniques should be preferred? The only randomized study by Seracchioli et al (2000)10 showed no statistically significant difference between the cumulative pregnancy rates after 2 years (41.75% in laparoscopic group v/s 47.07% in the laparotomy group). The myoma recurrence rate did not differ in the two groups (21.4 v/s 20.3%).

According to Li and Vercellini miscarriage rates are significantly reduced after myomectomy. (Li et al, 199911; Vercellini et al, 199912). Uterine scars are associated with a risk of placental implantation (acreta, increta, percreta, previa) and a risk of uterine rupture. Myomectomy may result in adhesion formation and a reduction in fertility. This aspect must be included in any counseling session prior to myomectomy. In the event of pregnancy after myomectomy, the need for cesarean section for delivery is controversial. Vaginal delivery may be attempted, however invasion of the myometrial cavity and extent of the myomectomy should be considered and obstetric plans individualized.

Conclusion: So the question remains: do fibroids influence fertility? A clear answer cannot be obtained at the present moment in the absence of appropriate prospective studies. Meanwhile every situation has to be judged separately and decision for myomectomy individualized. The literature does suggest that myomectomies may enhance fertility in certain settings. Submucous or intramural fibroids that distort the endometrial cavity regardless of the size or intramural fibroids larger than 4 cms regardless of the location appear to adversely

affect fertility and merit removal. Subserous fibroids unless larger than 7 cms do not require removal.





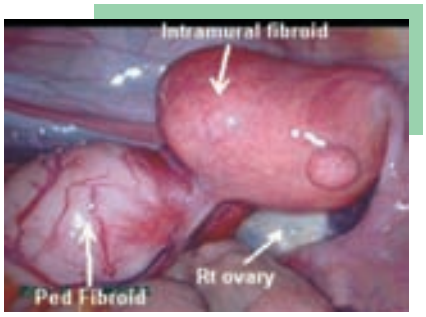


Table I. Pregnancy rate (PR) in women with fibroids distorting the cavity, in women with fibroids not distorting the cavity and in a control group (women without fibroids).

	Distorted cavity		Non-distorted cavity		Controls	
	PR%	n	PR%	n	PR%	n
Eldgar-Geva et al, 1998 93/318	10	1/10	16.4	9/55	30	
Stovall et al, 1998	37	34/91	53	48/91		
Farhi et al 1995 32/127	9	5/55	29	25/88	25	
Jun et al	30.5	43/141	41.6	169/406		

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Dr. Pranay Shah
Phone: 09820060177
Email: drpranay@hotmail.com

Dr. Narendra Malhotra

Endometriosis
-every infertility specialists nightmare

Dr. Nandita Palshetkar
Mumbai

INTRODUCTION

The term endometriosis refers to a benign and common disease in which cells like the ones that line the inside of the womb (endometrium) are established outside the womb e.g. on the ligament supporting the uterus. in the ovaries, tubes, pelvis, bowels, bladder, etc. In patients with endometriosis, these cells, like the When the woman with endometriosis menstruates, the endometrium is shed in the form of a period, the endometriosis breaks down in the same way but because these cells are trapped inside, and cannot escape, they form swellings filled with dark blood (known as chocolate cysts) and induces chronic inflammatory reaction and adhesions which may damage the tubes.

Endometriosis tends to occur in women who are in their 30s and early 40s, but occasionally occurs in those under 30 years of age.

Some patients with endometriosis may have no symptoms; some may experience considerable pain during their periods or during intercourse and their periods tend to be heavy.

In vaginal examination their may be tenderness and thickening. Ovarian cysts may also be felt.

The majority of women with mild endometriosis are fertile. However, some women may experience difficulty becoming pregnant.

How does endometriosis cause infertility?

The anatomical distortion caused by endometriosis, could explain a mechanical cause of infertility.

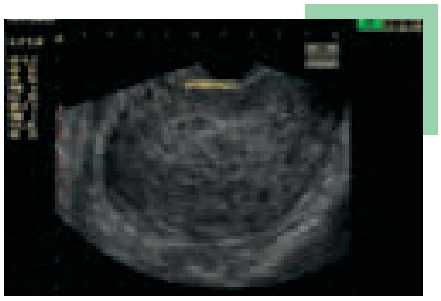
Altered peritoneal function due to increased volume of fluid, macrophages, prostaglandins, interleukin-1, tumor necrosis factor and proteases. These changes adversely affect the egg development, sperm, fertilization, tubal function .

Furthermore altered IgG & IgA antibodies and lymphocytes may be increased in endometrium of these patients thus interfering with implantation.

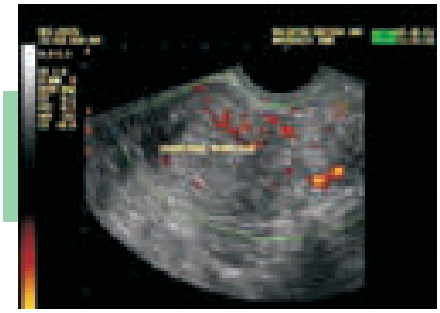
DIAGNOSIS:

The only means of diagnosis of endometriosis is by laparoscopy, which assesses the severity of endometriosis and the condition of the Fallopian tubes. There are a number of different classification systems for endometriosis, but the most widely used is that of the American Society for Reproductive medicine (ASRM) in which endometriosis is classified into four stages: minimal, mild, moderate and severe.

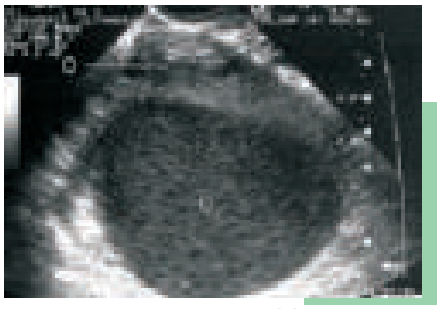
Ultrasound scans, CAT scans, or MRI scans, can identify cysts on the ovaries.



2D Image of Adenomyosis



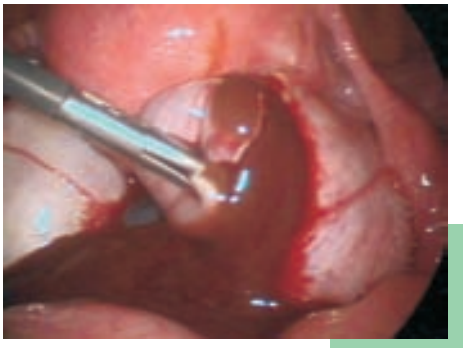
Adenomyosis on colour flow imaging



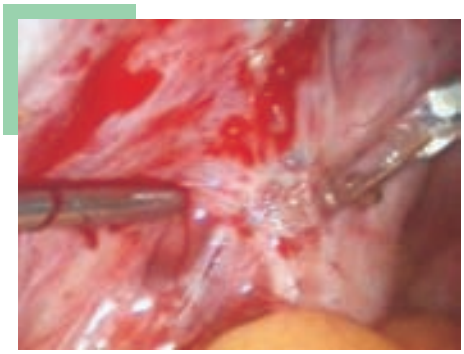
Endometriouma of Ovary

Laproscopy:

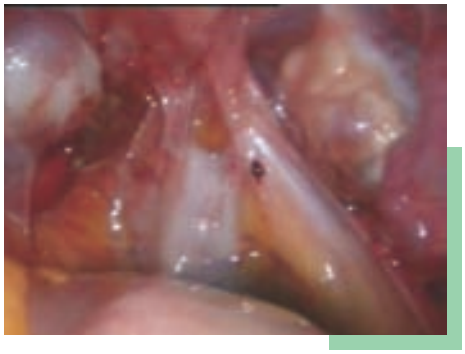
A study by Sarram M, 200 consecutive routine diagnostic laparoscopies, 31 cases (15.5%) of endometriosis were found. Of these 200 cases, 131 patients (65.5%) were of infertility. In 22 (71.0%) out of 31 patients with endometriosis infertility was the indication for laparoscopy. Half of the patients with endometriosis showed moderate or severe degrees of the disease. Seventy-one percent of the patients were below the age of 29. So laproscopy as a diagnostic procedure is mandatory in endometriosis.



right ovarian chocolate cyst



Peritoneal endometriotic implants



Rectovaginal Endometriosis

CAUSES:

The most widely accepted explanation for endometriosis is that viable cells from the lining of the womb pass upwards into the Fallopian tube and out into the pelvic cavity where they settle down. In most women these cells will be destroyed by the woman's immune system. However, in some women, these cells implant and proliferate, possibly due to a disorder of the womans' immune system.

