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Dedicated Issue:

Infertility - Recent Advances

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Message from the President

Dear AOGD friends,

Motherhood is a cherished dream of every woman. In the words of Robert Browning ''Motherhood: All love begins and ends here". But for some this dream is so elusive, more so, with the alarming increase in the incidence of infertility in the last two decades.

Friends, I am sure all of you agree that nothing is more rewarding for us than seeing a healthy infant in the arms of her radiant mother! We as gynaecologists are committed to promote the reproductive health of a woman which involves prevention of STI and RTI, as well as early detection and vigorous treatment of these diseases, so as to prevent infertility in them at a later date. In our endeavour to protect the rights of a woman on her body we should provide quality health services so that she can plan her pregnancy and subsequently deliver a healthy baby.

The ability to achieve pregnancy against all odds is the result of present scientific advances. However it also implies that the treating gynaecologist should be well informed about the guidelines and the legal perspective of various procedures. These services should be well within the reach of common man. Clarity regarding the present ICMR guidelines on adoption, donor semen and egg, and surrogacy is the need of the hour.

It is a matter of immense satisfaction for me that we have organized outreach activities for comprehensive health check up of women. The first one was done at Aliganj, in collaboration with Gynecology and PSM department of Safdarjung Hospital. Many of our colleagues have already volunteered their support for this noble cause and I will welcome the initiative of our other esteemed members also.

"Our lives begin to end the day we become silent about things that matter" - Martin Luther King.

Dr Pratima Mittal
President, AOGD
drpratima@hotmail.com

From the Secretary's Desk

I welcome you all to a happy reading of our second issue dedicated to infertility. It is ironical that in the world's second populous country, the problem of infertility affects a very large population. In our country it is not only a medical condition but an emotional and social stigma, besides being an economic burden. Every day new advancements are happening in diagnosis and treatment but still there is a substantial burden of unresolved and unexplained problems. The male factor infertility is still not been explored much but now there is a trend emerging which is focusing on sperm functions. I hope the contents of this issue will enrich your knowledge and help you in dealing more rationally with infertility and related issues.

This month, two events related to male infertility were held, a CME in Saket City Hospital included discussion on role of oxidative stress in sperm dysfunction; and a full day workshop was conducted by Army Research and Referral Institute dedicated to sperm function test. Besides that, May-June were happening months with many other activities.

From this month we have started outreach activities for comprehensive health checkup for women. The first one was done at Aliganj in collaboration with Gynecology and PSM department of Safdarjung Hospital. We plan to hold two activities every month with the help of AOGD members from different areas of Delhi. Dr Anita Sabharwal, Dr Roopam Arora, Dr NP Kaur and Dr Poonam Chawla have volunteered to participate. AOGD will arrange the cancer screening team with the help from Rajiv Gandhi Cancer Research Institute. With sincere support from our enthusiastic society members, we hope to do a lot of work. Any group of gynecologists willing to participate in outreach activities can contact us.

We have got some good news for you all! AOGD is organizing 'One Day Certification Course in Advance Laproscopy for AOGD members in collaboration with Jhonson and Jhonson. This certificate course is otherwise chargeable by Ethicon @ ₹10000 / day but we are arranging it free for our AOGD members. Dates will be circulated in advance.

The monthly clinical meeting was held at DDU Hospital on 29th May. It is creditable that our members braved the scorching afternoon sun to attend it. That's the true spirit of AOGD !

Dear members please stay connected and block 31st October and 1st November for your own Annual Conference. We are preparing enthusiastically for it. Your inputs for the conference program are welcome and very valuable for us.

Dr Achla Batra
Hon. Secretary, AOGD
achla_batra@yahoo.com

Annual AOGD Conference

Block your dates for Annual AOGD Conference on 31st October - 1st November, 2015 at India Habitat Centre

Attention AOGD Members

- Members who have not received AOGD notifications on their email should update their email id at official AOGD id - agodsjh2015@gmail.com
- Please note annual membership entitles you to FOGSI membership for the calendar year January to December, irrespective of the month of AOGD registration.

AOGD Monthly Clinical Meeting

Next AOGD Monthly Clinical Meeting is at SHL 3 Auditorium, Army Hospital (Research & Referral), Delhi Cant, on 26th June, 2015. All are cordially invited.

From the Editor's Pen

Dear Friends,

Warm wishes to all of you from the Editorial Team! It was very encouraging and heartening to receive the response of so many of our esteemed readers after the first issue. It will be our constant endeavour, to include quality disquisitions in our Bulletin and blend them with some light reading features.

Infertility has been a source of great concern in India lately, with a steady rise in incidence over the last decade. According to a 2013 World Bank estimate, the drop in fertility started about 10 years ago in India, with a steady 17 percent decline from the year 2000. In tune with the demand, the technological advances in the field of ART have been equally steep, and to keep abreast with them has become a trying task for the general gynaecologist.

This issue covers a range of recent advances in the field including the latest protocols for ovulation induction, means of improving the endometrium for implantation, fertility preserving surgery in adenomyosis and role of 3D ultrasound. The new drug corifollitropin alpha has been reviewed very skilfully and the role of gynaecologist in male infertility has been most proficiently summarized. How to make the IVF services more pocket friendly has been described most ably whereas the medico legal responsibilities of the gynaecologists in respect to donor gametes, have been effectively discussed.

"Meet the luminary" this time round, features Dr S K Das a much loved figure of our Association and a torch bearer in the field of gynae - oncology. A word of special thanks, to Dr Banashree Das and Dr Surveen Ghumman for their invaluable inputs in planning this issue.

Looking forward to the valuable feedbacks and contributions from our esteemed readers

So wish you all happy reading!

"A good editor doesn't rewrite words, she rewires synapses." - S Kelley Harrell

Dr Jyotsna Suri
Editor, AOGD

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REVIEW ARTICLE

Individualizing Ovarian Stimulation

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The main aim in ovarian stimulation is to give the right drug in the appropriate dose tailored to the patient's characteristics in order to minimize side effects like ovarian hyperstimulation or cycle cancellation without compromising the chance of pregnancy thus decreasing financial and psychological burden. The first step to this is to identify factors predicting the response of the patient.

Individualization would depend on

1. Response to previous cycle
2. Weight/ BMI
3. Age
4. Ovarian reserve markers like AMH, antral follicle count and day 2 hormones
5. Other factors like cause of infertility (PCOS, endometriosis etc), previous ovarian surgery which determine whether patient is poor or hyper responder

Response to previous cycle

Individualization is often based on performance of previous cycle. If the previous dose performed well then it may be repeated but if the previous cycle did not perform well then there is requirement to analyze the cycle and bring required changes in drug dose and the protocol.

Weight and BMI

Increased doses of gonadotropins are required with increase in the BMI of the patient.[1]

Age of the woman

Age is an important factor in fertility, and chances of conception decrease with advancing years, usually after the thirties thus requiring higher doses of gonadotropins.

Ovarian reserve markers

Since the prediction of patients response is dependent on ovarian reserve markers it is important to distinguish between the more sensitive markers and those that are less sensitive when basing the decision. It is also essential to identify a cutoff value which gives maximum sensitivity and specificity. No women should be denied a first attempt at stimulation on the basis of ovarian reserve tests as accuracy of these tests may be a poor prediction of pregnancy especially in younger women. There is a false positive rate of 10–20%.

1. Anti Mullerian Hormone (AMH)

AMH value of 1.36 ng/ml (9.7 pmol/l) (IBC assay) is seen to be associated with 75.5% sensitivity and 74.8% specificity for prediction of poor response.[2] According to published data a cut-off value of AMH ranging between 0.7–1.3 ng/ml may be considered acceptable for the prediction of poor response in IVF. [3]

AMH tailored protocols

AMH-guided, controlled ovarian hyperstimulation protocols can significantly improve pregnancy rate, reduce the incidence of complications like OHSS and reduce the financial burden associated with assisted reproduction. (Figure 1) [4]

2. Antral Follicle count (AFC)

The most frequently reported cut-off values of AFC for prediction of poor response ranged between <5 and <7.[5] A count of 8–10 in one ovary is considered as a predictor of a normal response.

3. Day 2 FSH

Pregnancy rates drop when FSH levels are greater than10 mIU/mL. It is important to realize that FSH levels have low sensitivity, meaning that not everyone with a diminished ovarian reserve will have an abnormally elevated FSH level. However, a normal level does not signify that everything is fine. When FSH levels are measured repeatedly, they can vary significantly from cycle-to-cycle. It is important to understand that it is the higher FSH level that is the best predictor of a woman's reproductive potential.

Prediction of poor response

There are clinical criterion and amnestic criterion like the outcome of previous IVF cycles, the woman's advanced age, the presence of short menstrual cycles (a clinical manifestation of ovarian ageing), ovarian reserve tests and previous ovarian surgery[6]. The incidence of poor ovarian response in IVF ranges from 10 to 20%, with a lower prevalence among women aged <34 years. AMH levels below 1.35 ng/l and antral follicle count less than

5-7 and FSH above10 mIU/ml predicts a low response to stimulation[7].

How do you identify a hyper responder?

The prevalence of a hyper responder is 7% on the average and is more with younger patients and less with older ones. Prediction of a high response prior to stimulation is useful in counseling patients on the risk of OHSS and helps modifying the stimulation protocol and reduce the incidence of OHSS. Identification of factors before stimulation predicting hyper response are enlisted in Table 1

Table 1: Risk factors for hyperstimulation

Predicting factors	High Risk	Low Risk
Age	Young (<35 years)	Older (>36 years)
Cause of anovulation	Polycystic Ovarian disease	Hypogonadotropic hypogonadism
Built/BMI	Asthenic habitus	Heavy build
History of OHSS	Present	Absent
Antral follicle count	>15	<15
Number of Follicles while stimulating	Multiple follicles (>35)	Fewer follicles (<20)
AMH	>3.5 ng/ml	< 3.5 ng/ml

What is the dose of gonadotropin to be used?

The CONSORT study developed a dosing algorithm which individualizes recombinant human FSH (r-hFSH) doses for assisted reproduction technologies, assigning 37.5 IU increments according to patient characteristics: basal FSH, body mass index, age and antral follicle count. (Table 2)[8]

Table 2: Factors influencing the dose of gonadotropin

1.	Weight
2.	Baseline FSH If > 10 IU/l-give higher dose.
3.	Age beyond 35 years-a higher dose is required.
4.	Higher effective daily dose in previous cycle.
5.	Poor responders.
6.	PCOS patients are usually started on a lower dose to avoid hyperstimulation.
7.	Prior down regulation with GnRH agonists-a higher dose is required.
8.	Hypogonadotropic hypogonadism.
9.	Unexplained infertility.
10.	Ovarian reserve parameters-AMH, Antral follicle count, Basal FSH, Estradiol

Initial dose of FSH

All ovarian stimulation drugs raise the FSH levels by exogenous FSH or increased secretion of endogenous FSH to reach the threshold and prolong the window in order to obtain specific number of follicles to be growing. Hence in women with a large antral follicle pool the administration of a high FSH dose may induce excessive ovarian response consequently leading to a high risk of OHSS.[9]

Typical starting doses of FSH are 225 IU in a normal responder. In high responders start with lower dose of 75 IU – 150 IU and step up in increments of 37.5 IU to 50 IU in case response is not seen. The gonadotrophin starting dose decreased with increasing AMH levels and the suggested gonadotrophin dose was 150 IU for expected high responders and 300 IU for expected poor responders in IVF.[10]

Which Gonadotropin to be used?

The choice of gonadotropin also depends on indication of controlled ovarian stimulation.

Hypogonadotropic hypogonadism: In women with hypogonadotropic hypogonadism where LH levels are low, the drug of choice is menotropin because it contains both FSH and LH.

PCOS: In patients with PCOS, LH levels are high. Recombinant FSH is given after down regulation (E2 < 30 pg/ml, LH < 4IU/L).

Unexplained infertility: In these, normally ovulating women where endocrinopathies have been ruled out, any available gonadotropin preparation can be used as aim is multifollicular ovulation.

Poor ovarian reserve: These patients show a better response to human menopausal gonadotropin and to recombinant FSH.[11,12]

Recombinant LH

It is known that the follicular selection and final stages of follicular maturation are equally if not more dependent on low circulating levels of LH.[13]

Indications for LH use:

- Women more than 35 years
- Poor responders
- Women down regulated with GnRH agonists having low LH levels.
- Hypogonadotropic hypogonadism

Which protocol should be used when?

Step up High Dose Protocol- For Normal responder

This conventional protocol is started with 150-225 IU of FSH per day. If estradiol levels are not increasing then the dose of gonadotropins needs to be increased. This regime is useful for normal responders.

Step up Low Dose Protocol- For Hyper responder / PCOS

It is started with an initial dose of 37.5 to 75 IU/day. If no response is seen in terms of estradiol level or follicle, it is increased in increments of 37.5 IU every week. It is useful in patients of PCOS who are prone to hyperstimulation as they have a large number of antral follicles ready to respond to FSH stimulation.[14]

Step Down Protocol- For PCOS as second line treatment

The treatment is usually started with 225 IU hMG/FSH (or 300 IU in some cases) until follicles of 10 mm is seen. The dose is then reduced to 112.5 IU and 3 days later decreased to 75 IU. This is an effort to promote continued development of the more sensitive dominant follicle while withdrawing support from less sensitive smaller follicles in the cohort. It is indicated in oligo-amenorrheic women with PCOS or in high responders as second line protocol where other regimens do not achieve success.

Mild stimulation Protocol- To prevent OHSS

In the recent years mild protocols with low stimulation give acceptable results with minimal risks and lower cost thus being good for poor responders who have not shown a response with high doses. Gonadotropins are administered at a lower than usual dose and/or for a shorter duration throughout a cycle in which GnRH antagonist may or may not be given as co-treatment, or a stimulation in which oral compounds (e.g. anti-estrogens) are used either alone or in combination with gonadotropins and GnRH antagonists.

Use of GnRH analogue- Individualize choice of analogue

GnRH antagonist and agonist down-regulate endogenous pituitary gonadotropin secretion and thereby prevent a premature LH surge.

GnRH agonist

GnRH agonist is the treatment of choice where high basal levels of LH need to be supressed as in PCOS patients. Agonist blunts the response to subsequent gonadotropin stimulation and increases the dose and duration of gonadotropin therapy increasing the total cost of treatment. There is also a higher incidence of ovarian hyperstimulation as only hCG trigger can be used.

Who should be given an agonist protocol?