Endometriosis has been associated with corpus luteum inadequacy and abnormalities of luteal phase progesterone (P) secretion. In a study conducted by Ayers et al , abnormal luteolysis, as a second factor of luteal dysfunction, was assessed in 13 women with endometriosis and 25 control patients by measurement of ovarian vein estradiol (E2) and P during the follicular phase. The results reveal that women with endometriosis have (1) significantly lower ovarian vein E2, (2) significantly higher both peripheral and ovarian vein P, and (3) threefold higher P/E2 ratios than controls during the follicular phase.

Data Support the continued P production from an active corpus luteum into following cycle. Failure of adequate luteolysis is a second aspect of luteal dysfunction in endometriosis and strongly supports the growing body of data confirming ovulatory asynchrony in the minimal; endometriosis infertility syndrome. (Fertil Steril. 1987 Jun;47(6):925-9.)

TREATMENT OF ENDOMETRIOTIC LESIONS (ESHRE)

Hormonal treatment

A	Suppression of ovarian function to improve fertility in minimal-mild endometriosis is not effective and should not be offered for this indication alone (Hughes et al., 2003).	Evidence Level 1a

Surgical treatment

A	Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal-mild endometriosis is effective (Jacobson et al., 2002).	Evidence Level 1a

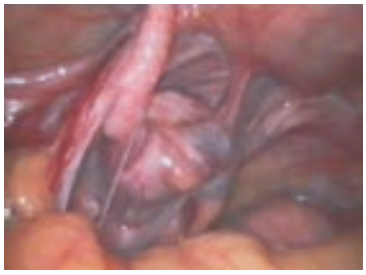
The recommendation is based on a systematic review and meta-analysis of two, similar but contradictory RCTs. In the other, larger study (Marcoux et al., 1997) there was a significantly higher monthly fecundity rate in the treated compared to the control group.

When endometriosis causes mechanical distortion of the pelvis, surgery should be performed. There seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis. However, studies can not easily be compared as the surgical procedures; extent of surgery, skill of the surgeon has certainly not been standardized. No randomized controlled trials or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances the pregnancy.

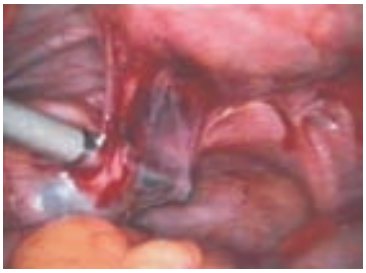
There is no consensus on the treatment of ovarian endometriosis cysts in women with subfertility. The presence of an endometriotic cyst in women undergoing IUI or IVF supposedly has a negative influence on the results of these treatments, (Olivennes et al., 1995; Arici et al., 1996). The advantage of surgically treating a cyst before IVF or IUI is the acquisition of a histological diagnosis. A disadvantage is the loss of ovarian tissue containing follicles close to the cyst.

it is difficult to decide which type of surgical treatment would be the most appropriate for ovarian endometriosis: fenestration and drainage, fenestration, drainage and coagulation of the cystic wall, or cystectomy (Fayez et al., 1988; Fayez and Vogel, 1991; Hemmings et al., 1998; Saleh and Tulandi, 1999). Fenestration and drainage does not seem to be sufficient, although no randomised

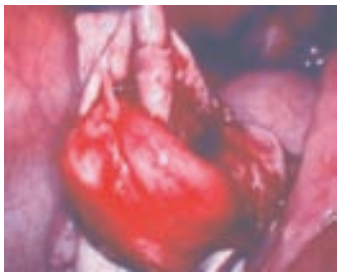
B	Based upon three studies (Adamson et al., 1993; Guzick et al., 1997; Osuga et al., 2002) there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was only reached in one study (Osuga et al., 2002).	Evidence Level 3
A	Laparoscopic cystectomy for ovarian endometriomas > 4 cm diameter improves fertility compared to drainage and coagulation. Coagulation or laser vaporization of endometriosis without excision of the pseudo-capsule is associated with a significantly increased risk of cyst recurrence.	Evidence Level 1b



Adhesions due to endometriosis



Adhesiolysis



Ovarian Cystectomy

study has been performed (Saleh and Tulandi, 1999). A prospective randomised trial compared cystectomy with bipolar coagulation of the cyst wall using recurrence and pregnancy figures as endpoints of the study: cystectomy was shown to be the better treatment for both endpoints (Beretta et al., 1998).

COH and IUI in stage 1/2 endometriosis

Several studies have shown that superovulation with CC or Gn when combined with IUI give superior results.in these studies several parameters have been compared e.g. coh with planned cycles,natural cyles with iui or no treatment at all. (1,2,3,4,5).

If the tubo ovarian anatomy is restored and patient is young then IUI may play a role.

Assisted Reproductive Technology

Infertile women with stage3/4disease syrgery is the first choice of therapy (6). For infertile women who have had one or more operations IVF-ETis the best answer..in one retrospective trial 23 women with stage3/4endometriosis underwent IVF-ET and 18 women underwent repeat surgery (5) . the pregnancy rate after 2 cycles of IVF-ET was 70%, wheras the cumulative pregnancy rate was 25%within 9 mths of repeat surgery.if initial surgery fails to restore fertility in patients with moderate to severe endometriosis ,IVF-ET is an effective alternate.

Ovulation induction and endometriosis

Case reports have shown that repeated COH during IVF may stimulate the growth of endometriotic lesions (7, 8)

Hoogie et al did a retrospective cohort study in which he tested the hypothesis that the gumulative endometriosis recurrence rate (CERR)after fertility surgery for stage 3&4 is increased in women exposed to very high e2 levels during COH for IVFwhen compared with a control group of women exposed to less high e2 levels during COH IUI(9).

Recurrent endometriosis

It is known that recurrence after surgery can be explained by incomplete surgery, persistence and growth of microscopic endometriosis, the development of new lesions, non-conception after treatment or a combination of these factors.

Other Studies:

Just recently, results of a study conducted in Japan at the Kanazawa University School of Medicine where released. From the study it was discovered that Pycnogenol, a chemical found in the pine trees that grow along French coastal regions, can significantly reduce the signs of endometriosis by as much as 33%.

In the upcoming edition of the Journal of Reproductive Medicine the clinical trial involved an extensive study of 58 women suffering endometriosis. The women were given either the conventional treatment (using Gn-RHA gonadotropin-releasing hormone agents) or an alternative treatment using Pycnogenol within a trial period of 48 weeks.

During the initial stage of the study, both groups had not shown improvement of their condition but within four weeks, they experienced some improvement with those taking Pycnogenol experiencing slow but yet steady relief, while those taking Gn-RHa experiencing faster alleviation.

However, after the 24-week mark, the Gn-RHa group exhibited significant relapse of the symptoms while their Pycnogenol-taking counterparts continued to improve.

SUMMARY OF MANAGEMENT OPTIONS

1. Age, duration of infertility, family history, pelvicpain and stage of endometriosis should be considered before treatment.
2. Laproscopy treat grade 1/2 endometriosis.
3. Expectant management or COU-IUI for grade 1/2.
4. Older pt. treated with COH-IUI or IVF-ET.
5. Conservative surgery for grade 3/4 disease.
6. grade 3/4disease with advance age and failed surgical treatment-IVF-ET should be offered
7. Women with recurrent endometriosis IVF-ET is an effective alternative

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Dr. Nandita Palshetkar
Phone: 9820032315
Email: nanditapalshetkar@hotmail.com

Dr. Gordon Baker
Australia

Managing Male Partner in present Era

INTRODUCTION

Role and importance of the male in infertility

Approximately one third of infertility is caused by female factors, one third by male factors and one third by factors in both partners. The advent of intracytoplasmic sperm injection (ICSI) has altered the approach to management of male infertility. Previously a decision was needed whether to continue attempts at natural conception or use in vitro fertilisation with the male partner's or accept donor insemination. Now donor sperm is usually only needed if no live sperm or elongated spermatids are produced by the patient. Progress has also produced tests for genetic conditions such as cystic fibrosis and evidence based medicine indicates traditional treatments such as varicocelectomy lack proof of efficacy in improving fertility.