1. Women with high basal LH level who need downregulation.
2. Patients with endometriosis as suppression with agonist gives better results in stimulation
3. Patients who cannot be monitored closely.
4. Normal responders

GnRH antagonist

The duration of treatment for an antagonist is substantially shorter than for an agonist. The total dose and duration of gonadotropin stimulation required is less. However antagonists cannot reduce raised basal LH levels

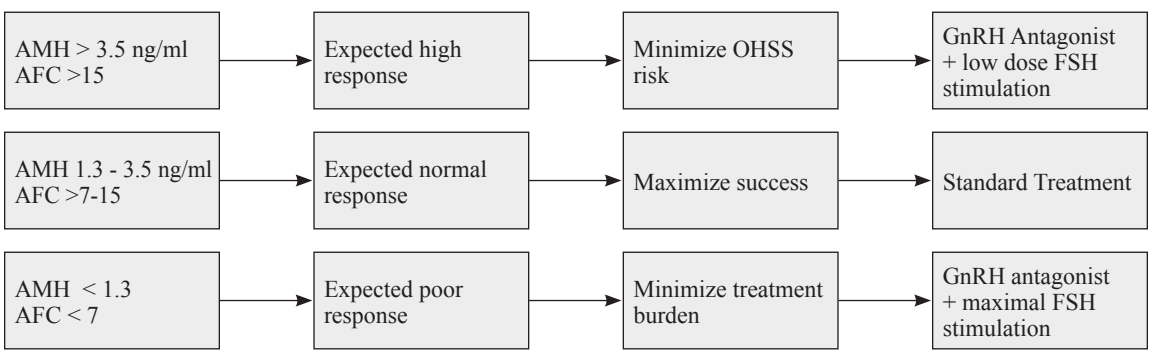
When should GnRH antagonists be used?

1. Hyper responder**:** Antagonists are associated with a reduced incidence of OHSS as GnRH agonist can be given as a trigger. Low gonadotrophin doses and GnRH antagonist seems to be ideal for women at a high risk of OHSS. (Figure 1)
2. Poor Responder: Using a GnRH antagonist instead of a long-acting agonist with lower doses of FSH ensures minimal drug usage to prevent financial and pschological burden thus decreasing drop out rates.[10,15] (Figure 1).

Cycle monitoring to individualise dose adjustments in ovarian stimulation

The response to stimulation is monitored with serial measurements of serum estradiol and transvaginal

Fig 1: Individualization of treatment on basis of AMH and AFC



ultrasound imaging of ovarian follicles. The adjustments in the dose of gonadotropin treatment are made accordingly.

Adjuvants- When and which?

Growth Hormone: The use of growth hormone in poor responders has been found to show a significant improvement in live birth rates.[16]

Androgen supplementation: It is seen that androgen supplementation in the form of testosterone patches or DHEA may improve response in poor responders specially those who are young. [17]

Dexamethasone: Dexamethasone diminishes the androgen level in the microenvironment of the ovary It may be continued for 3 to 6 cycles if successful and should be discontinued if not.[18]

Metformin: In agreement with the previous reviews, metformin was associated with improved clinical pregnancy but there was no evidence that metformin improves live birth rates.[19] It does decrease the incidence of OHSS.

Cabergoline: Cabergoline appears to reduce the risk of OHSS in high-risk women and is given along side.[20]

To conclude, the ultimate goal in individualization would be the selection of an effective protocol for ovarian stimulation which has to be well balanced between the risk of maximal and suboptimal ovarian response.

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REVIEW ARTICLE

Thin Endometrium: A Challenge in Infertility Management

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One of the most challenging problems faced in treatment of infertility is to deal with poor endometrium during ovulation induction or preparing endometrium before embryo transfer. Successful implantation requires receptive endometrium besides good quality embryo. Though there is tremendous advancement in ovarian stimulation protocols which enable development of dominant follicles even in refractory cases, implantation still poses a challenge in cases with poor endometrial growth.

Histologically, endometrium consists of basal layer (lower1/3rd) and superficial functional layer (upper2/3rd). During proliferative phase all components of endometrium (glands, stroma and endothelial cells) demonstrate proliferation and it is maximum on 8 to10th day of cycle, which corresponds to peak oestrogen level along with maximum oestrogen receptors. There is increased mitotic activity, increased nuclear DNA and cytoplasmic RNA synthesis to prepare for blastocyst implantation.

Endometrial receptivity during the implantation window depends on the following:

1. Endometrial thickness
2. Endometrial pattern
3. Endometrial and sub endometrial blood flow

Evaluation of endometrial pattern, thickness and blood flow is done by ultrasonography with colour doppler. Patients with thin endometrium also merit a hysteroscopy, if it was not done before, which may detect asymptomatic endometrial pathology. Patients with normal hysteroscopy findings may be further benefitted by the novel technique of chromohysteroscopy in which instillation of dye causes staining of areas of silent chronic endometritis. A study using this technique in our hospital revealed association of poor endometrial growth (in terms of pattern and thickness) with chronic endometritis detected by chromohysteroscopy in otherwise normal looking endometrium. Persistent thin endometrium should always be evaluated for latent tuberculosis as incidence of genital tuberculosis is very high in India.

A number of researchers have proved that thickness of pre-implantation endometrium is directly related to positive pregnancy outcome. Pregnancy rate was found to be highest among the group who had trilaminar endometrium with 10-12.9 mm thickness and no pregnancy when thickness is less than 7mm[1]. Dickey and colleagues(1993) found no pregnancy if endometrial thickness was <6mm. Pregnancy rate was higher (21% vs 8%) in the trilaminar vs non trilaminar group and even higher at 39% when endometrium is both, more than 6mm and trilaminar.

Important causes of poor endometrial growth during ovulation induction are:

1. Endometrial resistance to oestrogen.
2. Reduced blood flow.
3. Over-exposure to testosterone.
4. Permanent damage to the basal endometrium.

Clomiphene citrate (CC) is most commonly used and most effective drug for ovulation induction. But because of its anti oestrogenic effect on endometrium, pregnancy rate is much lesser than ovulation rate (40% vs 80%), and 25% of those who conceive may end in abortion. Clomiphene most consistently affects the thickness of endometrium. Histologically there is reduction of glandular density and increase in the number of vacuolated cells. On molecular level, while serum oestradiol level increases in women on clomiphene, but the oestrogen receptors in endometrium decrease as the endometrium becomes thinner. According to Ohno and colleagues (1998) oestrogen and progesterone receptor ratio is related to endometrial echo pattern. Ratio of progesterone oestrogen receptor concentration is less in non trilaminar endometrium.

Akihisa Takasaki at al[2] reported that thin endometrium is due to high blood flow impedence of uterine radial arteries. Uterine blood flow is an important factor for endometrial growth. According to this study, high blood flow impedence of uterine radial artery (RA) impairs growth of glandular epithelium and results in decrease in vascular endothelial growth factor (VEGF) which in turn causes poor vascular development leading to poor blood flow to endometrium. Decreased blood flow is associated with decreased endometrial growth. Evaluation of resistive index (RI) in radial artery of uterus shows a negative correlation between RA-RI which was measured in late follicular phase.

Excessive ovarian androgen can also compromise

oestrogen induced endometrial growth. Luteinizing hormone (LH), primarily acts on ovarian stroma to produce androgen. Only a small amount of testosterone is required for optimum oestrogen production. In conditions like polycystic ovarian syndrome (PCOS), high LH level leads to elevated androgen level which may be the cause for poor endometrial development besides poor egg / embryo quality. LH containing preparation for ovulation induction should be used with caution in this group of patients. Older women tend to have more circulating bioactive LH than younger women.

Permanent damage to basal endometrium may occur due to severe endometritis or due to vigorous curettage following abortion etc. Severely damaged basal layer usually leads to synechiae or amenorrhoea. For all practical purposes, completely damaged basal endometrium cannot be regenerated.

Management

There is no consensus regarding management of thin endometrium encountered during ovulation induction. No standard protocol or guideline is available yet. Based on aetiology, a number of drugs/methods have been used with the aim of improvement of oestrogen level in the endometrium and increased blood supply to basal endometrium.

Oestrogens

In the group of patients where clomiphene induction is associated with thin endometrium, letrozole and tamoxifen use for ovulation induction have the advantage of avoiding peripheral anti estrogenic effects. However, these drugs remain off –label for ovulation induction; and hence cannot be recommended at present.

In this group of patients, addition of oestrogen is seen as the logical step in combating antiestrogenic effect on endometrium. However, the dose, the regimen and type of oestrogen used vary widely with little consensus to the treatment approach.

In a meta-analysis done by Torres RF et al[3] who examined use of pure *ethinyl estradiol* for treatment of thin endometrium, the observations made were:

- Addition of Ethinyl estradiol (EE) does improve the endometrial thickness in comparison to patients where only placebo was used.
- Best results were achieved when EE was used in dose range of 0.02-0.05mg/day
- EE given for 5days had better outcome than when given for 7 to 8 days.
- Administration of EE starting on 7th to 10th day of menstrual cycle had better result compared to starting it before 7th day.

Other oestrogen preparation and doses schedule reported in literature are:

Conjugated equine oestrogen:	0.625mg from day 7th for 5days.
Transdermal ethinyl oestradiol:	4mg/day from day 8th till the day of ovulation
Vaginally administered local estrogen:	To avoid the first pass of systemic oestrogen

Kadir Cetinkaya et al[4] used vaginally administered local oestrogen 25mcgms from 4th day for 15 days in CC induced cycle. They reported significant increase in ET on the day of ovulation (7.6+/- 1.4mm vs8.3+/-2.1mm) than the group where only CC was used, but there was no change in pregnancy rate.

Oral oestrogens are also used for preparation of endometrium for frozen embryo transfer, where previous IVF failure was thought to be due to thin endometrium. Dose schedule is different from fresh cycle. Jimenez PT et al[5] used oral estradiol 2mg thrice daily from day one for 12 days. They reported appropriate development of endometrium in 67% patients.

Others used stepwise increased dose of oestradiol, 2mg/day from 1st to 4th day, 4 mg from 5th to 8th day and 6mg from 9th to 12th day of cycle and reported better ET development.

Oestrogen was also found to improve blood circulation to radial artery which was evident by improved flow in radial artery.

Various drugs and intervention have also been used aimed to increase blood supply to the endometrium.

Vitamin E: Vitamin E at the dose of 600mg/day (200mg three times daily) orally given throughout the menstrual cycle to improve ET.

Akihisa Takasaki et al[2] observed adequate ET in 52%. patients following treatment. 72% showed improved RA-RI and 20% conceived. Each of these parameters registered statistically significant improvement when compared to previous untreated cycle. Author also found that Vitamin E improves growth of the glandular epithelium and number of blood vessels and VEGF protein expression was also increased.

L arginine treatment: Akihisa Takasaki et al[2] also tried L arginine in patient with low ET and increased RA-RI at the dose 1.5gms four times (6gms). 1875/day from 1st day till the day of hCG injection. It improved RA-RI in 89% of patients and 67% patients developed endometrium more than 8mm. This difference was statistically significant when compared to previous cycle in these patients.

Sildenafil Citrate treatment: Sildenafil citrate, a type

Table 1: Evaluation of the role of sildenafil in thin endometrium

Study	Dose of Sildenafil	Duration of therapy	Mode of administration	Results
Takasaki et al[2]	100 mg	1ST day till day of ovulation	intravaginal	92% patients showed improvement in endometrial thickness and RA-RI Intravaginal route reduces side effects like headache and hypotension
Firouzabadi et al[6]	50 mg	1st day till 45-72 hours prior to embryo transfer	oral	Endometrial thickness and triple line pattern significantly higher with sildenafil and estadiol valerate as compared to estradiol alone Clinical pregnancy rate was higher but not significant
Malgorzata Jerzak et al[7]	25mg X four times a day	3-6 days	Intravaginal suppository	Endometrial thickness was significantly increased Dose independent reduction in NK cell activity Successful use of sildenafil in two infertility patients with Asherman syndrome

5–specific phosphodiesterase inhibitor, augments the action of Nitric Oxide on vascular smooth muscle. It is thought to improve uterine blood flow and along with oestrogen lead to oestrogen induced proliferation of endometrial lining.

Tumor suppressor factor (p53), Plasminogen activator inhibitor 1(PAI-1), and Vascular endothelial growth factor (VEGF) genes need to produce necessary proteins to digest the endometrial cellular matrix to regulate cell growth and angiogenesis to facilitate implantation. Sildenafil citrate markedly enhanced p53 and stimulated angiogenic responses with increased VEGF.

Various studies have been conducted so far evaluating the role of sildenafil in improvement of thin endometrium in patients of infertility (Table 1)

Pentoxifyline, a xanthine derivative ,which is primarily used in medicine for treatment of of intermittent claudication resulting from peripheral arterial disease has also been tried to increase endometrial circulation.

Micronized low dose aspirin has also been tried for but no randomised trial is available in literature.

Granulocyte colony stimulating factor (GCSF)

G-CSF has the potential of a new promise in patients with poor endometrial growth especially when it is due to destruction of subendothelial layer where other more common treatment for vasodilatation fails. Norbert Gleicher et al was the first to use it in four patients with dramatic improvement. Various reported studies are shown in Table 2 But this is still in experimental stage and it needs more well planned research with large sample size to be able to recommend it as a standard treatment.

Neuromuscular electrical stimulation and biofeedback therapy (NEMS)

Another very recent experiment on improvement of poor endometrial growth is neuromuscular electrical stimulation and biofeedback therapy. Madafeiton MA et al[11] in their study investigated the effect of NEMS for improvement of thin endometrium. 41 infertile women with thin endometrium in previous treatment were recruited in this study. All women were subjected to NMES of pelvic floor muscle from 9th or 10th day for three or four times consecutively (qid for 20-30 mins/ day) by using biofeedback machine. These women were also advised for Kiegel manoeuvers for 15 minutes daily. NMES therapy was stopped when ET reached 8mm. They reported significant improvement in endometrial thickness in majority of patients. Though clinical pregnancy rate was better in NMES group but it was not statistically significant.

Conclusion

To summarize, adequately thick, trilaminar pattern endometrial milieu is important for implantation of the embryo and continuation of pregnancy. Various modalities have been studied for improving the endometrium (thickness and vascularity) and to support

Table 2: Evaluation of the role of G-CSF in thin endometrium

Study	Dose of GCSF	Duration of therapy	Results
Norbert Gleicher et al 2011[8]	1ml 30MU (300mcg)	2-7 days before embryo transfer (ET) by ET catheter	Dramatic improvement in endometrial thickness and all four patients conceived with one intramural ectopic pregnancy.
Y Kim et al 2012[9]	1ml 30MU (300mcg)	On the day of hCG injection	Significantly higher endometrial thickness (85% showed improvement), implantation and ongoing pregnancy rate
Maryam Eftekhar 2014[10]	1ml 30MU (300mcg)	12th-13th day of cycle but repeated once more if endometrial thickness below 7mm within 48-72 hours.	No difference in endometrial thickness Chemical pregnancy rate and clinical pregnancy rate were found to be better (39.30% vs. 14.30% and 32.10% vs. 12.00%respectively), Not statistically significant

embryo growth. Improving the endometrial blood flow to enable an estrogenic milieu for proliferation remain the cornerstone of achieving adequate endometrial growth and receptivity.

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NEW DRUG ON THE BLOCK

Corifollitropin alfa- A Novel Approach to In Vitro Fertilization

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Assisted reproductive technologies (ART) provide highest chance of success for infertile couple. However, the ovarian stimulation regimens applied for in vitro fertilization (IVF) and intra cytoplasmic sperm infusion (ICSI) are expensive, complex, require daily injections and frequent visits to IVF clinics which can be very stressful. Psychological burden of treatment has been found to be the primary reason for drop out from ART programme[1]. To reduce the burden of daily injections, corifollitropin alfa (Elonva), a long acting hybrid recombinant follicle stimulating hormone has been developed for the induction of multifollicular growth in an IVF cycle. One injection of corifollitropin alfa can replace seven days of daily injections of FSH.

A brief review of pharmacological properties of corifollitropin alfa will be followed by treatment outcome of its use in ART cycles.

Structure of corifollitropin

Corifollitropin alfa is a recombinant molecule constructed by combining the carboxy terminal peptide (CTP) of β subunit of hCG to FSH β subunit[2]. Presence of CTP component gives prolonged half-life which makes it different from regular rFSH. It is first of a new class of gonadotropin with different pharmacokinetic properties but similar pharmacologic features as rFSH. It interacts only with FSH receptors and not LH receptors.

Mechanism of action

Ovarian stimulation in IVF cycle involves administration of relatively high doses of exogenous FSH in a timely manner to maintain serum FSH concentration above the threshold necessary to support multifollicular growth. Due to the relatively short mean half life of rFSH of about 30h, daily FSH injections are needed during the stimulation period to prevent serum FSH levels from falling below the threshold and subsequent follicular growth arrest (Fig 1). After each injection of FSH, peak steady states are reached within 10-12h and then decline until the next injection. Steady state levels are reached only after 3-5 days of treatment, thus dose adjustment before day 5 is not advised.

Single injection of corifollitropin alfa in early follicular phase, causes persistent rise in FSH levels for first 3 days and then slowly declines lasting for total of 7 days. So it actually mimics step down protocol. The table below shows comparison between corifollitropin alfa and r FSH (Table1).

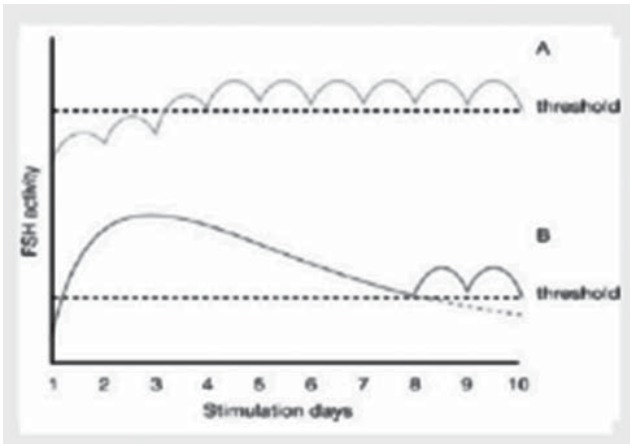

Figure 1: FSH threshold/window concept using (A) daily FSH treatment or (B) a single injection of corifollitropin alfa to induce and sustain multifollicular development during the first week of stimulation (Courtesy: Fauser et al 2008)

Table 1. Comparison between corifollitropin alfa and rFSH

Features	corifollitropin alfa	r FSH
1. Structure	Hybrid rFSH with hCG β subunit	Recombinant FSH
2. Dosage	Fixed dose formulations 150/100μg stat	Dose can be titrated
3. Follicular development	Always multifollicular	At low dose, can cause monofollicular
4. Protocol where it can be used	Antagonist protocol	Agonist/antagonist protocol
5. Risk of OHSS	7% risk; similar to r FSH	6.9 % risk
6. Hyper responders/ PCO	Avoid	Can be used
7. Patient compliance & convenience	++++	++

Mode of administration and monitoring

Ovarian stimulation with corifollitropin alfa can be started from day 2/3 of menstrual cycle. The optimal dose of corifollitropin alfa has been calculated to be 100µg for women weighing ≤ 60kg and 150µg for women ≥ 60 kg[2]. To prevent premature LH surge, GnRH antagonist 0.25 mg can be started from day 5/6 of stimulation and continued till the day of hCG. After seven days of stimulation, daily FSH 150/200IU can be given if required. Human chorionic gonadotropin (hCG) or GnRH agonist can be used as trigger depending on number of follicles which are developing. (Figure 2)

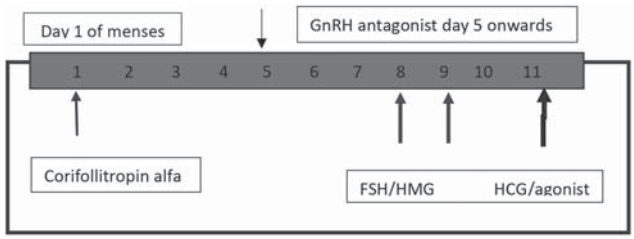

Fig. 2: Mode of administration

Drug metabolism

The mean half-life ($t_{1/2}$) of corifollitropin alfa is approximately 65 h for all doses tested between 60 and 240 mg as compared to rFSH which is approximately 35h where as peak levels are reached within 36–42 h vis-a-vis 10–12 h for rFSH[1]. Further, corifollitropin alfa shows slower rate of excretion in women weighing ≤ 50 kg compared to women above 80kg. Weight of patient affects its clearance and volume of distribution suggesting lower dose requirement in lean patients[3]. In short, the single-dose pharmacokinetics of corifollitropin alfa is characterized by a slow absorption resulting in peak levels within 2 days after injection. Thereafter, serum corifollitropin alfa levels decrease steadily, though the FSH activity may be retained above the FSH threshold for an entire week if the administered dose of corifollitropin alfa is sufficiently high.

Clinical outcome with corifollitropin alpha: what does evidence say?

The use of corifollitropin alfa in IVF cycles has been evaluated by four randomized controlled trials (feasibility study, dose finding study, ENGAGE, ENSURE trials)[1,2,3]. More than 2500 women have participated in these trials. Duration of stimulation varied from 9-11 days in all trials. One third of patients did not require any additional FSH after corifollitropin alfa injection. Serum FSH levels increased rapidly till post injection day 2/ day 3 of cycle in participants of corifollitropin and then started falling (corifollitropin 100/150 vs. rFSH 225 IU; ENSURE/ENGAGE trial)[3]. Serum estradiol levels at the time of hCG trigger were similar in all groups. Number of total oocytes, MII oocytes, fertilization rate, total number of embryo and good quality embryos in both corifollitropin and rFSH group were comparable. Even clinical pregnancy rate, ongoing pregnancy rates (38.9% vs. 38.1%) and multiple pregnancy rates (28.15 vs. 23.1%) were similar in phase III ENGAGE & ENSURE trials.[4]

Incidence of premature LH surge was significantly higher in corifollitropin group compared to rFSH in ENGAGE trial but not in ENSURE trial.[4] This high incidence of LH surge with corifollitropin alfa seems to result from higher FSH exposure during the early follicular phase. This was easily taken care by flexible GnRH antagonist protocol. This resulted in similar pregnancy rates in both groups.

No rise in progesterone was noted during stimulation period in both corifollitropin alfa and FSH groups. Luteal phase hormone profile was also normal in both groups.

Adverse effects

Use of corifollitropin alfa in IVF stimulation did not show any major side effects in any subject at any given dose or even during repeated cycles. TRUST trial assessed safety and immunogenicity profile of corifollitropin. It is well tolerated as no moderate or severe reactions were observed. Most common adverse effect noted was nausea and headache. This hybrid molecule has a carbohydrate chain which is foreign to humans and can be immunogenic.[4] This can lead to drug related hypersensitivity reaction. However, over 1000 women were tested for the same and none of them showed any hypersensitivity reaction.

Ovarian hyper stimulation syndrome is always a concern with use of corifollitropin alfa because of its fixed high dose formulations. Surprisingly, similar incidence of OHSS was reported in both groups in all four RCTs (5.4% vs. 8% in feasibility study, 2.6 % vs. 2.4 % in dose finding study, 7 % vs. 6.3% in ENGAGE trial, and 6.7% vs. 4% in ENSURE trial).[4]

Disadvantages

Main disadvantage of corifollitropin alfa is that it cannot be used in situations where monofolliular development / milder stimulation is required. In case of hyper- response, dose reduction cannot be made. *This characteristic limits its use in PCOS and hyper- responders.*[1]Also, like any other gonadotropin, it may show reduced response in advanced maternal age and premature ovarian ageing.

Conclusion

Corifollitropin alfa is a hybrid molecule with long plasma half life compared to rFSH. In an IVF cycle, single injection of corifollitropin alfa effectively replaces 7 days of daily FSH in normo-responders. Optimal suggested dose in women > 60 kg is 150 µg and 100µg in women <60kg. Addition of GnRH antagonist on day 5 of stimulation effectively prevents premature LH surge and allows use of GnRH agonist as trigger in case OHSS is suspected. So far none of the studies have suggested any major side effect with the drug. Reduced number of injections improves patient convenience and compliance, which ultimately increases cumulative pregnancy rates.

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CLINICAL UPDATE

Male Infertility: What a Gynaecologist Should Know?

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About 15% of couples do not achieve pregnancy within one year of cohabiting and seek medical treatment for infertility. A male factor is solely responsible in about 20% of infertile couples and contributory in another 30-40%[1]. Fertile partner may compensate for the fertility problem of the man and thus infertility usually becomes manifest if both partners have reduced fertility.

When a report of semen analysis is presented before the gynaecologist, a clear understanding of the implication of each parameter vis a vis aetiology and treatability of the cause is imperative. As in other diseases, a detailed medical, surgical and reproductive history is mandatory. History of any hernia repair, kidney transplant /surgery, scrotal surgery can suggest either injury to vas or neurological damage and related ejaculatory dysfunction. Also history of trauma to testes, or infection like mumps in childhood should be elicited.

Investigations for male infertility

Semen analysis

It remains the most important investigation for infertile couple. Ejaculate analysis has been standardised by the WHO[2]. A normal semen analysis is reassuring but does not guarantee its deposition in the female tract as in premature ejaculation, peyronie's disease and hypospadias.

Semen collection

Abstinence of 2 to 3 days is required. Sample is collected by masturbation, in a wide mouthed container in a private room, in the laboratory or if collected at home carried within one hour while maintaining temperature between 20° to 37° C.

Frequency of semen analysis

If the results of semen analysis are normal according to WHO criteria[2], one test is sufficient. There is substantial variation in semen quality between samples in the same male. An abnormal semen analysis should be confirmed with at least one more sample. An examination by a urologist/andrologist is indicated if two of the semen samples are abnormal.

Lower reference limits (5th centiles and their 95% confidence intervals) for semen characteristics, as defined by WHO guidelines 2010[2] (Table1)

Table1

Parameter	Lower reference limit
Semen volume (ml)	1.5 (1.4-1.7)
Total sperm number (10^6 per ejaculate)	39 (33-46)
Sperm concentration (10^6 per ml)	15 (12-16)
Total motility (PR + NP, %)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
White blood cells (leukocytes)	1×10^6 /ml
pH	≥7.2

In 90% of men the first portion of split ejaculate is the sperm rich fraction. Macroscopic evaluation of semen includes evaluation of colour, semen volume, pH, viscosity and liquefaction.

Volume- semen volume <1.5 ml suggests possible collection error, less period of abstinence, partial loss while collecting or retrograde ejaculation, inflammation of accessory glands and their blockage or congenital absence of both vas (CBAVD). Semen volume >5ml may suggest active exudation of accessory glands needing antibiotics.

pH- Obstruction of ejaculatory duct will be associated with semen pH <7 as contribution from alkaline secretions of seminal vesicle will be missing. An acidic pH (pH<7.2) suggests problems with seminal vesicle function. It is usually found in association with a low volume of the ejaculate and the absence of fructose.

Viscosity- Semen normally liquefies in half an hour and can be poured drop by drop. Delayed liquefaction, may indicate prostate dysfunction.

Morphology- Abnormal morphology of sperms (teratozoospermia), with an increase in abnormal forms may be transitory and associated with stress, gonadotoxic drugs intake, varicocele or idiopathic reasons. It may be associated with other abnormal parameters or may be an isolated abnormality. Repeat testing in 2 to 3 months should be done.

Sperm count- Azoospermia or absence of sperms suggest complete obstruction of both vas or absence of sperm synthesis consequent to testicular failure. Oligozoospermia may be due to hypogonadotropic hypogonadism, hyperprolactinemia or idiopathic.

Abnormal motility (Asthenospermia)- Forward progression abnormalities may be due to antisperm antibodies, non immunologic agglutination, genital tract infection, varicocele and idiopathic causes.

Leukocytes- All semen samples have white blood cells or leukocytes. If WBC's are present in concentrations of more than 1million/ml, then it may be suggestive of infection. Semen culture for bacterial sensitivity is indicated.

Antisperm antibodies- Screening for antisperm antibodies should not be offered as there is no effective treatment to improve fertility. However, its testing can be done if there is isolated asthenospermia with normal sperm concentration or in unexplained infertility.