Management Options: Males suspected to be infertile should have a detailed medical history and physical examination. Semen analysis is the main investigation. Unless the clinical picture is clear, several semen analyses need to be done because of the day-to-day variability. Measurement of gonadotrophin and testosterone levels is helpful in distinguishing primary from secondary testicular failure. Testis biopsies are useful for confirming obstructive azoospermia and determining the type of spermatogenic defect with primary seminiferous tubule disorders. Other investigations: karyotype, genetic tests for Yq microdeletions, cystic fibrosis gene screening, imaging for pituitary tumour or ejaculatory duct obstruction, are performed where indicated. A number of conditions are untreatable and cause sterility, in particular primary spermatogenic disorders where no live sperm are produced. These patients need to consider other alternatives for having a family by donor insemination or adoption. Over the last 15 years it has become clear that sperm or elongated spermatids that can be used for ICSI may be found in a proportion of patients with severe testicular disorders such as Klinefelter syndrome and Sertoli cell only syndrome, either in the semen or in testis biopsy specimens. Conditions that may be treatable to increase the chances of natural conception include: gonadotropin deficiency or suppression, sperm autoimmunity, genital tract obstruction and reversible toxin exposures or illness effects and some coital disorders. However ICSI is often a better alternative for conditions such as sperm autoimmunity. The remaining patients have less severe abnormalities of the semen, ranging from oligospermia to normal standard semen analyses but defective sperm function. These patients may have varicoceles, features of low-grade genital tract inflammation,

increased abnormal DNA in the sperm and increased production of reactive oxygen species by their sperm. There are no good controlled trials that prove treatment of these problems will increase natural conception rates. These patients are subfertile rather than sterile and pregnancies may occur but at lower than normal rates. Infrequent or mistimed coitus and female factors such as ovulatory disorders may be contributing. Thus the male and female partners should be treated as a couple and reversible factors treated where possible. The estimation of prognosis for natural conception is also important. If this is low, ICSI is usually effective. Pregnancy rates depend on female age and with a few possible exceptions such as increased chromosomal abnormalities and low birth weight, the birth outcomes are similar to those in the general community.

VARICOCELE LIGATION :

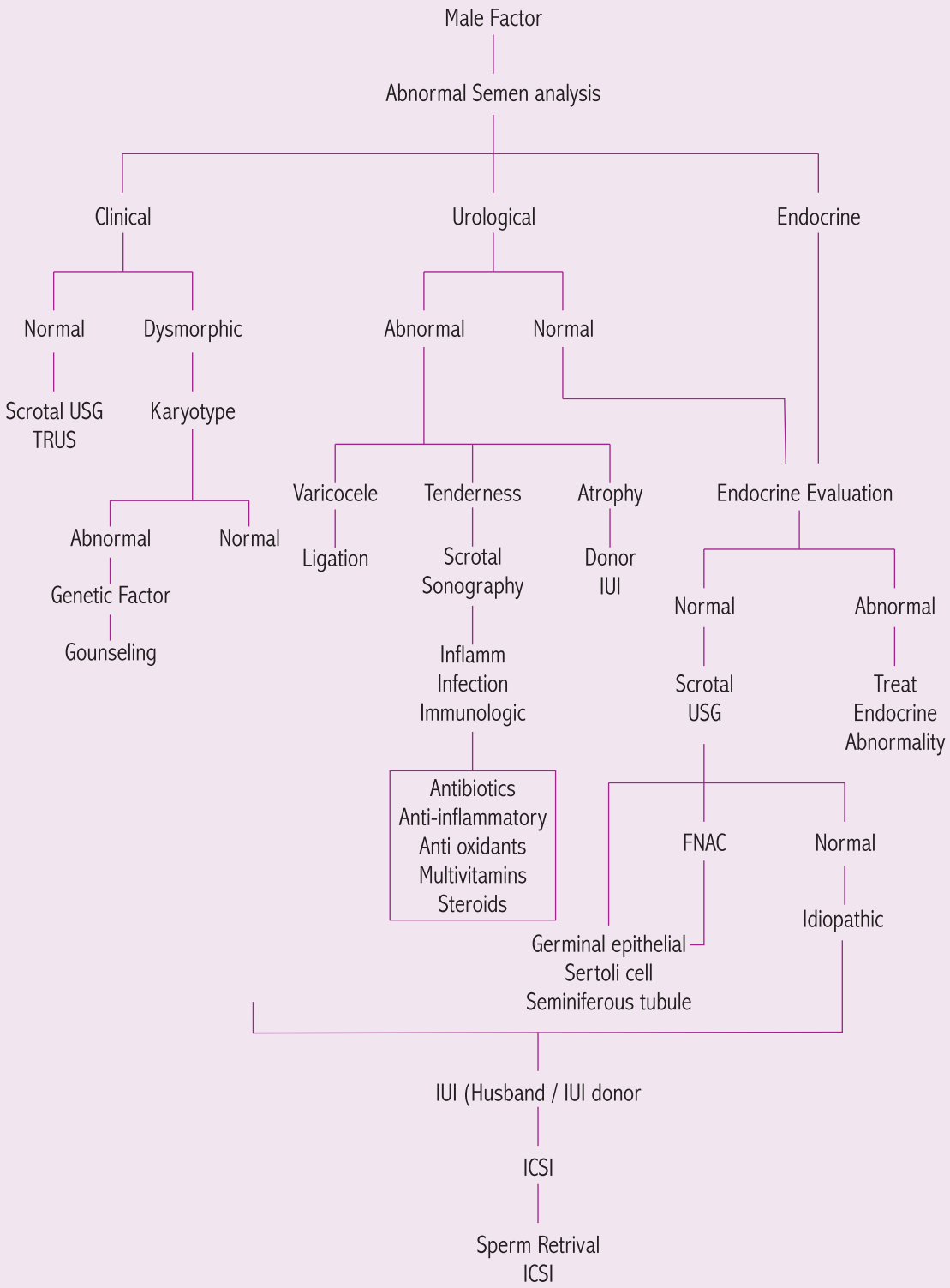
Indications for treatment of a varicocele

1. a varicocele is palpable
2. the couple has documented infertility
3. the female has normal fertility or potentially correctable infertility
4. the male partner has one or more abnormal semen parameters or sperm function test results.

AUA Best Practice Policy & ASRM - Practice Committee Report.

HWG Baker
Phone: 61 3 9344 2130 Direct: 61 3 9344 2620 Fax: 61 3 9347 1761
email: g.baker@unimelb.edu.au

MANAGEMENT: MALE FACTOR



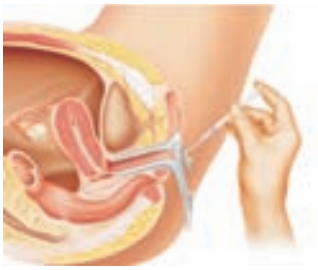
Basics of Assisted Reproductive Techniques

Dr. Sujal Munshi
Ahmedabad

Assisted reproduction

The collective name for treatments designed to lead to conception by means other than sexual intercourse. Assisted reproduction techniques include intrauterine insemination, in vitro fertilisation, intracytoplasmic sperm injection and donor insemination

Artificial Insemination including Intra vaginal, intra cervical and Intra uterine insemination is considered to be a well established and basic assisted reproductive technique.



Intrauterine insemination: Placement of prepared wash semen into the uterus of a woman.

Indications:

* Male Factor Fertility Problems including oligozoospermia & erectile dysfunction where IUI is associated with increased pregnancy rates per cycle in both natural cycles and induced cycles.
* Unexplained fertility problems
* Endometriosis (generally minimal-mild).

Basic Steps

* Induction of Ovulation if required
* Ovulation monitoring with ultra sonography
* Ovulation trigger with injectable hcg if required.
* Intra uterine insemination of washed/prepared semen sample.

Success rate varies from 8-14 % /cycle depending upon age and other factors for subfertility.

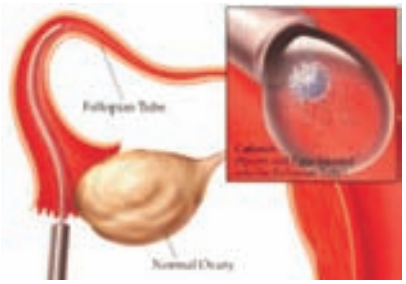
Donor insemination The placement of donor sperm into the vagina, cervix or womb.

Donor insemination is considered in following conditions:

* obstructive azoospermia
* nonobstructive azoospermia
* infectious disease in the male partner (such as HIV)
* severe rhesus isoimmunisation
* severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection. (ICSI)

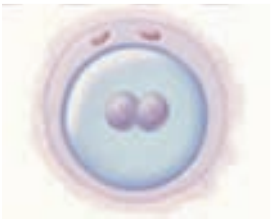
Donor insemination should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring. Until ICSI became available, the main technique for treating male factor infertility where azoospermia or severe abnormalities of semen quality were present was insemination with donated sperm.