In India, there is a high prevalence of TB, however it does not very commonly present as infertility. It is associated with obstructive azoospermia, irreversible vas damage with tell tale nodularity and fibrosis and has a poor prognosis. STD (sexually transmitted diseases) especially chronic gonnorrhea causes urethral strictures which can cause epididymo-orchitis. Ureaplasma impairs sperm motility. STI are associated with HIV and increasing immuno suppression is associated with poor semen quality. *The most common type of male infertility is idiopathic (30-40%) where oligoasthenoteratospermia exists in repeated samples with no abnormal anatomic or endocrinologic cause.*

Hormonal analysis

Along with semen analysis hormonal profile should be done i.e. FSH, LH, testosterone, and prolactin if required. The interpretation of the hormonal levels in guiding the diagnosis and management of the condition is shown below (Table2)

Table2: Interpretation of hormonal levels in male infertility

FSH	LH	Testosterone	Diagnosis	Action
↑↑	↑	↓	Testicular Failure (cong./acq)	FNAC, genetic testing
↓	↓	↓	Hypogonadotropic Hypogonadism (1%)	Drug therapy
n	↑	↑	Androgen insensitivity syndrome	FNAC
n/↓	n/↓	↓	Prolactin high, Pituitory tumour	Treat the cause
n/↑	n	n	Varicocele, infection, obstruction vas	Treat the cause
↑	n	n	Isolated Sertoli cell dysfunction	FNAC

Ultrasound doppler of scrotum /trans- rectal USG

Ultrasound doppler of scrotum with valsalva manoeuvre is done to diagnose varicocele and rule out any hydrocele, spermatocele, epididymal cyst, and to evaluate size of testes. Transrectal ultrasound is especially useful to diagnose obstructive azoospermia.

Testicular FNAC

It differentiates between Non Obstructive and Obstructive Azoospermia. Azoospermic sample warrants the need for FNAC (fine needle aspiration cytology) of testes. In testicular failure, there will be no sperms in contrast to obstructive azoospermia. If repeated FNAC yields no tissue then testicular biopsy needs to be done and it may be timed with harvesting of isolated sperms for ICSI.

Vasography

This is done by injecting a dye through penile urethra and site of block is defined, this may be done in OT followed by corrective surgery.

Genetic counselling & karyotyping

It should be offered to all cases with non-obstructive azoospermia and severe oligozoospermia (<5 million sperm/ml). *Y chromosome microdeletions* may be present in 13% of men with non-obstructive azoospermia or severe oligospermia[3].

In patients with AZF a & b microdeletions, successful sperm extraction has not been seen, and where AZF c microdeletion is present and ICSI is performed successfuly after sperm retrieval, the male fetus may be affected.

Treatment

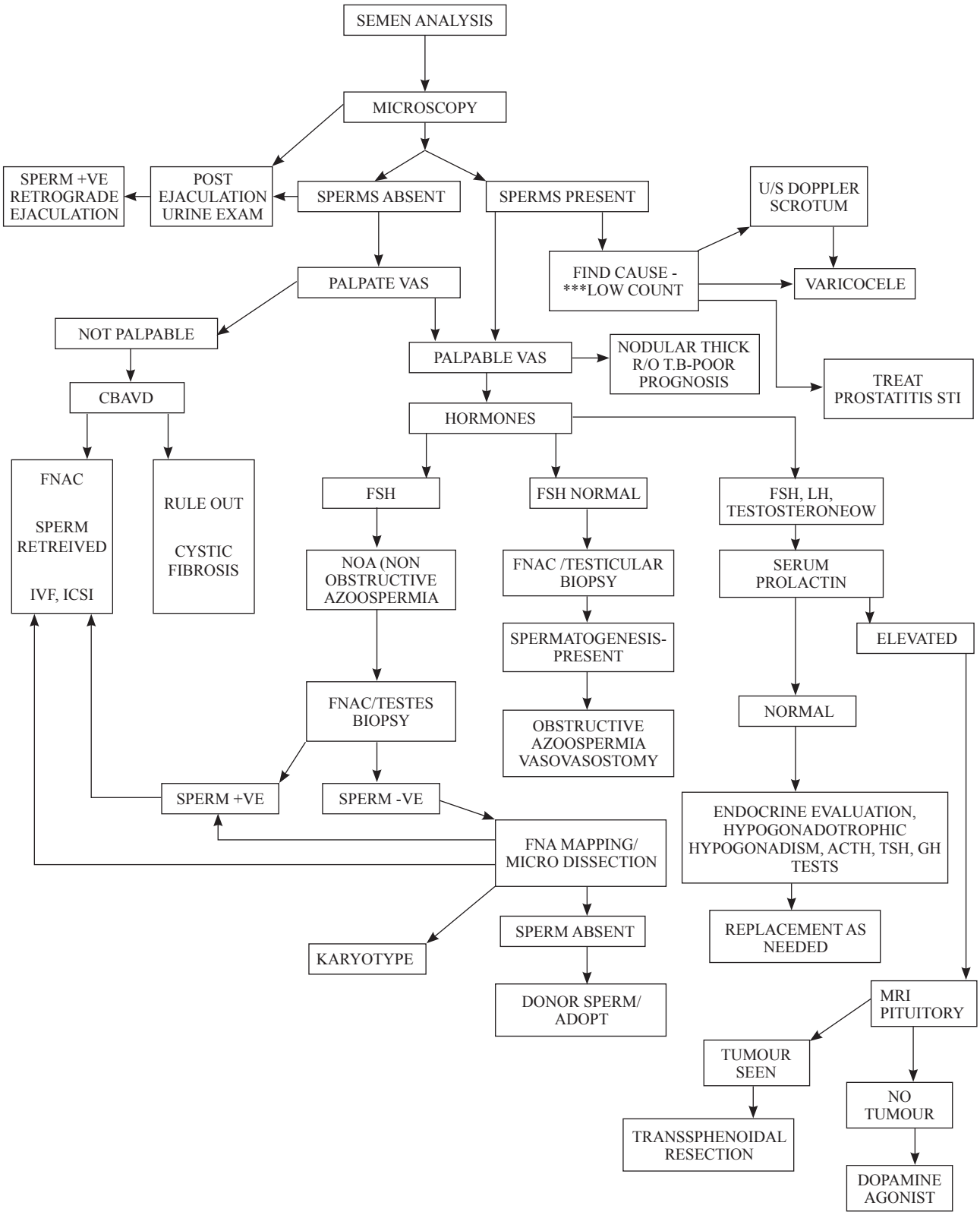
Counselling

Advise to stop smoking, alcohol abuse, use of anabolic steroids, excessive strength sports marathons, lose weight if obese. To avoid sauna, hot baths, thermal under wears and drugs affecting spermatogenesis (cimetidine, spironolactone, gentamycin, nitrofurantoin, erythromycin etc.).

Medical treatment

1. Treat Infections.
2. In males with idiopathic oligoteratozoospermia, antioxidants- like Vitamin A, E, and C, N-acetyl-L-cysteine, Zn, lycopene, carnitine, selenium, CoQ and astaxanthine have been used alone and in various combinations over a period of 3 months to 6 months. These drugs show lot of promise. However, lack of definite scientific evidence, i.e. due to paucity of good RCTs, their use is at present empirical only.
3. Treatment of erectile and ejaculatory dysfunction with drugs and mechanical means.
4. Hyperprolactinemia- treated with dopamine agonists, cabergoline being better.
5. Hypothyroidism/Hyperthyroidism- is associated with

Algorithm for management of male infertility



count and motility disorders which is amenable to medical therapy

6. Hormonal (sex steroids) treatment:

   Testosterones- Exogenous testosterones in Hypogonadotropic Hypogonadism should be used with HCG, as if used alone, they inhibit the HPT axis resulting in decrease in intratesticular testosterone level (ITT), which further inhibits spermatogenesis and is an iatrogenic cause for oligozoospermia. If HCG is given along with testosterone ITT level is maintained. Testosterone depot 200mg I/M every two weeks relieves the symptoms of hypogonadism in hypergonadotropic hypogonadism where it is not possible to achieve fertility.

   Antiestrogens- They block the estradiol feedback site of hypothalamus and result in increase in gonadotrophins. In oligozoospermic men, it is useful if FSH is normal or low. Clomiphene Citrate 25 mg daily for 25 days, with 5 days off, continued for 3 months.

   Aromatase enzyme inhibitors- They are useful for infertile men with low serum testosterone to estradiol ratio. These agents inhibit aromatase enzyme, resulting in increase in FSH. Steroidal agent-Testolactone 100-200mg/day, Non-steroidal agent Anastrazole-1mg/day, are off label as yet.

   GnRH therapy- Start HCG alone for 3-6 months, 1500 IU S/C 3 times per week, this increases the testosterone levels in the body and also in the testes, which is further helped (in spermatogenesis) on adding HMG or rFSH 75-150 IU IM three times per week. Response period for spermatogenesis is 6 to 9 months.

   Steroids for sperm antibodies are not recommended as doses needed for suppression are high and not well tolerated. Also, alternatives like IUI and ICSI are available.

Surgical treatment

Varicocele repair- is useful in patients with subnormal semen parameters and associated clinical varicocele and in otherwise unexplained infertility. *Microsurgery for Obstructive causes*- vasovasostomy, vasoepididymostomy.

Other Treatment Modalities

IUI- It is indicated in mild to moderate male subfertility. ie in oligospermia, asthenospermia, teratospermia, OAT, highly viscous semen, and if delayed liquifaction and in retrograde ejaculation.

IVF/ICSI in severe OAT- Sperm retrieval is done by microsurgical Testicular sperm extraction (micro-TESE) in men with NOA.

Donnor sperm IUI and adoption.

Conclusion

A well informed gynaecologist can do much to allay the anxiety of her infertile patient couple and along with andrologist guide them into following a fruitful path.

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Sniglets on Infertility

- ***Pregnitude:*** *the joyful and confident attitude one has during their monthly cycle when they believe it will be THE ONE in which they become pregnant.*
- ***Preganatory:*** *the two-week wait; in between waiting times*
- ***Mucusology:*** *the inexact science of attempting to determine the timing of ovulation*
- ***Eggspectation:*** *the period of waiting prior to ovulation.*
- ***Eggsplosive:*** *what a woman on fertility drugs is like.*
- ***Eggcessive:*** *another word for hyperstimulation.*

Contributed by Dr Sumitra Bachani

Beyond Semen Analysis

Pankaj Talwar VSM[1], Nagraja N[2], S Mohan[3]
[1]Professor (Colonel), [2]Lieutenant Colonel, [3]Professor (Brigadier), Consultant and Head
[1,2]Department of ART, [3]Obstetrics & Gynecology Department, Army Hospital (Research and Referral), New Delhi

Introduction

Approximately 10-15% couples of reproductive age group seek fertility assessment at various clinics worldwide. With an increasing population of working women who postpone marriage and initial child bearing, infertility services are being increasingly asked for now a days in elderly age group. With the advent of assisted reproductive techniques and advances in embryology the evaluation of the male partner is often overlooked though male factors account for approximately half of the infertility cases. It is essential to identify the pathology and treat the male partner, which may allow couples to improve their fertility potential and conceive naturally too.

The new WHO guidelines on semen analysis are enthusing and make one wonder whether we have over treated the male partners previously. The oligo-astheno-teratospermia known as OTA syndrome is commonly encountered problem in male infertility. This creates a challenging situation for the andrologists as this is a treatable condition if diagnosed at correct time and treated accordingly.[1,2,3]

Diagnosis of male factor

The semen analysis is the most basic laboratory test performed for the clinical assessment of the infertile couples. The semen evaluation parameters provide information on sperm production by testes, patency and function of the male reproductive tract and activity of the accessory glands. The clinical usefulness of the semen evaluation is refining rapidly as more objective, standardized methodologies are being introduced. Semen analysis provides essential information on the clinical and reproductive status of the individual. A number of clinical approaches have been used to identify the minimum standards for ideal semen sample. Results are inconsistent as some of the criteria used for evaluation rely on a single or multiple microscopic semen evaluation for prediction of the reproductive outcome.[4,5]

When to do semen function test

With absolutely normal semen analysis values as per WHO 2010 edition, it may not be necessary to advise any specialized tests to the males but in many cases of borderline parameters it becomes obligatory to do a battery of sperm function tests to evaluate functionality of the sperms.Various sperm function tests have been proposed and further endorsed by different researchers in addition to routine evaluation of semen sample. These tests detect functioning of a certain part of spermatozoon and give insight on the events during the fertilization of a mature oocyte. It is arduous to depend on a single group of tests for predicting fertility outcome as the fertility is dependent upon the sum total of all the functional parameters of the sperm and reliance on any one of them will be inappropriate in long run.

Ideal Sperm function test

Fertilization requires sperms to get nutrition from the seminal plasma in the form of fructose and citrate. These chemicals provide energy to the ever-moving and progressing spermatozoa. Fructose qualitative and quantitative estimation test are available to us commercially. Further sperms should be protected from bad effects of pus cells and excessive reactive oxygen species (ROS). Leucocyte detection test and ROS estimation test may be offered to such males. Ejaculate should have sperms in sufficient numbers which are morphologically normal. They should have intact and functioning plasma membrane to survive harsh environment of vagina and oxidative stress. These can be assessed by carrying out Hypo-osmotic swelling (HOS) and vitality testing. Further spermatozoon should have adequate mitochondrial function to reach the eggs and fertilize them. This can be assessed by mitochondrial activity index test, which is presently not available to us for routine clinical use. Sperms require adequate acrosome function to be able to penetrate zona pellucida and acrosome function test on the lines of hyaluronic binding and gelatin assay may be offered when required. The nuclear DNA should be tightly packed in their nucleus for them to be able to transfer the male genes properly in the oocyte and form male pronucleus. Nuclear chromatic de-condensation and DNA fragmentation test may be carried out for such assessments.

Principles of common sperm function test which are commercially available in India are as explained below:

a. *HOS test* is based on the ability of live spermatozoa to withstand moderate hypo-osmotic stress. With

moderate hypo-osmotic stress, membranes swell and reach steady state where fluid passing into the cells and that pumped out by intact functional membrane is of equal quantity. The cells will swell to varying degrees and demonstrate curling of tails at this stage but will not burst open. Dead spermatozoa whose membranes are no longer intact do not swell in hypotonic media[6]. (Fig 1)

b. The *sperm vitality* is reflected as the proportion of spermatozoa that are "alive" in the semen sample. It is measured by assessing the ability of sperm plasma membrane to exclude extra-cellular dyes. Sperm vitality should be determined in semen samples with less than fifty percent motile spermatozoa. Plain eosin staining can be used to assess vitality in wet smears. This provides quick assessment at the same time of count and motility assessment. Spermatozoa that are white (unstained) are counted as alive and those showing any degree of pink or red color are dead and non functional. Eosin-Nigrosin staining is also used for assessing vitality. The technique is based on the principle that dead cells will take up the eosin, and as a result stain pink. The Nigrosin provides a dark background, which makes it easier to assess the slides[7, 8, 9]. (Fig 2, Fig 3)

c. The *chromatin* in spermatozoa is in highly condensed state pre fertilization. Nuclear chromatin de-condensation (NCD) and subsequent male pronucleus formation is essential for fertilization and normal zygote development. Highly condensed nuclear chromatin state in nucleus is maintained due to existence of S-S cross links between its histone units. The cleavage of these S-S bonds can be induced in vitro by Sodium Dodecyl Sulphate and EDTA. Appropriate de-condensation of the nuclear chromatin is predictor of good fertilizing ability of the spermatozoa[10,11]. (Fig 4) DNA fragmentation index which is based on the sperm chromatin dispersion assay is also being offered by many laboratories. Here the percentage of sperms having healthy halo around the sperm heads are assessed. Halo depicts good quality sperms[12]. (Fig 5)

d. *Fructose levels* may also be assessed in the semen sample when indicated. Fructose is a marker for seminal vesicle functioning and has a role as a substrate for the glycolytic (anaerobic) metabolism of the spermatozoa. This is an important energy source for the sperm and exclusion of the seminal vesicular component from the ejaculate will result in almost completely immotile sperm. Concentration of fructose in semen ranges from 63 to 500 mg/dl (3.5 to 28 mmol/l).