Gamete intrafallopian transfer (GIFT) A procedure in which eggs are retieved from a woman, mixed with sperm and immediately replaced in one or other of the woman's fallopian tubes so that they fertilise inside the body



GIFT is not now widely used because of the need for a laparoscopy. It has been most commonly used in the management of people with unexplained male factor fertility problems, and where transcervical embryo transfer is impossible.

Zygote intrafallopian transfer (ZIFT) A process in which eggs are fertilised outside the body and then transferred into the fallopian tubes.



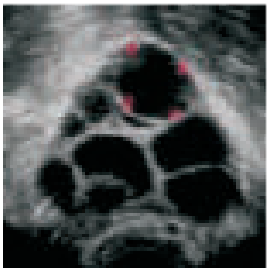
ZIFT is a technique that is not widely practised; it has been developed alongside IVF using much of the same technology.

In vitro fertilisation (IVF) A technique whereby eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually, upto three resulting embryos are then transferred to the womb with the aim of starting a pregnancy.

The first IVF pregnancy was achieved in 1978. Since then, the number of IVF centers and IVF procedures performed has increased dramatically.

Procedures involved in IVF treatment are:

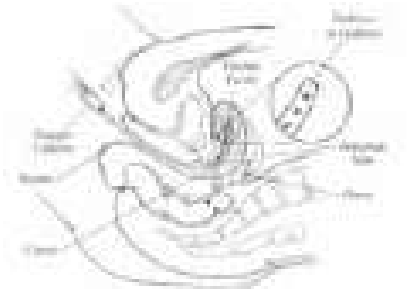
* pituitary downregulation: switching off the natural ovulatory cycle to facilitate controlled ovarian stimulation.
* ovarian stimulation: administration of gonadotrophins to encourage the development of several follicles followed by administration of hCG to mature eggs ready for collection



* egg collection followed by semen production or sperm recovery

* IVF: fertilization of the eggs in the laboratory with prepared sperms.

* transfer of resulting embryos to the uterus



* luteal support: administration of hormones to aid implantation of the embryos.

The recognised indications for in vitro fertilisation treatment include:

* male factor fertility problems where medical/surgical management and intrauterine insemination have not resulted in a live birth or are judged to be inappropriate
* tubal disease where tubal surgery has not resulted in a live birth or is judged to be inappropriate
* endometriosis where surgery and IUI have not resulted in a live birth or are judged to be inappropriate
* unexplained fertility problems of three years' duration where medical management and IUI have not resulted in a live birth or are judged to be inappropriate
* failure of spermatogenesis caused by prior treatment for cancer where cryopreserved semen is unsuitable for IUI
* ovarian failure caused by prior treatment for cancer where eggs or embryos have been cryopreserved
* a requirement for egg donation.

In addition, female age should be considered when determining the timescale over which other treatments should be explored before proceeding to in vitro fertilisation treatment.

According to Indian National ART Registry survey Pregnancy rate / Embryo transfer varies from 27.55%(2001) - 34.2(2005) % with a abortion rate of 5.39 % - 19.9 % and Ectopic Pregnancy rate of .67 % to 2.9 % respectively.

Society of Reproductive Technology USA 2005 results of IVF cycles.

Fresh Embryos From Non-Donor Oocytes	<35	35-37	38-40	41-42
Percentage of cycles resulting in pregnancies	42.8	35.5	26.7	17.5
Percentage of cycles resulting in live births	37.1	29.2	19.7	10.6

Micromanipulation :

Intracytoplasmic sperm injection: Fertilization of the eggs by injection of a single sperm under magnification using the micro manipulator.

The recognised indications for treatment by ICSI include:

* severe deficits in semen quality
* obstructive azoospermia
* nonobstructive azoospermia.

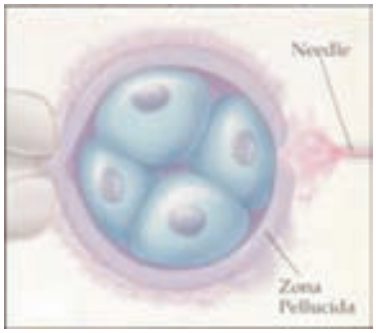
In addition, treatment by intracytoplasmic sperm injection should be considered for couples in whom a previous in vitro fertilisation treatment cycle has resulted in failed or very poor fertilisation.

Intracytoplasmic sperm injection improves fertilisation rates compared to in vitro fertilisation alone, but once fertilisation is achieved the pregnancy rate is no better than with in vitro fertilization.

The potential transmission of a genetic abnormality is a possibility when ICSI is performed. The normal barrier for morphologically abnormal sperm that tend to have genetic abnormalities (ie, zonal pellucida) is bypassed with ICSI. Approximately 10% of sperm from healthy men have chromosomal abnormalities. Men who are infertile have a 5-7% chance of having a chromosomal abnormality. Chromosomal abnormalities include microdeletions of the long arm of the Y chromosome in areas AZFa, AZFb, and AZFc (DAZ or deleted in azoospermia region). These deletions can be passed on to male offspring, with resulting oligospermia. The risk of having a child with a birth defect from ART with ICSI goes from a normal baseline of 3% to, at most, 4%.

Assisted hatching:

Assisted hatching has been proposed as a method to disrupt the zona pellucida, which may facilitate and enhance implantation and pregnancy rates. Based on current evidences assisted hatching might be suggested for women aged over 38 years, those with elevated day-three serum FSH and repeated IVF failures.

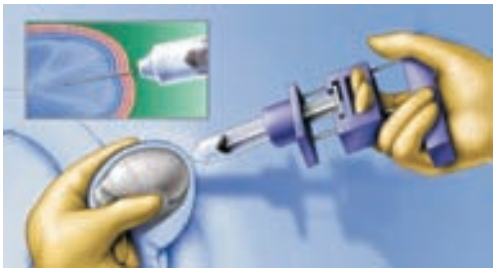


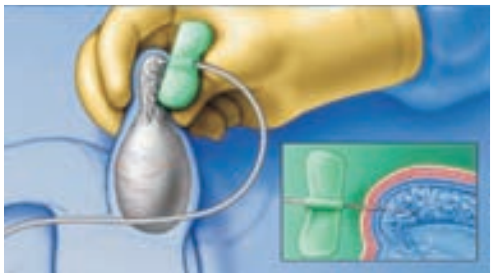
Sperm recovery

Spermatozoa can be retrieved from both the epididymis and the testis using a variety of techniques with the intention of achieving pregnancies for couples where the male partner has obstructive or nonobstructive azoospermia. Sperm recovery is also used in ejaculatory failure and where only non-motile spermatozoa are present in the ejaculate.

Surgical techniques for sperm retrieval from the epididymis or the testis include:

* percutaneous epididymal sperm aspiration (PESA)
* testicular sperm aspiration (TESA) / testicular fine needle aspiration (TEFNA)
* testicular sperm extraction (TESE) from a testicular biopsy
* microsurgical epididymal sperm aspiration (MESA).





In obstructive azoospermia, sperm can usually be obtained from the epididymis (PESA or MESA)and from the testis (TESA or TESE). In some men, sperm can be recovered from naturally occurring spermatoceles by percutaneous puncture.

In nonobstructive azoospermia, sperm needs to be obtained directly from the testis by aspiration (TESA) or biopsy (TESE). The chance of finding sperm is reduced. PESA and TESA can be performed under local anaesthesia in an outpatient clinic. PESA does not jeopardise future epididymal sperm retrieval

Oocyte donation The process by which a fertile woman donates her eggs to be used in the treatment of others or for research.

The use of donor oocytes is considered in problems associated with the following conditions:

* premature ovarian failure
* gonadal dysgenesis including Turner syndrome
* bilateral oophorectomy
* ovarian failure following chemotherapy or radiotherapy
* certain cases of in vitro fertilisation treatment failure.
* Transmissible genetic disease in female.

Cryopreservation

* Men and adolescent boys preparing for medical treatment that is likely to make them infertile should be offered semen cryostorage .
* Women preparing for medical treatment that is likely to make them infertile should be offered oocyte or embryo cryostorage as appropriate if they are well enough to undergo ovarian stimulation and egg collection, provided that this will not worsen their condition and that sufficient time is available.

Frozen embryo treatment cycles

Embryo cryopreservation allows any supernumerary embryos arising from the initial egg collection and fertilisation to be stored for some time before a subsequent attempt at replacement either because the fresh embryo transfer has not resulted in a live birth or because further children are desired. The ability to preserve embryos routinely has the added benefits of increasing the number of potential embryo replacement cycles without additional egg retrievals thereby improving the overall pregnancy rate and decreasing the risk to the patient of OHSS by substituting frozen-thawed embryo transfer in unstimulated cycles. Embryo quality has the most significant impact on post-thaw survival. Methods of embryo freezing, protocols for post-thawing embryo selection and culture conditions may affect outcome.

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Dr. Sujal Munshi
Phone: 9825037000
Email: sujalmunshi@gmail.com

Unexplained Infertility:
Challenges in Management

Dr. Abha Majumdar
New Delhi

The term unexplained infertility is applied to a couple that has failed to establish a pregnancy despite standard evaluation uncovering no obvious reason for infertility or after correction of factors recognized as probably responsible for infertility. What constitutes a standard evaluation is debatable. However, most experts agree for the female partner it includes a history, examination, assessment of ovulation, hysterosalpingogram (HSG) and often laparoscopy. For the male partner, evaluation usually includes a history, examination, and semen analysis.

Various studies reported that 0-26% of infertile couples have unexplained infertility. The incidence is inversely related to the knowledge of infertility, diagnostic tests applied and intensity of the effort to find a specific cause. There are limitations to our ability to evaluate human fertility. For example for each of the tests mentioned above there are limitations to how far they can evaluate the cause.

- Ovulation: Ovulation is assessed by history of regular periods, urine LH testing, serial ultrasounds and progesterone levels, all of which provide only indirect evidence of egg release, very little information about egg quality and no information about egg pickup at all.
- Pelvis: A normal HSG indicates normal uterine cavity and patent tubes. However, HSG is usually unable to detect filmy adhesions involving the tubes and ovaries or minimal endometriosis, which can have significant impact on a woman's fertility and can be detected by laparoscopy. However, neither method guarantees detection of function of the fallopian tubes. In fact, even the tubes of a fertile woman do not pick up every egg that is released. Capturing the egg is only one of many critical functions of the tube, the others being, transportation of the egg and sperms, nurturing of the developing pre-embryo and transporting it to the uterus where implantation occurs.
- Sperm: Fertilization results from the union of only one sperm and one egg, yet the average ejaculate contain over 20 million motile sperm per cc. It is even unlikely that intrauterine insemination (IUI) will result in conception if less than 1 million motile sperm are placed in the uterus. Semen analysis evaluates numbers, movement, and the appearance of the sperm. Various specialized tests are used to assess sperm function. Again, like with assessment of ovulation, unless conception occurs or one witness's fertilization as with IVF, the functionality of sperm is an assumption.
- Age: Women deferring pregnancy until their mid to late 30's have difficulty conceiving as age is known to affect egg and therefore embryo quality negatively, reducing the likelihood of fertilization and implantation. Ovarian reserve can be assessed by a number of tests, of which the most popular is cycle day 3 FSH and E2 level.

Fecundity in unexplained infertility: Studies have estimated that a young couple has about a 20% chance of conceiving per month for the first 3 months of trying. This decreases to

about 10% if conception has not occurred by months 9-121. Early on, couples with unexplained infertility may experience spontaneous conceptions. However, couples with unexplained infertility of greater than 3 years duration have a spontaneous conception rate of only 1-2% per month.

Putative causes of unexplained infertility

- Ovulatory dysfunction
- Sub-clinical infection leading to tubal dysfunction
- Minimal to mild endometriosis
- Sperm dysfunction
- Immunological problems
- Sub-clinical pregnancy loss
- Psychological factors

Empirical medical intervention: Because treatment is not specific to a particular cause as the infertility is "unexplained" it is called empirical. In 1998 a retrospective analysis of 45 studies on unexplained infertility was published2. Without treatment, the monthly chance of conception was estimated to be about 2% (1.3-4.1%). Treatment with intrauterine insemination (IUI) alone did not raise this conception rate significantly (3.8%). Treatment of unexplained infertility with Clomiphene citrate or letrozole plus IUI increased chance of conception per cycle 2-3 fold (from 2% to 8.3%). Treatment with gonadotropin injections plus IUI raised the conception rate even further to 17% per treatment cycle. Lastly, IVF conception rates for unexplained infertility are typically among a center's highest, usually at least 40 to 50% with the transfer of two embryos. IVF allows assessment of egg and embryo quality and the fertilization capability of the sperm. If egg quality is poor, these women may be candidates for donor egg program.

Surgical intervention: Removal of ovarian or para-ovarian cysts or flimsy adhesions from ovaries & tubes may improve the tubo-ovarian relationship resulting in better fimbrial pickup and release of oocytes. Surgical ablation of endometriotic patches improves the chance of conception by 1 in 9 as compared to none in no ablation group by possibly changing the immunological milieu.

Why does empirical treatment work? Fertility drugs may correct unrecognized defects of ovulation or hormone production. Intrauterine insemination places a much larger number of sperm into the upper uterine cavity so that a greater number of capable sperm may reach the egg and overcome issues of chance. Increasing the number of eggs released further enhances fertility in a given cycle. If a woman's tubes never pick up an egg, IVF will be needed to achieve conception. If a man's sperm is unable to fertilize his partner's eggs, IVF often with intra-cytoplasmic sperm injection will be needed. Empirical treatment of unexplained infertility is often very successful.

Thus, there are literally hundreds of molecular and biochemical events that have to function properly in order to have a pregnancy develop. The standard tests for infertility barely scratch the surface and are really only looking for very obvious factors, such as blocked tubes, abnormal sperm counts, ovulation etc. These tests do not address the molecular issues at all. That is still for the future...

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Dr. Abha Majumdar

Phone: 011-28742454, 09810315807

Email abhamajumdar@hotmail.com

The future of Infertility treatment

Dr. Bruno Lunenfeld
Israel

INTRODUCTION:

The " conquest of infertility" is an incredible achievement, it is a victory of human will, endurance and technology. However, continuously new challenges are arising in relation to scientific, ethical and humanitarian aspects in infertility management . How do we use current and evolving technologies to allow parents to achieve the joy of having children with dignity, to make treatment available to all, secure universal reimbursement and to increase short and long term safety and decrease any adverse impact on the health of both mother and child. These are formidable goals and in order to reach them a constant battle for obtaining new detailed information regarding physiology ofd devising new efficient treatment methods must be pitched. The ethical, socio-political and economic problems related to these goals must not be underestimated. They have to be discussed, taken into consideration and dealt with. In the near future, we should expect significant advances in reproductive basic and applied research, diagnostic tools, in the clinical management of infertility and in drug development.. The pace at which advances are made often seems to exceed our ability to incorporate them in our life styles. Nearly every new advance brings a host of new ethical, social or even political changes with it. We must remember that society can not survive without biotechnology and at the same time can not survive its unethical use. Therefore the hopes of accumulating and applying the information needed to advance to the next phase of technological evolution in reproductive medicine must also be amalgamated with clear guarding directives. What sort of ethics do we need to connect scientific progress to a future which is not only human but humane. Let us direct our action, including, indeed above all, our scientific actions in such a way that we aim at a humane world, and not conduct unreflected experiments either on ourselves or on the world of our creation

Pharmacological agents for the managemnet of infertility treatment:

The concept of ovarian stimulation was first introduced almost 100 years ago. At this time, radiation of the pituitary and ovarian region was the preferred treatment. It was only some decades later that the problem of radiation-induced cancer emerged. Non-human gonadotrophins, such as pregnant mare serum gonadotrophin (PMSG), were then used for ovarian stimulation. However, use of PMSG lead to antibody formation, and had to be withdrawn. Following the withdrawal of PMSG, human pituitary gonadotrophins (HPG) and urinary menopausal gonadotrophins hMG) appeared on the market. HPG produced good results, but its use came to an end in the late 1980s when it was linked to the development of Jacob-Creutzfeld disease. HMG preparations containing a high percentage of unknown urinary proteins, making quality control almost impossible were then the only gonadotrophins

remaining on the market. With the availability of hMG, Clomiphene citrate, Ergot derivatives and GnRH, algorithms were developed for their optimal utilization and were used for the next three decades. The introduction of recombinant gonadotrophins with more then 99% purity, produced from transfected mammalian cell lines gradually replaced hMG preparations world wide. The next challenge was to improve the calibration process from the traditional in vivo bioassay, with a large range of variability (80-125%) to the measurement of the gonadotrophin content through size-exclusion high-performance liquid chromatography. Filling gonadotrophins by mass units with a variability of <3% significantly improved reliability, predictability and batch to batch consistency of gonadotrophin preparations which are key elements to avoid unexpected over-dosing or delivering a sub-optimal dose. The steady improvements in gonadotrophin preparations are demonstrated in Fig 1 and Fig 2 shows the developoment of pharmacological agents in the conquest of infertility.