Clinical applications of sperm function test

Ideally an accurate and inexpensive test is needed to determine which men require ICSI and which do not. The current fascination with ICSI has largely stifled the development and implementation of such a test. Potential benefits of sperm function testing remain high as we certainly require tests that can help us in diagnosing sperm dysfunction and offer appropriate treatment. Large number of patients can't afford and insist on less expensive options than ICSI and hyaluronic binding assays.

Conclusion

Understanding of the human sperm morphology, fertilization principles and biochemistry has improved over the years since WHO started standardizing the semen analysis and new research results became available. Objective data and information about important measures like kinematics of sperm capacitation, hyper activation of sperm, and the ability of the sperm to bind zona pellucida, penetration and acrosome reaction has improved. The knowledge of ability of sperm to finally de-condense its nucleus to form male pro-nucleus has enhanced our knowledge of events leading to fertilization and formation of embryo. This new information is helping us to diagnose new forms of male sub-fertility, predict success of attempts at natural or assisted conception and to design in vitro sperm function tests and treatments to overcome the diagnosed dysfunction.

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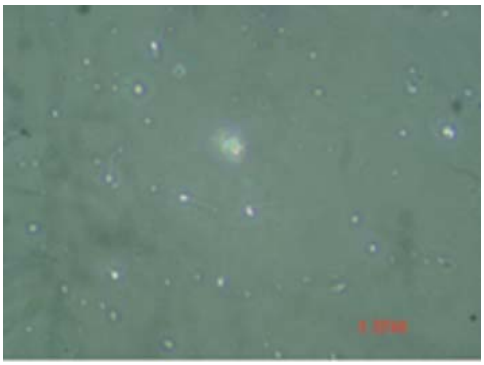


Fig 1: HOS testing - Healthy spermatozoon showing swelling and curling of the tail region

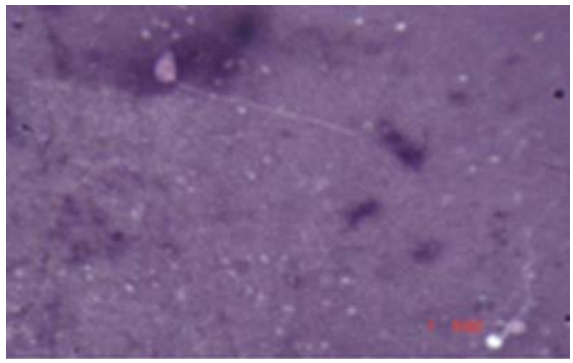


Fig 3: Eosin Nigrosin staining: Pink stained sperms are non-viable sperms. Nigrosin provides dark background

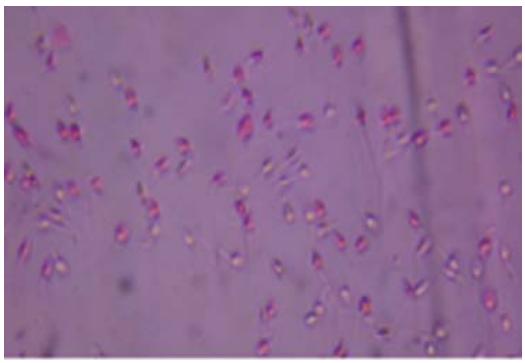


Fig 2: Eosin staining: Pink stained sperms are non-viable sperms as compared to white ones with intact membranes

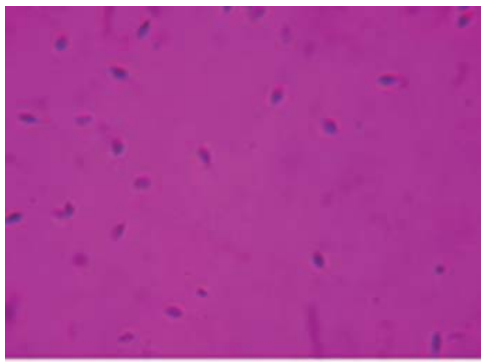


Fig 4: NCD Test: The cells showing swelling of nucleus with uniform chromatin are considered positive and the cells showing intact nucleus are considered negative for NCD

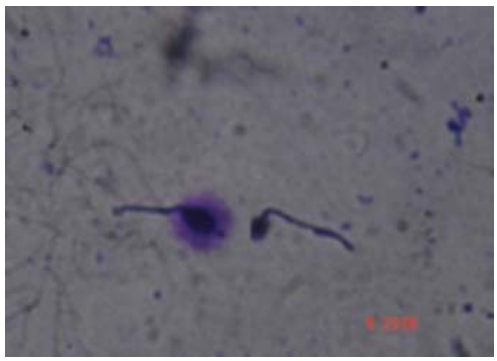


Fig 5: DNA fragmentation test: Cells showing halo around the head are good sperms with fertilizing potential

Meet the Luminary

Down the Memory Lane with..... Dr S K Das

It is always a pleasure to meet Dr SK Das, our most loved and respected teacher who is also an infallible surgeon and above all a sublime human being. The time we spent with her gave us an insight into what lies behind that ever smiling persona. Thank you Madam for sharing these amazing facets of your life with all of us!

Dr Jyotsna Suri, Dr Rekha Bharti

Birthday 14th August	**Place of birth** Allahabad (born and brought up)	**Graduation** KGMC, Lucknow	**MD** Safdarjung Hospital, Delhi University
If not a gynaecologist, what would you have been? A singer or a teacher	**What makes your day?** Operating successfully a challenging case	**Your strategy in a crisis** Keep cool and calm, never lose temper	
How do you de-stress? Listening to music	**Any regrets?** None, I have achieved all that I wanted, even if it was late	**One habit that you are proud of** My smile and a nice temperament	
What ruins your day? An argument or a fight			

A brilliant student

A dedicated clinician

Most loved teacher

Achievements galore - His Excellency President S D Sharma releasing the colposcopy atlas

Music: her passion

Propagating gynae oncology: the purpose of her life

The avid traveller

High point of your life The first one was getting a MD seat in Delhi University after facing many challenges; and the second was release of my 2 books - "An Atlas of Colposcopy, Cytology and Histopathology of Lower Female Genital Tract", in 1995 by Shri Shankar Dayal Sharma, President of India; and second book "Colposcopy: Practice and Atlas", in 2014 by Dr S. N. Mukherjee.

What disappoints you? If I am not been able to operate successfully and neatly.

Your role model Amitabh Bachchan and in medical field it is Dr Ansuiya Das and Dr Perviz Heera.

A book that has made a lasting impression Ramcharitmanas

Favourite Movie Kagaz Ke Phool

Favourite Singer Mohammad Rafi, all-time favourite.

Favourite Food Vegetarian

Your favourite pastime Travelling and my favourite destination is the Himalayas.

Your professional journey Joined Safdarjung hospital in 1964 as a postgraduate student followed by a small stint of lecturership in CMC Ludhiana. Worked as specialist for 6 years at Dhanbad, Jharkhand and back to Safdarjung Hospital from where I superannuated in 1996 as Head of Department. Practiced as Gynae Oncologist at Rajiv Gandhi Cancer Institute & Research Centre before joining Action Balaji Hospital. Presently, Head of Department, Gynaecologic Oncology at Action Cancer Hospital.

What motivated you to take up this profession Family decision

What inspired you to become a gynae oncologist? Interest in surgery and the fact that gynae oncology is a challenging surgical branch. I also realised that a lot needs to be done in this field. Wanted to promote gynae oncology and inspire other gynaecologists.

Helpless moment of your early professional life? Once while posted in Ludhiana, I did hysterectomy on a very obese patient. Woman had gaped wound in the postoperative period, she was very loving and while I did her dressing she would bless me daily for taking care of her; I felt very guilty.

Any unfulfilled tasks? Wanted to start Mch Gynae Oncology in various Delhi Institutes.

Your current state of mind Most peaceful

What does AOGD mean to you From first year of coming to Delhi, I postponed every commitment even travelling, to attend the monthly AOGD meeting. Held the post of President AOGD from 1988 to 1990.

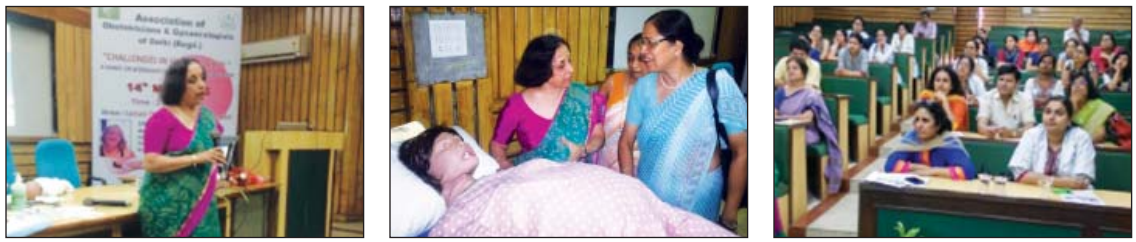
A piece of advice you want to give to budding gynaecologist Preventive oncology should be practiced more sincerely by all gynaecologists. Be sincere in your task and enjoy life with positive thoughts.

Any other message This is the fourth generation when AOGD office is at Safdarjung Hospital since I became President of AOGD. I wish the new team headed by Dr Pratima Mittal good luck and bless her for the outstanding work expected from the team.

Events Held

Events held under the aegis of AOGD in May 2015

- CME – Workshop on 'Challenges in difficult vaginal birth' on maternal fetal simulator on 14 May, 2015 at VMMC & Safdarjung Hospital, New Delhi.
- CME on 'Breastfeeding and lactation' under the aegis of AOGD on 16 May, 2015 at PGIMER, RML Hospital, New Delhi.
- CME on 'Demystifying menstrual endocrinology' by Endocrinology Sub-committee of AOGD on 19 May, 2015 at Fortis, Shalimar Bagh, New Delhi.
- CME on 'Medico legal aspect for gynecologists and male infertility' under aegis of AOGD on 22 May, 2015 at Saket City Hospital.
- Workshop on 'Sperm function test' under aegis of Indian Fertility Society, ACE and AOGD Infertility Committee on 24 May, 2015 at ART centre, Army Hospital, New Delhi.
- The Rural Health Committee under the aegis of AOGD conducted general health camp in Rotary Community Center Sangam Vihar on 24th May, 2015 from 10.30am to 2.00pm. This was organized in collaboration with Rotary club Delhi Ridge and Rotary eye care center.
- Perinatal Thyroid Screening Workshop under Reproductive Endocrinology Sub Committee on 25th May, 2015 at Fortis, Shalimar Bagh.
- 'Cervical cancer awareness programme for ASHA's' under aegis of AOGIN India, AGOI, AOGD & FOGSI oncology committee on 26 May, 2015 at UCMS & GTB Hospital, New Delhi.
- 3 day hands on Hysteroscopy-Laparoscopy workshop at Fortis, Vasant Kunj from 25th to 27th May, 2015.
- One day certification course in 'Advanced Laparoscopy' for AOGD members on 27 May, 28 May, & 29 May, 2015 at Ethicon Surgical Education Institute, Kirti Nagar, New Delhi.
- AOGD Monthly Clinical Meeting was held on 29 May, 2015 at DDU Hospital, New Delhi.



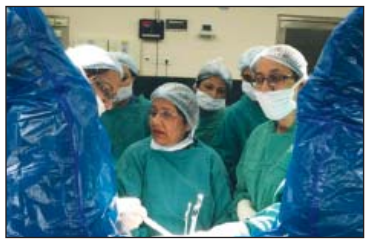
Workshop on Challenges in Vaginal Birth at Safdarjung Hospital

Workshop on Challenges in Vaginal Birth at Safdarjung Hospital

CME on Lactation in RML Hospital

Workshop on Sperm Function Tests at R & R Hospital

Cervical Cancer Awareness Program for ASHAs at GTB & UCMS



Hands on Hystero- Lapro Workshop at Fortis Hospital, Vasant Kunj

Monthly AOGD Meeting at DDU Hospital

Laparoscopic Flap Adenomyomectomy: A Fertility Sparing Procedure for Adenomyosis

Nikita Trehan
Consultant Gynaecologist and Laparoscopic Surgeon
Sunrise Hospital, New Delhi

Adenomyosis is classically defined as *'Benign invasion of the endometrial glands and stroma into the myometrium surrounded by hypertrophy and hyperplasia of the myometrium'*. It is extremely important to highlight that there is hypertrophy and hyperplasia of the normal myometrium. Hence the basis of 'Fertility sparing surgery' in adenomyosis raises a dilemma that if the entire pathology is removed i.e. the adenomyomatous tissue, then a large amount of normal myometrium will also be removed leading to a weak scar with a higher chance of antenatal scar rupture in subsequent pregnancies versus incomplete removal of the adenomyomatous tissue with no respite from the disease itself. Hence several workers like Osada came with the concept of *reinforcing flaps*[1]. Describing briefly our experience of the '*Laparoscopic Flap Adenomyomectomy'* for diffuse adenomyosis.

Procedure

1. The primary trocar is inserted at the modified Palmers point and then 3 secondary trocars are placed under vision - 2 lateral to the inferior epigastric vessels on each side and one supra pubic.
2. Dilute Vasopressin is infiltrated into the uterus (40 units in 200ml of normal saline).
3. A vertical incision is then given over the uterus up to the endometrial cavity 1 cm. of margin of myometrium is left over the basalis layer of endometrium.
4. On the serosal layer side, 1cm. of margin of myometrium is left inside by tunneling. All the in between myometrium is then excised.
5. The end result is thus that the uterus is left with 1 cm myometrium over the endometrium and another 1 cm myometrium under the serosa.
6. To make this remaining myometrium withstand subsequent pregnancy the uterus is then sutured with Vlock continuous sutures as reinforcing flaps.

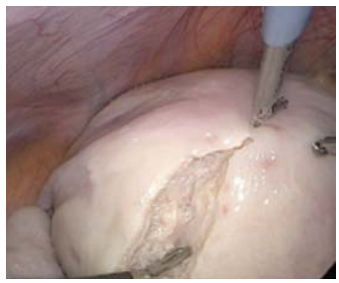


Fig. 1: Incision after injecting vasopressin

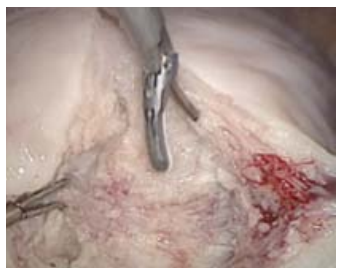


Fig. 2: 1 cm myometrium left behind with serosa by tunneling

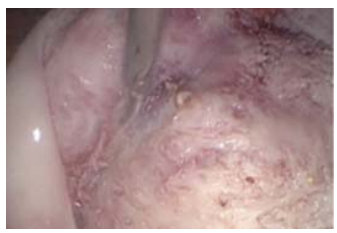


Fig. 3: Completion of serosal tunneling on one side

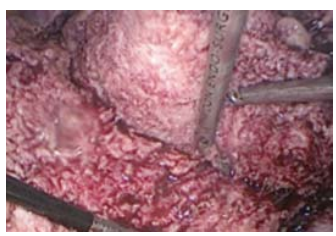


Fig. 4: 1 cm margin of myometrium left over endometrium

Fig. 5: Flap suturing being done

Results and Discussion

In our cohort of 26 patients operated by the above mentioned technique, at Sunrise Hospital, between February 2014 to February 2015, in which all the surgeries were performed by a single laparoscopic surgeon, the observations made were as follows: The average intraoperative time taken was 120 mins and the average blood loss was 150ml. Only one patient required blood transfusion (as her pre op haemoglobin was 7gm% she was given 2 units preoperative and 1 unit blood postoperatively). As a standard protocol all patients were started on oral intake 6 hours after surgery and were discharged 24 hours after surgery except for 4 patients. Two of them had post op ileus , the third required post op blood transfusion and the forth one was from outstation. In our patients a postoperative follow up was maintained and on the standard menstrual bleeding assessment questionnaires we found more than 80% reduction in menstrual blood loss and dysmenorrhoea. There were 50% spontaneous conceptions in 8 months following the surgery. As the long term follow up of this cohort is ongoing the results on fertility are still awaited. Various authors have previously reported a higher than normal incidence of miscarriage in women suffering from untreated adenomyosis reducing the take home baby rate significantly. After this procedure the miscarriage rate is also reported to reduce, increasing the take home baby rate significantly. In a study by Osada et al for massive adenomyosis in which triple flap at open surgery was used, results similar to our patients were seen[1]. Eun et al found in a study of 355 patients that dysmenorrhea decreased in 85% of the patients and menorrhagia decreased in 95% of the patients[2].

Conclusion

Laparoscopic Flap Adenomyomectomy for diffuse adenomyosis is a very useful procedure with very good results in women who want to preserve their reproductive functions.

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REVIEW ARTICLE

Challenges Faced for In Vitro Fertilization in Low Resource Set Up

Sudha Prasad[1], Ashwathy Kumaran[2], Saumya Prasad[3]
[1]Professor, Head and IVF Coordinator,[2] FNB Resident (Repro Biology), [3]Resident
[1,2]IVF & Reproductive Biology Centre, MAMC, New Delhi, [3]Department of Obs. & Gynae, VMMC & Safdarjung Hospital, New Delhi

Infertility in India

Since the first scientifically documented IVF birth of Harsha on August 6, 1986, in KEM Hospital, Mumbai, delivered by Dr Indira Hinduja, the field of assisted reproduction has rapidly grown in India.

Infertility, though not life threatening, can inflict devastating influence on the life of an individual for not fulfilling the biological role of parenthood. The incidence of infertility in India is between 10 and 15%. Approximately 13 to 19 million couples are likely to be infertile in the country at any given time. Among these 1.3 million (8%) require the use of advanced ART (Assisted Reproductive Technology) procedures such as IVF (In vitro Fertilization) or ICSI (Intracytoplasmic Sperm Injection)[1].

ART can help these couples to overcome physiological barriers to reproduction that, in previous generations, would have made it impossible for them to have children. However, the costs and the expertise involved are such that many Indians cannot afford nor access the treatment required, as these facilities are largely available only in the private sector.

Indications for ART[2]

1. Irreversible pathology of the fallopian tubes
2. Male infertility:
   a. Total motile sperms (TMC) < 1million- ICSI
   b. TMC > 1 million but < 10 million – IVF
3. Endometriosis – multifactorial
4. Idiopathic or unexplained infertility of >3 years or earlier if women >36 years
5. No conception after 3 or 4 IUI cycles
6. Failure of donor semen insemination
7. Failure of ovulation

Why is IVF expensive?

The exorbitant cost of IVF treatment is because of:

1. High capital investment required
   - The cost of establishment of the IVF centre
   - Choice of area and locality for the turnover viability
   - Infrastructure development to meet the standards
   - Purchase of fool proof high-end equipments and their backup
2. Exorbitant Current /Recurrent Expenses
   - The cost involved to pay for the staff expertise and their backup
   - The electricity and maintenance charges.
   - The cost of drugs especially the hormones used for IVF protocols
   - The cost of laboratory and USG evaluation
   - The cost of disposables required for Ovum Pick Up, Embryo Transfer
   - The costs for the media and instruments needed in the embryology lab
   - Cryopreservation of sperms/embryos
   - Charges for donor oocyte, donor sperm, surrogate,

Therefore IVF treatment per cycle often costs the patient 1-2 lakhs in private sector so that they have a profit beyond the expenses incurred. Even then, the cost of an IVF cycle in India is less than half of that in the developed countries, making India, with its relaxed ART regulations especially regarding surrogacy and gamete donation, a booming destination for fertility tourism with private IVF centres opening up in every nook and corner.

Though good for the national financial income, this scenario makes it difficult for the multitude of economically backward sub fertile couples to avail affordable ART. Thus, the Government- run IVF centres offering free treatment and hormones at subsidized rates are proving to be a boon for this group of patients.

Difficulties faced by Government-run IVF centres

1. Approval from administration to be taken to start an IVF centre:

   Due to lack of general awareness about infertility and ART, there was initial reluctance by the Government to approve the establishment of ART centres in the Government sector in India where we are trying desperately to contain the explosive population growth.

   But sustained effort from the ObGyn faculty managed to convince the need for ART as

a. Infertility is a medical problem that requires medical treatment.
b. If not managed, it can affect the holistic wellbeing of the affected person.
c. Tuberculosis causing irreparable tubal damage is rampant among the financially backward.
d. Three fourth of the couples requiring ART cannot afford private setups.
e. To further medical education

2. The lack of legislation regarding ART:
   The lack of legalised standard guidelines is another hurdle faced while setting up an IVF centre.

3. Lack of expertise:
   Reluctance to learn expertise of IVF by the team in government set up, shortage of dependable indigenously made equipment, fluctuating patient turnover owing to competition, no special incentives from the government as for a humanitarian cause - all these make establishing IVF in a government set up challenging.

4. Procurement of the necessary equipment and space:
   Initial investment required for setting up an ART centre is substantial. Hence, while starting an IVF centre in a low resource set up, exhaustive planning is required to optimally use the space allotted and modifying it to meet the specifications in the guidelines. The equipment procured should also be acquired aiming for maximum productivity involving least possible expenditure rather than extravagance**.**

Advantages of Government- run IVF centres

Prevention and appropriate treatment of infertility has been included in the ICPD (International Conference on Population and Development) Programme of Action; it follows that alleviation of infertility should be included as a component of the primary health care system.

1. Government-run IVF clinics have proved to be a boon for infertile couples requiring ART. Comparatively cheaper IVF cycles, as man power is already available in public sector. However there is requirement of special training program for all stratum of manpower working in IVF sector so as to inculcate expertise and dedication.
2. One time requirement of non-recurring machineries with appropriate justification is provided by the government.
3. Daily documentation of stock of consumables and disposables required for IVF/ICSI cycles is an exhausting task.
4. Only expenses which patient has to pay is the cost of drugs required which may be Rs 20,000 to 40,000.
5. Success rates are comparable to the best of private set ups.
6. Strictly adhere to the ART rules and guidelines laid down by ICMR.
7. Ethical, genuine and standardised system

The IVF and Reproductive Biology Centre, MAMC, New Delhi

The IVF and Reproductive Biology centre at Maulana Azad Medical College, New Delhi started in 2008 is the first government IVF centre in India. The centre has over 7 years, developed from the grass root level and now has more than 50 induction cycles per month. The success rate is 40 % and the average patient expenditure is just Rs 35000 (for the hormones required for IVF cycle).

Over the last seven years, with the exhaustive and dedicated effort of the team, this centre has developed a world class IVF centre and is presently fully equipped for:

- Screening and Monitoring IVF cycles
- Availability of GnRH analogues, Gonadotropins and hormones at subsidised rates
- TVS guided Oocyte pick up
- USG guided embryo transfer
- Embryology culture lab for fertilizing and extended embryos culture.
- Cryopreservation of sperms, testicular tissue and vitrification of embryos.

Being part of the medical college set up, it has the back up from the surgeons and urologists for Andrology related problems and can always fall back upon the full fledged OBGYN department for fertility evaluating endoscopies as well as enhancing surgeries and obstetric care of the ART conceived patients. Another huge advantage of this Government run IVF centre is the quick access to all departments of medicine in case need arises.

Steps to facilitate satisfaction of patients

This is also one of the initial hurdles that the low resource IVF centre has to face as the patients tend to keep going to ill affordable private centres due to ignorance and prejudice about the quality of care available in the government sector. After draining all finances and ovarian reserve, these frustrated poor patients return back to public sector with great hope.

Decreasing the cost of IVF

1. After the establishment of Govt-run IVF centres,

definitely there is a competitive expenditure at IVF centres of private and public sectors.

2. In established Govt Obstetric centres public campaigns should be done to promote awareness regarding the prevention of infertility and facilities available at Govt-run IVF centres.
3. Starting more standardised courses to train doctors, embryologists and other staff specifically for reproductive medicine will help overcome the expertise shortage.
4. Developing indigenous technology to produce international standard equipments and Drugs.
5. The expensive hormones used in IVF cycles are the GnRH analogues and Gonadotropins. Hence using IVF protocols like antagonist cycles, mini/ mild IVF and natural cycle IVF can substantially reduce the drug expense. Even while long agonist cycle is required patient tailored dose of GnRh analogues and antagonist protocol can be useful. Contrary to the long agonist protocol, the antagonist protocol for COH is more patient-friendly[3]. Gonadotropins are started to stimulate the ovarian follicles and gonadotropins antagonists regulate LH surge (Fig 1). This protocol is ideal for women with PCOS as the antagonist decreases the risk of OHSS.

Mini/ Micro/ Mild IVF[4]

Stimulation and monitoring with combination of clomiphene with or without low dose injectable medications

⇩

One or two quality oocytes are retrieved.

⇩

All matured eggs are injected with sperm (ICSI)

⇩

Embryos are cryopreserved

⇩

Frozen Embryo Transfer (FET) done for better pregnancy rate.

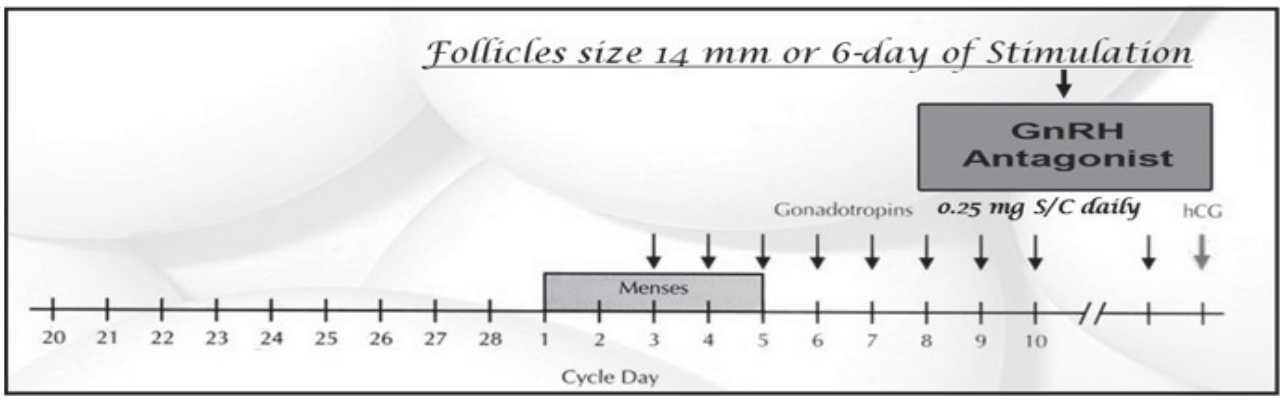

Fig 1: Antagonist protocol [3]

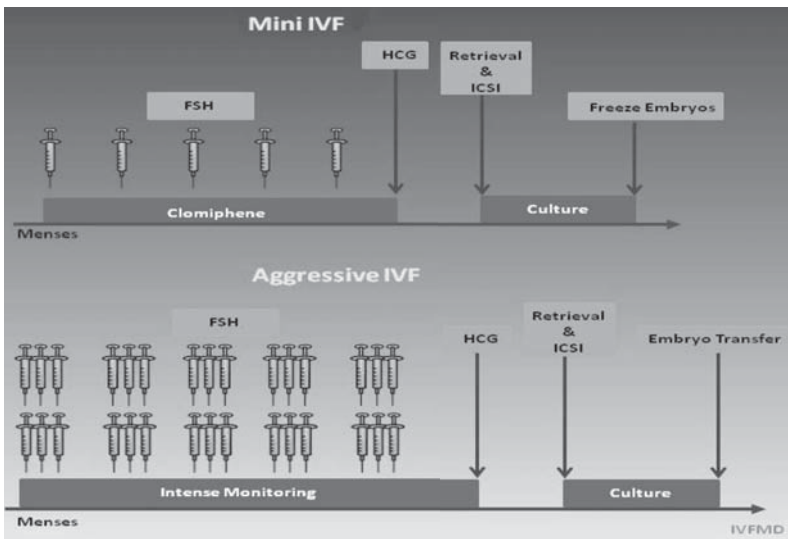

Figure 2: Mini IVF Protocol

Advantages

- The IVF stimulation process is easier for the woman
- Medications are cheaper
- The cost for one cycle of IVF should be substantially less.

but

Pregnancy success rate is much lower compared to conventional in vitro fertilization - only 15%.