Fig 1 Steady improvements in gonadotrophin preparations

Period	Product	Quality and consistency	Patient convenience
1930s	Pregnant mare serum	Immunogenicity"Limited efficacy	Pain and local side-effects
1950s	Human pituitary FSH	Low purity"Inconsistency"Limited availability	Safety"Risk of varient Creutzfeldt–Jakob disease (vCJD)
1960s	u-hMG	Low purity Inconsistency, Protein contaminants	Intramuscular injections Local reactions
1980s	Separation of FSH from hMG	Low purity Inconsistency, Protein contaminants	Intramuscular injections Local reactions
1990s	Highly purified u-FSH	High specific activity Low LH content, Low protein contaminants	Subcutaneous injections
1995	r-hFSH	Highly purified, Unlimited and consistent source Extensively characterized Controlled safety	Subcutaneous injections Multidose Pen
2003	r-hFSH FbM	Consistent and reproducible characteristics and specific activity enabled transition from IU to mass	Consistent ovarian response

1. Lunenfeld. Hum Reprod Update 2004;10:453–67 2. Bassett et al. Reprod Biomed Online 2005;10:117–118

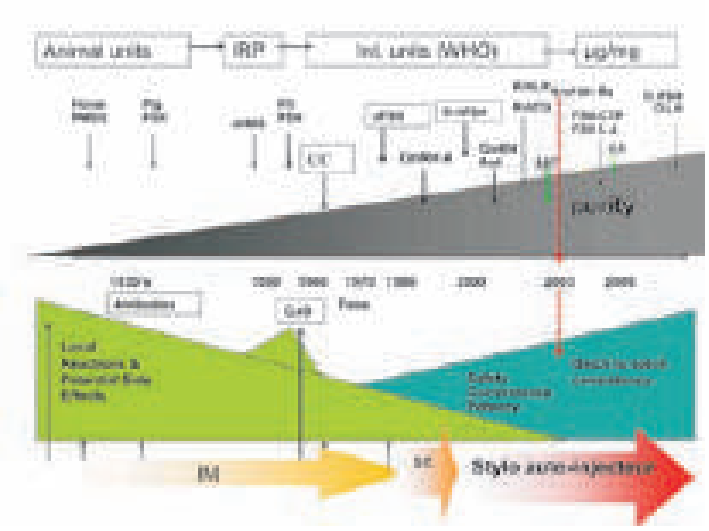


Fig 2

New pharmacological agents for ovarian stimulation protocols are appearing in the market. Aromatase inhibitors may replace Clomiphene citrate and Metformin may improve the treatments of PCOD patients with insulin resistance. The completion of the Human Genome Project and the wide diffusion of Pharmacogenomics (PGx.) may predict efficacy, safety as well as the probability of response to drugs. With this methodology and high quality pharmaceuticals it will be possible to design algorithms for patients tailored treatments. These will take into account the pathogenesis of the specific disorder ,genetic factors e.g. polymorphisms non-modifiable factors like age , relatively modifiable factors , like body mass and life habits to decide on the protocol and product to be used, the initial dose to be applied , monitoring and dose adjustment.

Future developments

Protein engineering offers an approach for expanding the range of recombinant gonadotrophins available for infertile women. Using today's medications, daily injections of FSH are necessary for effective ovarian follicle stimulation; for the future, new FSH molecules may be developed that are engineered to possess an extended half-life and duration of therapeutic action. Such molecules will enable the physician to provide single injections to drive follicle growth for up to a week, in a controlled and predictable fashion.

Recombinant DNA technology permits the design of potent therapeutically active gonadotrophin agonists and antagonists by altering key proteins and carbohydrate regions in the alpha and beta sub-units of FSH and LH. FSH has a relatively short half-life, and HCG has a relatively long half-life. The long half-life of HCG is in part due to the presence of 4 serine O-linked oligosacharides attached to an extended hydrophilic carboxyterminus. Site-directed mutagenesis and gene transfer techniques made it possible to fuse the carboxyterminal extension of HCG beta (CTP) to the 3'end of the FSH coding sequence. (Fig 3) The recombinant FSH-CTP fusion protein

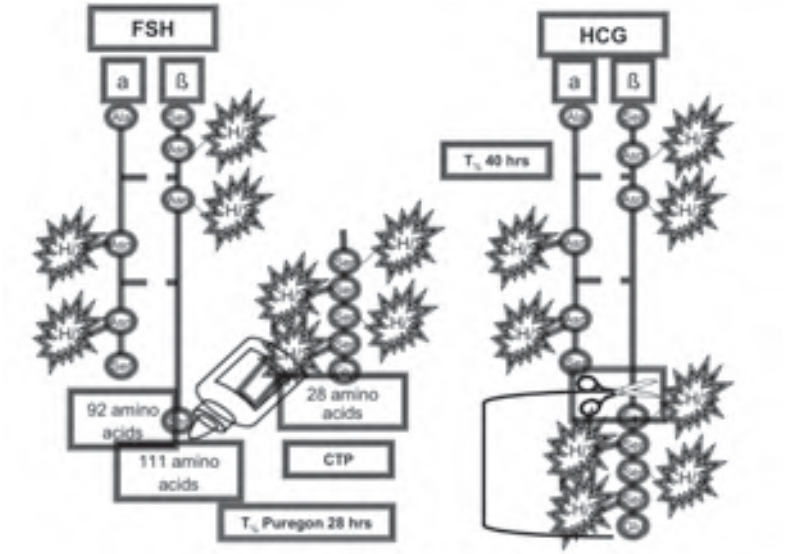


Fig 3 corifollitropin alfa is a novel recombinant gonadotrophin molecule, in which the FSH- chain is fused with the carboxy-terminal peptide of the hCG- subunit.

"corifollitropin alfa" retained the same biological activity as native FSH in vivo, but had a prolonged circulating half-life. This gives the molecule an in vivo potency significantly higher than native FSH, making it an obvious candidate as a long-acting FSH agonist The results achieved with this long-acting FSH molecule in an international, multicentre trial were published recently. No severe drug-related adverse events were observed and pregnancies recorded. Antibodies to either component of the FSH molecule were not observed, and the elimination half-life was reported to be 94.7 26.2 hours, which is 2-3 times longer than that of natural FSH

Serono International S.A. is also developing a novel, long-acting formulation of recombinant FSH. The new formulation is based on Alkermes' ProLease injectable sustained-release drug delivery technology, which involves the encapsulation of a drug into small polymeric microspheres. These degrade slowly and release the encapsulated drug at a controlled rate following subcutaneous or intramuscular injection. The new formulation is designed to offer patients the alternative of a single injection rather than multiple daily injections. Data on this formulation are yet to be published.

We are also seeing the appearance of small, orally active molecules capable to stimulate follicle growth and inducing ovulation. Some prove to be specific, and even capable of bypassing many parts of the receptor conformation. These will perhaps one day remove the need for the classical gonadotrophins in clinical work.

For companies committed to developing a wider range of innovative medicines for infertility, a generation of orally bioavailable gonadotrophin mimetics has been the 'holy grail' of drug development research for several years. As knowledge about the activating sites of gonadotrophins and GnRH analogues has increased, it has become possible to create small, non-peptide molecules that induce signal transduction without binding to the extracellular domains of membrane proteins. Such molecules will ultimately be converted into highly potent orally active therapeutic preparations, and will either replace the dimeric glycoprotein hormones or act as antagonists. One classical approach is high-throughput screening of large chemical libraries to find small molecule (< 500 Da) agonists of human FSH or LH receptors. Indeed, work on the human LH receptor illustrates that this approach has met with some success: a pyrazolyl tyrosineamide molecule has been shown to activate LH receptors expressed either heterologously in CHO cells or naturally on the surface of testicular Leydig cells. Organon recently reported the first human exposure study using a low molecular weight LH agonist (Org 43553) in female volunteers of reproductive age. In this study oral administration of Org 43553 up to single doses of 2700 mg was well tolerated and safe. The mean peak concentrations of Org 43553 were at 0.5-1 h and the mean elimination half-life (t 1/2) varied between 30 and 47 h. Based on follicle rupture observed by ultrasound and rises of serum progesterone (> 15 nmol/l), treatment with a single oral dose of Org 43553 resulted most frequently in ovulation in the 300 mg and 900 mg dose groups (Mannaerts, 2004). Figure 4 illustrates the range of non-peptide molecules currently under investigation that are gonadotrophin-mimetic, and orally active.

It is therefore feasible that the future of ovarian stimulation will be a simple treatment schedule composed of different tablets, taken at certain

time points during the ovarian stimulation cycle.