Natural cycle IVF - Oocytes pick up is done without COH. Chances of no oocytes being retrieved are as high as 50% and hence not advocated in ART.

Holistic approach to improve ART Outcome

Any treatment is fully effective only when we cater to all aspects of the ill person. Especially in the sub fertile woman the psychological milieu and the stress levels are closely linked to the ART productivity.

Role of counseling and Yoga

In our centre at MAMC, women undergoing treatment are counseled and their pre treatment stress levels evaluated by trained personnel. The women are taught suitable Yoga techniques according to their stress levels and requirements. These women were noted to have less stress levels on subsequent psychologic evaluation. In addition, they showed improved uterine artery PI and RI in the luteal phase and had significantly more pregnancies than the women who were not willing for counseling and Yoga.

Reducing the Burden of ART

Careful exclusion of patients should be done who actually don't require ART. Plan of timed intercourse or intra uterine insemination with washed sperms should be advocated in suitable patients.

Role of Tubal cannulation

Around 15 % of women with proximal tubal block can successfully conceive without ART using simple techniques like USG or tactile tubal cannulation[5].

Conclusion

Government- run low resource IVF centres are not only feasible endeavors but have ART treatment outcomes as good as in private set ups. Hence, they are of immense help to the financially backward requiring ART. Stress levels are mitigatory to ART outcomes and indigenous relaxation techniques like Yoga are useful adjuncts to improve ART productivity.

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The miracle

There a baby cuddled in her mother's lap
Another walked hand in hand with her
I lay barren waiting for the embryo
to sprout in me
The autumn never seems to halt
My eyes get flooded and dry away like a setting sun
But for the dawn I waited
Then came a wave of pills n injections
And jolts of null results
Life felt trapped in a calendar
Till the grass turned greener and flowers blossomed
Miseries went bygones n bygones

- Dr Sarita Singh
Specialist, VMMC & Safdarjung

With a baby or without, you are valuable, you are whole and you matter. - Anonymous

FLOW CHART

Steps of IUI

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Pretreatment counselling and screening:
- Day 2/3 FSH> 10mIU/ml, Day 2/3 estradiol> 80pg/ml, AMH< 0.2-0.7ng/ml, inhibin B< 45pg/ml **(low ovarian reserve)**
- Day2/3 first scan: antral follicle count, ovarian volume & reserve, ovarian cysts/pathology, uterine pathology, endometrial thickness <2-4mm & cavity empty
- Tubal patency

Ovulatory patients (ovarian stimulation), **Anovulatory patients** (ovarian induction)

Ovulation monitoring with transvaginal ultrasonography from day 8
- Follicular number, size, growth (2-3mm/ day)
- Endometrial thickness and appearance

Ovulation trigger by injectable HCG 10,000units / GnRH agonist:
- Leading Follicle ≥ 18mm
- No. of follicles > 16mm not more than 4, > 12mm not more than 8.
- Endometrial thickness ≥ 7mm and ≤ 12mm

Best conducive to pregnancy:
- Perifollicular vascularisation, RI 0.4-0.48, PSV > 10cms/sec
- Triple layered ("5 line") appearance of endometrium
- Myometrial contractions (wave like motion of endometrium)
- Homogeneous myometrial echogenicity
- Endometrial blood flow within zone 3
- Uterine artery blood flow PI < 3
- Myometrial blood flow

Washed/ prepared semen sample:
- Semen processing soon after liquefaction/ within 30min of collection
- Inseminate volume 0.2 – 0.5 ml, count 5-10million/ml, motility 80%, velocity 20-25μm/sec

Technique of IUI:
- Timing : 36 – 40 hours of HCG injection, as soon as semen processed/within 90min of semen collection
- Disposable, nontoxic, semi rigid, rounded tip catheter, minimal dead space,
- Correct identification of semen sample, processed sample maintained at 37^0C.
- Asepsis, atraumatic, done slowly over 1-2 min.
- Difficult IUI: traction on cervix to straighten angle between cervix & uterus

Documentation of ovulation

Post insemination:
- Luteal phase support: micronized progesterone 200-400mg / dydrogesterone 20 mg daily
- UPT 15 days after IUI
- No coitus restriction, no bed rest

Three Dimensional Ultrasound in Infertility

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Three dimensional ultrasound represents the best tool in evaluating the uterine cavity, the endometrium, and for assessing its volume and vascularity pattern. It also offers a very good image of the uterine structure, the adnexal morphology and their relationship. It performs a thorough pelvic assessment by a single examination. Even though it is technically more difficult and time consuming, a good practice and high quality ultrasound equipment offer a series of benefits over any other kind of investigation. Normal uterus is easily assessed using 3D ultrasound, where the coronal plane gives a good image of the endometrial cavity, the surrounding myometrium and of the uterine external contour, a fact of most importance. Conventional ultrasound, with a thorough scan in both sagital and transverse sections, offers an almost complete description of the uterus, endometrial thickness and vascularisation pattern. **Three dimensional ultrasound does not substitute, but completes the examination by offering a complete image of the uterine cavity in one single acquisition (Fig 1).**

Timing of scan

The scan should preferably be done on on Day 2 of the cycle for the ovary and in postovulatory phase of cycle to look at the endometrial cavity and for fibroid mapping.

For the ovaries baseline scan is done on *day 2nd or 3rd* of the cycle. This scan is done to find out what drugs and what doses will be required to achieve adequate ovarian stimulation. This is important because there are some low reserve ovaries, which would not produce many follicles in spite of high doses of stimulation and there are some polycystic ovaries which would produce multiple follicles even with lower doses for stimulation. Therefore stimulation should be started only after doing the baseline scan and deciding the dose according to the findings.

For the endometrial cavity and for fibroid mapping, scan is done *in peri / postovulatory phase* of cycle, at this time endometrium is thick, contrast between endometrium and myometrium is marked and septae / synechiae are better evaluated.

Preliminary to the transvaginal scan, an abdominal scan on a full bladder must be done. This will rule out any subserous fibroids which may be present and could be entirely overlooked on a vaginal scan alone. Approximately 15% findings are added (Fig 2).

Uses of 3D USG in infertility

- to look at congenital anomalies of the uterus,
- to detect endometrial polyps
- for fibroid mapping,
- uterine synechiae
- evaluating tubes and ovaries

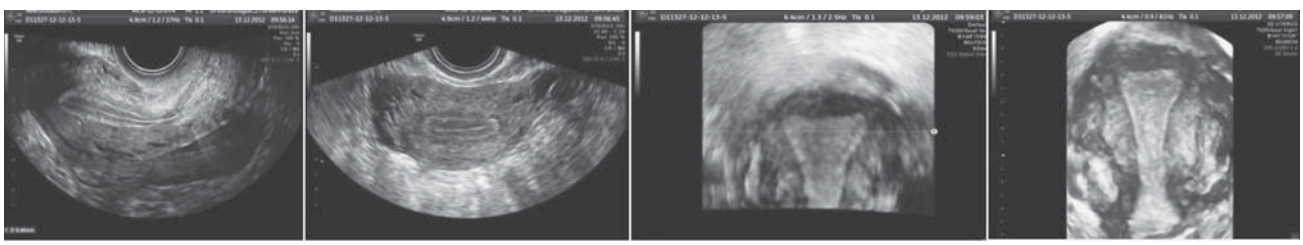

Fig.1: Sagital, Transverse & re constructed coronal views

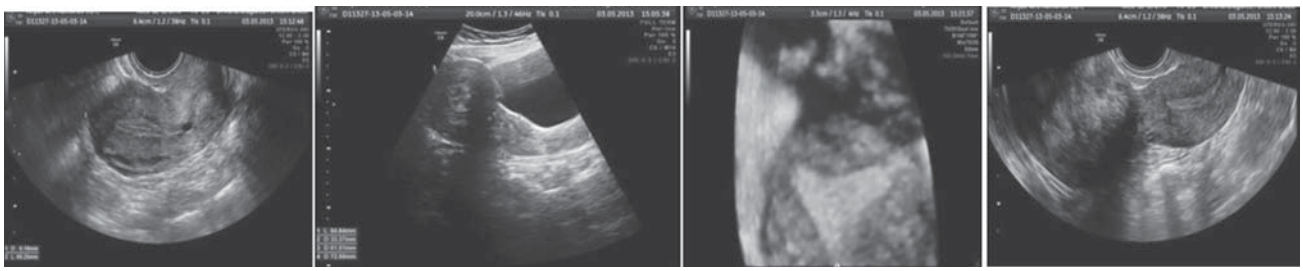

Fig.2: large fundal fibroid could be completely missed on "TVS only" scan

Congenital uterine anomalies

The exact incidence of congenital uterine anomalies is difficult to determine since many women with such anomalies are not diagnosed, especially if they are asymptomatic, but it seems to be around 2 to 4% of live births. There is a special mention regarding the association with spontaneous first trimester abortions. Among all types of congenital uterine anomalies, the septate uterus presents the highest rate of miscarriage. Clinically, this is of greatest importance, as septate uterus is considered a "mild" anomaly and the differential diagnosis with bicornuate uterus, anomaly with a better fertility prognosis, is difficult. An accurate diagnosis in all cases implies a very good visualization of the uterine cavity, with focus on the fundus, and a delineation of the uterine external contour. So far, the most commonly used diagnostic method was hysterosalpingography (HSG). It provides excellent view of the uterine cavity and cervical canal as well as, information related to tubal patency, but no data regarding the fundal shape. Moreover, it exposes the patient to ionizing radiation and requires an X-ray laboratory. Alternative method for external visualization of the uterus is laparoscopy, which is expensive, invasive and gives no information regarding the endometrial cavity. MRI may be employed in certain cases, with very good results, but at high cost.

*Arcuate/septate uterus***:** The septate/arcuate uterus develops from a defect in canalization or resorption of the midline septum between the two müllerian ducts. The degree of septation varies from a small midline septum to total failure in resorption resulting in a septate uterus with longitudinal vaginal septum. Partial and complete uterine septa are defined by the proximity of the septum to the internal os; depth of **septum >5mm** (Fig.3) is considered significant. The presence or absence of a complete or partial vaginal septum is not relevant to the classification. A septate or arcuate uterus has a normal external surface, but two endometrial cavities, in contrast to a bicornuate uterus which has an indented fundus and two endometrial cavities. The distinction between arcuate and septate uterus is rather difficult and up to some point, subjective. It is accepted that the arcuate uterus has a slight midline septum with a broad, fundal base and normal external surface, while the septate uterus presents a more important septum and sometimes may have a small indentation that does not exceed **5 mm** depth. Sonographically, the two uterine cavities are seen as split endometrial echoes, best visualized during secretory phase. The degree of septation may be assessed by conventional scan or, much better, by three dimensional sonography. The coronal plane offers a very good diagnostic image of the endometrial cavity, as well as the fundal contour (Fig 3).

Bicornuate uterus: This refers to a uterus in which the fundus is indented (arbitrarily defined as 1 cm) and the vagina is generally normal. This anomaly results from only partial fusion of the müllerian ducts. This leads to a variable degree of separation of the uterine horns that can be complete or partial. Characteristically, there is only one cervix. Thus, the diagnosis depends on the very good visualization of the two endometrial cavities and the cervix (Fig 4).

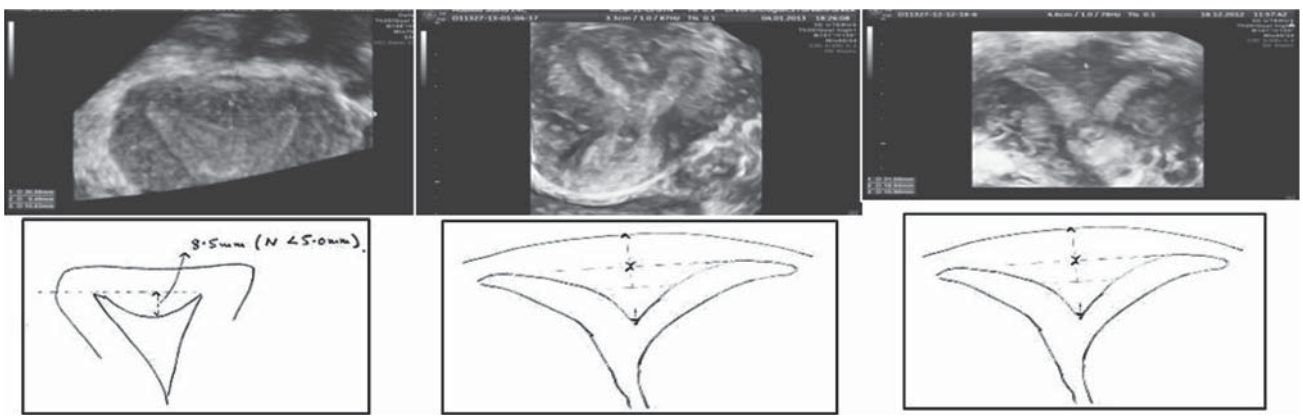

Fig. 3: Depth of septum

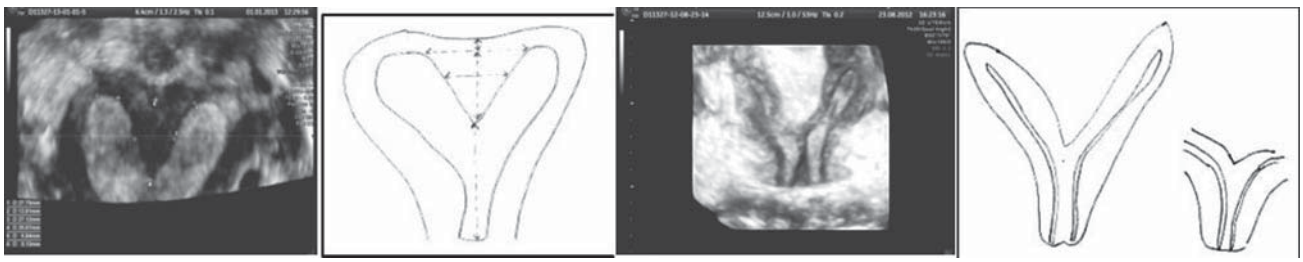

Fig. 4: Note Depth of fundal notch (on fundal contour), in Bicornuate uterus

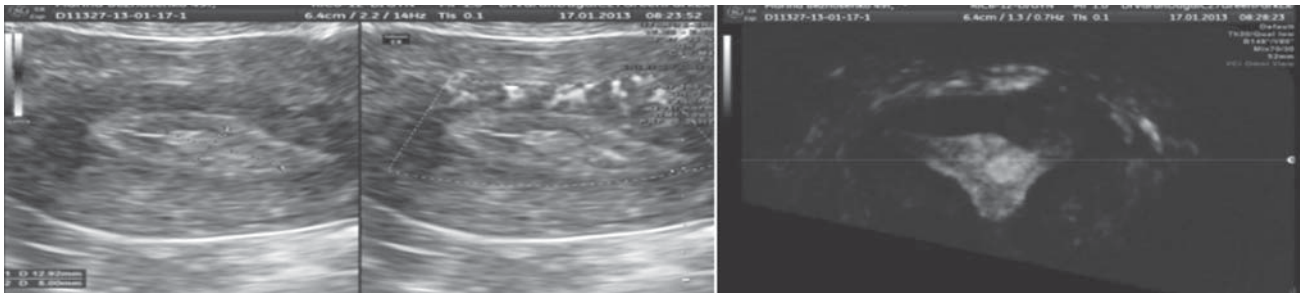

Fig.5: Endometrial polyp

Didelphic uterus: Uterine didelphys, or double uterus, occurs when the two müllerian ducts fail to fuse, thus producing duplication of the reproductive tract. Generally the duplication is limited to the uterus and cervix [uterine didelphys and bicollis (two cervices)] although duplication of the vulva, bladder, urethra, vagina, and anus may also occur. Women with a didelphic uterus and bicollis often have good reproductive outcomes. A septated vagina occurs in 75 % of cases.