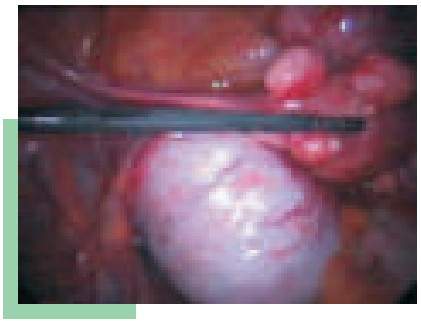
Besides Pharmacological developments also other techniques are being developped . Gonadal cryopreservation is still in its early stages of experimental development, both in males (testicular tissue cryopreservation and in vitro spermatogenesis) and female (ovarian tissue cryopreservation and in vitro follicular maturation) but with better techniques this should become feasable in the not to distant future. Ovarian and oocyte cryopreservation is essential to conserving the fertility of young women. The hope of developing oocyte cryopreservation as a major IVF option is becoming increasingly realistic, but major efforts are still required to clarify the authentic implications of oocyte cryopreservation at the cellular level and identify freezing conditions compatible with the preservation of viability and developmental ability.The mammalian oocyte is especially sensitive to cryopreservation. Because of its size and physiology, it can easily undergo cell death or sub-lethal damage as a consequence of intracellular ice formation, increase in the concentration of solutes and other undesired effects during the conversion of extracellular water into ice. The oocyte plasmalemma possesses limited permeability to ethylene glycol (EG) and EG exposure causes considerable osmotic stress. However, post-thaw rates of survival and normal meiotic spindle organization may be preserved by protocols which are designed in order to minimize osmotic stress.Results of mature oocyte freezing techniques have improved significantly over the past few years. Vitrification is a prospective technology in ovarian tissue cryopreservation, but it is still in an initial stage. Mature oocyte vitrification is progressing well, but requires safety validation in view of the high cryoprotectant concentrations used.

The "conquest of infertility" is an incredible achievement; however, continuously new challenges are arising in relation to scientific, ethical and humanitarian aspects in infertility management. How do we use current and evolving technologies to obtain the ultimate goal of successful patient friendly and cost effective ovarian stimulation - the birth of a healthy singleton child with no maternal complications?

Dr. Bruno Lunenfeld
Email: brunolo@netvision.net.il, bruno_lunenfeld@mail.vresp.com

Multiple fibroids and infertility

Dr. M. L. Goenka
Guwahati



Mrs. S.D., a computer engineer, aged 33 years came to us in 1999 with 3 years of primary infertility. She tried three IUI cycles at another centre. On investigations she was found to have enlarged uterus with multiple subserous and intramural fibroids of 15mm to 30mm in size. One fibroid of 25mm was touching endo-myometrial junction (Photo-1). HSG: no distortion of cavity with normal peritoneal spillage. Hysteroscopy: normal. Laparoscopy: frozen pelvis with stage-IV endometriosis. Husband, a pediatrician, showed oligozoospermia. Danazol was given for six months & followed by IVF/ET/ICSI. She conceived with IVF. Her pregnancy was uneventful upto 28 weeks. At around 28 weeks she suddenly started having severe uterine contraction and delivered, within 6 hours, a premature baby (wt 700gms) with no congenital malformations. Baby died after 6 hours. Just a day before delivery all investigations including USG were normal.

Patient again approached us in 2003.Repeat investigations showed slight increase in the size of myomas (max: 4cm). Myomectomy was advised but couple refused. IVF was done again. She conceived but again aborted at 10 weeks.

Patient again approached us in 2005. Investigations showed further increase in size of fibroids (myomectomy was again refused). Her D3 FSH went up to 14m I.U./ml. Considering her h/o two previous abortion, complete thrombophilia profile was done. Fasting homocysteine level was high (45 µmol/l). We planned IVF with oocyte donation after a three months course of Lupride Depot (3.75 mg lupreolide acetate IM). Folic acid, methylcobalamin, pyridoxine, acetylsalicylic acid (75mg) were started immediately. Low molecular weight heparin (LMWH); Fraxiparine 2850 IU/0.3ml daily was started from the day of Embryo Transfer (ET) and continued till delivery. Patient conceived with twin pregnancy. Pregnancy was uneventful. At 34 weeks we stopped acetyl salicylic acid and at 35 week stopped LMWH. Elective LSCS was planned at 37 weeks. But fetal doppler at 36 weeks showed fetal hypoxia so LSCS was done immediately. Patient delivered two healthy male babies weighing 2.0 kg and 2.2 kg in January 2006.

Editor's Comment: Though women are known to convieve and deliver with fibroid uterus but there is a definate association of presence of fibroids with infertility and big firboids, fibroids in denting cavity should be treated first surgically before IVF to improve outcome.

Dr. M. L. Goenka
Phone: 0361 - 2544560,2518619
Email : dgoenka@satyam.net.in

Dr. Jatin Shah
Mumbai

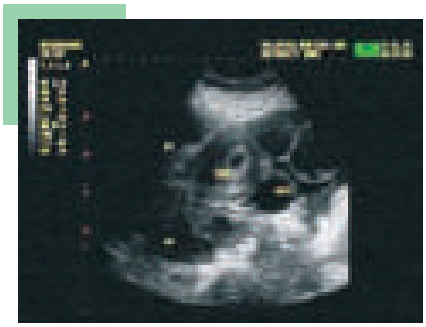
Oocyte donation

Mrs F N, aged 56 years presented with primary infertility of 40 years duration. She had failed IVF in the UK on three attempts 15 years ago. In view of her menopausal status, she was recruited for oocyte donation with IVF (the case was performed before the introduction of the ICMR guidelines restricting patient age to 45 years). Pregnancy was successfully established in the third cycle with ongoing twins. In the 26th week of pregnancy she developed massive pedal edema. USG revealed severe deep vein thrombosis affecting the entire femoral vein. She also developed PIH and gestational diabetes. She was placed on antihypertensives, insulin and heparin. Also, a mesh was introduced in the inferior vena cava by a vascular surgeon to prevent pulmonary embolism. The pregnancy continued until the 29th week at which time LSCS was done to prevent any further maternal complications. She delivered a female baby (BW:1025gms) and a male baby (BW 950 gms). Both were kept in the NICU. The female baby expired after 3 days of complications related to prematuriy, the male child survived and went home in perfect condition after a 46 day stay in the NICU. The mother had an uneventful and complete recovery. Oocyte donation is a magic tool in the armamenterium of the ART specialist but should be restricted to the < 45 years age group to avoid such high perinatal and maternal morbidity.

OHSS

Mrs S P, aged 32 years presented with primary infertility related to PCOS and asthenozoospermia with three failed IUI attempts in the past. She was recruited for ICSI and in view of her lean status, she was given a standard down regulation protocol with rFSH 200 IU per day. She developed about 16 follicles, peak E2 on day of hCG being 4800 pg/ml. hCG 5000 was given instead of 10000 and OPU was scheduled at 36 hours. 14 oocytes were aspirated and ICSI was performed. On the day of ET (48 hours post OPU), the patient had mild abdominal discomfort and distension. All embryos were cryofrozen and transfer was postponed to a subsequent cycle. On the next day, 72 hours post OPU, the patient had further distension and free fluid on USG. As per routine management of OHSS, the patient was admitted and given DNS and albumin. Surprisingly, the hematocrit was found to be lower than normal and HB was only 8% (pre-oeprative Hb being 11 gm%). With increasing tachycardia and patient discomfort it was decided to perform an ascitic tapping. The first tap revealed fresh blood. On suspicion of ovarian cyst rupture, the patient was shifted to an institute and subjected to an emergency laparoscopy. Bleeding was observed from the surfaces of both ovaries. In view of the extreme fragile nature of the ovaries, it was found impossible to achieve hemostasis with laparoscopy. Emergency

exploratory laparatomy was performed and in view of the deteriorating hemodynamic status of the patient, it was decided to perform a bilateral oophorectomy as a life saving procedure. The patient required 6 units of whole blood and ICU management for 48 hours before being completely stable.



Severe OHSS in the thin lean PCOD patient is a known phenomenon. This is the first case report of bilateral ovarian cyst rupture and hemorrhage 72 hours after OPU. Such an occurrence should always be kept in mind when dealing with the thin PCOD patient. Avoiding down regulation and prefering the short antagonist protocol with agonist trigger and embryo cryofreezing should be the method of choice for the thin, lean PCOD patient.

Editors Comment:

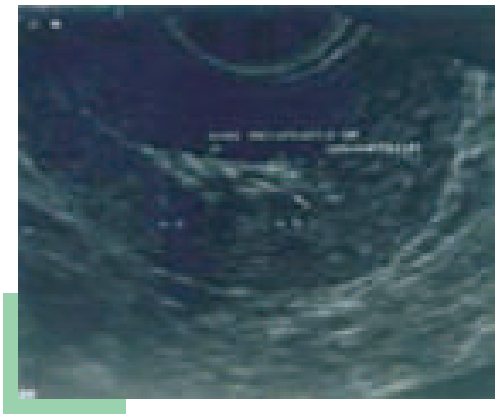
1. Even though oocyte donation is an important part of ART treatment, proper selection and screening of cases is vital.
2. OHSS is an infertility specialist's nightmare and can present at any stage in any form.

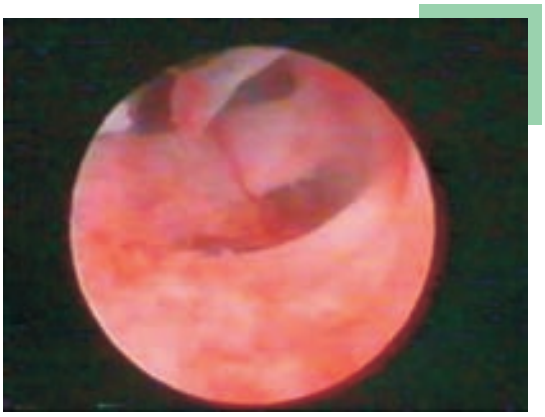
Dr. Jatin Shah
Phone: 022-23873196,9820080449
Email : drjatin2000@yahoo.com

Ashermann's Syndrome

Dr. Rajat Ray
Dr. Monu Patnaik
Cuttack

Mrs. Manorama Nayak, aged 28yrs presented to our hospital with primary infertility for 4 years. She had undergone diagnostic D&C at peripheral hospital 2 yrs back. husband had normal semenogram. Transvaginal sonography revealed normal functioning ovaries, but a thin irregular endometrium. Diagnostic laparoscopy & hysteroscopy was done.There were dense fibrous bands inside the uterine cavity. Hysteroscopic adhesiolysis was done with electrocautery & the cavity was enlarged. Both the tubes were also blocked. After two months of tab progynova, IVF was planned. Long protocol regimen was followed Down regulation started with inj. buserelin from 21st day of cycle. From 2nd day of subsequent cycle stimulation was started with in. FSH. Step up regimen was followed. Inj HCG was given on 13th day & oocyte retrieval was done on 14th day.Day 3 embryo transfer was done on 14th oct'06. Luteal support was given with vaginal micronised progesterone. The antenatal period was uneventful. Pt delivered a term male child on 21st jun'07. this case is a bright example how a simple diagnostic D&C can become a causative factor of infertility.





USG and Hysterescopic picture of Ashermanns Syndrome

Editors comment:
Injudicious use of even a simple procedure like D&C can be dangerous.

Dr. Rajat Ray
Email : rajatkuray@rediffmail.com; monuse123@hotmail.com

Dr. Monu Patnaik

Dr Mandakini Parihar
Mumbai

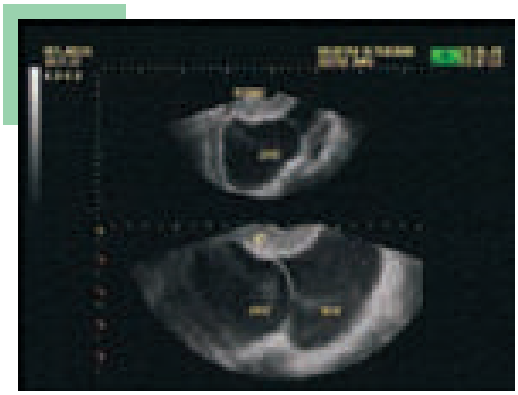
Case of Infertility..Enigma called endometriosis

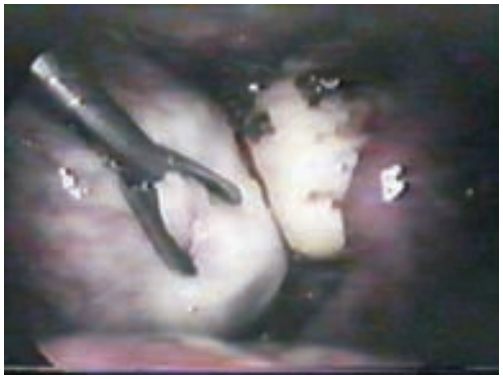
Mrs. MS , a 29 year old nurse came to me for treatment of primary infertility. She has been married for 5 years and has not been using any contraception for the last 3 years. Husband was using barrier contraceptive for the first two years. She has regular menstrual cycles, but accompanied by severe dysmenorrhoea.

Semen analysis was within normal limits.
She gave past history of a laparotomy being done, 3 years ago for a large right sided endometrioma. The exact operative notes were not available but she said most of her ovary was removed due to the size of the cyst.
She was then advised 3 doses of GnRH depot, which she took and asked to follow up after that with missed period.

She followed on that advice and went back to the operating surgeon after one year, who then advised an ultrasound of the pelvis. This showed the presence of another large cyst on the opposite side and hence was advised surgery again. She sought a second opinion from another doctor. She was advised a HSG, which showed open tubes and hence she was advised her expectant management for another 6-9 months and then to follow-up if there was no pregnancy.

I saw this patient 9 months later seeking advise and help for infertility. Her ultrasound showed presence of bilateral large endometrioma of





6-8cms. HSG done earlier did suggested peritoneal spill, but it was loculated along with evidence of adhesions. She was advised laparoscopy along with hysteroscopy to evaluate her pelvis and offer corrective surgery. She underwent a post-menstrual hysteroscopy with operative laparoscopy with removal of the bilateral endometrioma, and adhesiolysis. It was Grade 3 endometriosis, but both her fallopian tubes were patent with free flow of methylene blue at the end of the procedure.

She was advised COH from the immediate next cycle along with IUI for 3 cycles and if no pregnancy, then to consider IVF with ET. Patient underwent COH using highly purified HMG, and ovulation trigger given with 10,000 units of hCG

and a single IUI done 38 hours later. Patient was given luteal support using natural micronized progesterone in the dose of 600mg per day vaginally. She became pregnant in the second cycle of treatment. There was increased requirement of the gonadotropins dose, but she responded well with 150 IU daily for 10d ays and had 2 good follicles. Early ultrasound showed a single viable pregnancy. The luteal support was continued in the first trimester. The rest of the pregnancy was uneventful and patient underwent an elective C. Section at 39 weeks and delivered a healthy female child weighing 3.1kg. Post operative recovery was uneventful.

Editors comment:
Severe endometriosis many times requires a multipronged approach.

Dr Mandakini Parihar
Phone: 09869008854
Email : map@parihar.com

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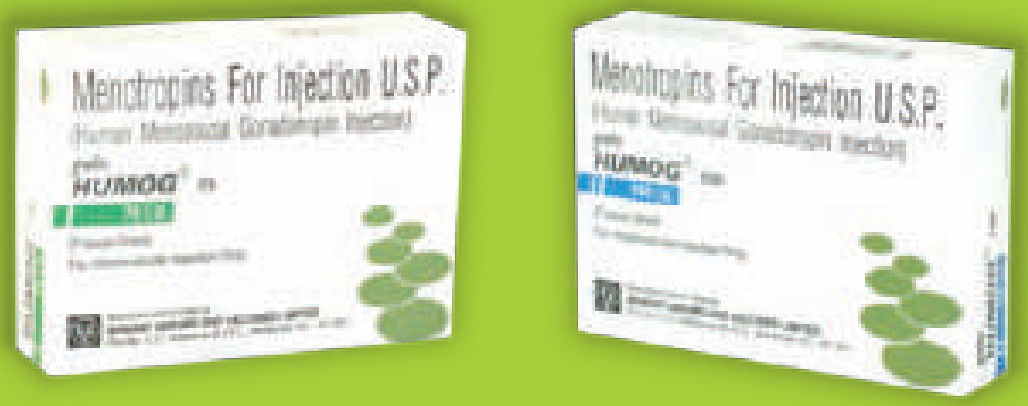

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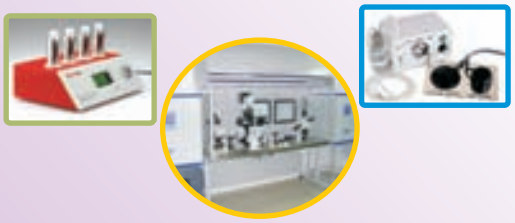

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