Endometrial polyps

Conventional ultrasound presents the endometrial polyp as a focal, unequal thickening of endometrium, of higher echogenicity than the myometrium, with an easily detectable single feeding vessel. Large polyps may appear as diffuse endometrial thickening, being difficult to differentiate from simple hyperplasia. Three dimensional sonography may facilitate diagnosis. The differential diagnosis from a sub mucous myoma in questionable cases is easily set. Also, the shape, the dimensions, the origin and the impact on the endometrial cavity are clearly visualized (Fig 5).

Fibroid mapping

The exact position, the impact on the ostium tubae and the uterine cavity may be difficult to assess by conventional ultrasound. A very easy solution in many cases is offered by 3D acquisition. The increased echogenicity of the endometrium improves the visualization of the uterine cavity contour. This image may offer exact data regarding the dimension, position of the tumor and degree of distortion of the cavity. 3D creates a very good hysterographic image. It guides the therapeutic procedure in cases referred for hysteroscopic resection, by evaluating the degree of protrusion in the uterine cavity. In the same manner it, also, selects the cases to benefit from laparoscopic or classic myomectomy (Fig 6 & 7).

Table1: Differentiating fibroids from adenomyoma

	Fibroid	Focal Adenomyosis/ Adenomyoma
1	Almost never tender on TV probe pressure (except during pregnancy and when undergoing infarction)	Tenderness means adenomyosis
2	Few or no cystic areas	Often have tiny cysts
3	Hypoechoic rim of compressed myometrium	No rim
4	Distal shadowing	Streaky shadows
5	Calcification	No calcification
6	More peripheral vessels circumscribing mass	More diffuse central vessels
Microbubble I/V contrast ultrasound may be necessary in very confusing cases		

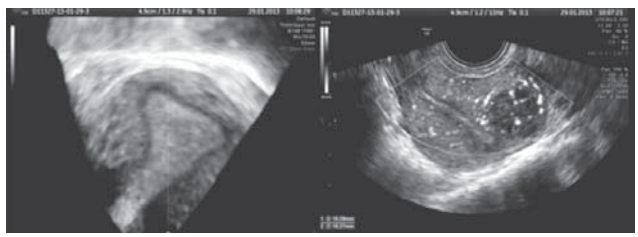

Fig. 6: Endometrial cavity not indented by fibroid

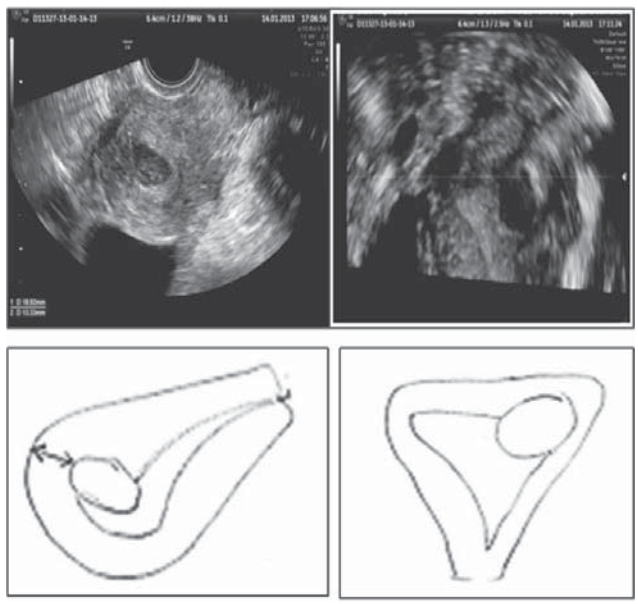

Fig. 7: Submucosal fibroid indenting the central uterine cavity

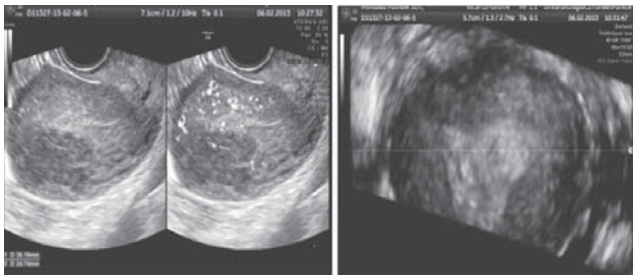

Fig. 8: Focal adenomyoma indenting uterine cavity

Uterine synechiae / Ashermans syndrome

3-D ultrasonography is very useful in detection of uterine synechiae / Ashermans syndrome (Fig. 9,10)

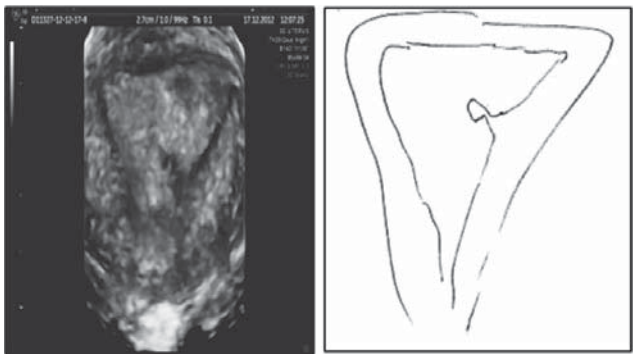

Fig. 9: Intrauterine synechiae –seen as an incisura on left wall

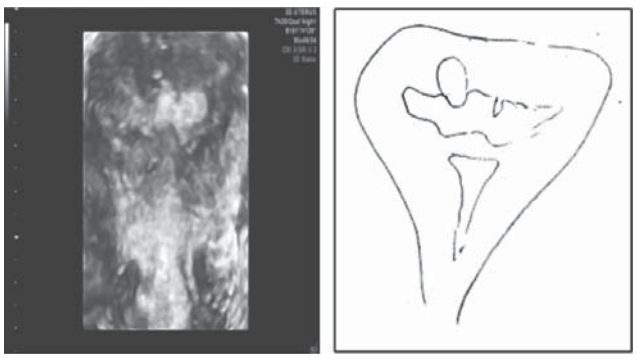

Fig.10: Multiple bridging synechiae

The fallopian tubes

Evaluating the tubal patency represents a key step in the assessment of the infertile couple, especially in situations with risk factors for tubal damage. Obstruction and damage of the fallopian tubes are accounting for almost 35% of all infertility cases. Normally, the fallopian tubes are not accessible to ultrasound evaluation, unless their diameter is increased by a pathological process, such as hydrosalpinx, pyosalpinx, ectopic pregnancy, tubal carcinoma or torsion. The diagnosis of tubal patency has changed very little over time, laparoscopy with chromo-pertubation being still considered the "gold standard", as it was 20 years ago, along with HSG.

The ovaries

Sonographic evaluation of the ovaries is directed towards their size, location, presence of dominant follicle; correlates follicle size to endometrial appearance and measurements; evaluates the cul-de-sac; assesses the corpus luteum and notes the presence of persistent follicular cysts. The ovarian volume is age dependent, as well as the follicular size and number and the degree of stromal vascularity. All these parameters may be easily assessed by 3D sonography. In case of a solitary ovarian cyst, 3D ultrasound offers a graphic representation of the structure, its shape and relations. A cyst offers a fluid environment, facilitating the view of inner structures, such as intracystic papillae or vegetations thus defining the etiology and the prognosis.It can help differentiate a paraovarian cyst from an ovarian cyst.

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There is a unique pain that comes from preparing a place in your heart for a child that never comes. -David Plum

GUIDELINES

Medico-Legal Implications of Gamete Donation

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World over, Assisted Reproductive Techniques have offered hope to millions of couple who have been trying to conceive. Now with the concept of donor eggs, sperms or surrogacy, many more couples have been able to fulfil their dreams. However, "third-party reproduction" (use of donor eggs, sperms or surrogacy) is a complex process requiring consideration of social, ethical, and legal issues, not only for the couple and the donor, but also for the offspring.

To resolve these legal and ethical issues in our country, 'National Guidelines on Regulation, Supervision and Accreditation of ART clinics in India', was released by the Indian Council of Medical Research (ICMR) in 2005[1]. This was however, non-binding in nature. In 2008, the Ministry of Health and Family Welfare (MOHFW) and the ICMR released the ART (Regulation) Bill and Rules 2008, which was further amended and the revised version, the Draft ART (Regulation) Bill and Rules 2010[2], was sent to the Ministry of Health & Family Welfare for approval. It was further revised and is now incorporated in the Cabinet Note as Assisted Reproductive Technology (Regulation) Bill – 2014.[3]

Sperm donation

Artificial insemination using donor sperm has been practiced for over a century, although the first published reports about the practice were in 1945. Over the past 10 years, the use of donor sperm has decreased as the use of intra-cytoplasmic sperm injection (ICSI) for the treatment of male infertility has become widespread.

Indications for sperm donation

Currently, therapeutic-donor insemination (DI or TDI) is appropriate when the male partner has severe abnormalities in the semen parameters and/or reproductive system.

- Obstructive azoopermia (caused by a blockage of the ejaculatory ducts), congenital absence of the vas deferens.
- Non-obstructive azoospermia
  - o Primary testicular failure
  - o Secondary testicular failure- previous radiation treatment or chemotherapy
- Severe oligospermia (decreased sperm count) or other significant sperm or seminal fluid abnormalities
- Male is a carrier or affected with a significant genetic defect and would prefer not to pass this gene on to his children.
- If the female is Rh-sensitized and the male partner is Rh-positive.
- Treatment for a single woman who desires a pregnancy but who lacks a male partner.

Sourcing of semen donors

Couples eligible for donor insemination can get donor semen preparations from authorised ART banks. On request for semen by an ART clinic, the bank will provide the clinic with a list of donors (without the name or the address but with a code number) giving all relevant details.

Characteristics of a sperm donor

- The age of the donor must not be below 21 or above 45 years.
- The individual must be free of HIV and hepatitis B and C infections, hypertension, diabetes, sexually transmitted diseases, and identifiable and common genetic disorders such as thalassemia.
- An analysis must be carried out on the semen of the individual, which should be normal according to WHO method manual for semen analysis.
- The blood group and the Rh status of the individual must be determined and placed on record.
- Other relevant information in respect of the donor, such as height, weight, age, educational qualifications, profession, colour of the skin and the eyes, record of major diseases including any psychiatric disorder, and the family background in respect of history of any familial disorder, must be recorded in an appropriate proforma.

Oocyte donation

The first pregnancy achieved with oocyte donation was reported in 1984. Since then, there has been increasing use of egg donation to help infertile couples/individuals conceive.

Oocyte donors are identified, and these women then undergo stimulation protocols to retrieve eggs, which are donated to the intended recipient. Sperm obtained

from the recipient's partner (or a sperm donor) is used to fertilize these eggs, and embryos are transferred into the recipient's uterus.

Indications for Oocyte Donation

- Normal ovulatory women who appear to have an egg factor as the cause of their infertility.
  - women with multiple failures to conceive after IVF
  - women of advanced reproductive age
  - women with inadequate response to ovulation induction.
- women who have prematurely menopause due to disease, chemotherapy, radiation therapy, or surgical removal of their ovaries
- women born with streak ovaries (e.g. Turner's syndrome)
- women affected by or be the carrier of a significant genetic disease who would prefer not to pass this disease on to her offspring.

Who are oocyte donors?

There are several ways of obtaining donor oocytes (eggs).

Anonymous donors

Donors recruited through established ART banks and not known to the couple are anonymous donors. As per the ICMR Guidelines, It is the responsibility of the ART clinic to obtain egg donors from appropriate banks. They are authorized to appropriately charge the couple for the eggs provided and the tests done on the donor. The oocyte donor may be compensated suitably (e.g. financially) by the ART bank when the oocyte is donated. It is the responsibility of the bank and the clinic to ensure that the couple does not come to know the identity of the donor.

Oocyte sharing

Some infertile women undergoing IVF may volunteer to donate their excess eggs to anonymous recipients in return for a monetary compensation, which would take care of the expenses of their own IVF procedure.

Known or directed donors

Use of eggs donated by a relative or a known friend of either the wife or the husband may appear to be an easier option, but is not recommended under the ICMR Guidelines.

Characteristics of an oocyte donor

- The age of the donor must not be less than 21 or more than 35 years.
- The individual must be free of HIV and hepatitis B and C infections, hypertension, diabetes, sexually transmitted diseases, and identifiable and common genetic disorders such as thalassemia.
- The blood group and the Rh status of the individual must be determined and placed on record.
- Other relevant information in respect of the donor, such as height, weight, age, educational qualifications, profession, colour of the skin and the eyes, and the family background in respect of history of any familial disorder, must be recorded in an appropriate proforma.

Guidelines for ART banks

- Either an ART clinic or a law firm or any other suitable independent organization may set up an ART bank. If set up by an ART clinic it must operate as a separate identity.
- A bank may advertise suitably for semen/ egg donors who may be appropriately compensated financially.
- The ART bank should not supply semen of one donor for more than seventy five times.
- The bank must be run professionally and must have facilities for cryopreservation of semen, following internationally accepted protocols. Each bank will prepare its own SOP (Standard Operating Procedures) for cryopreservation.
- Semen samples must be cryopreserved for at least six months before first use, at which time the semen donor must be tested for HIV and hepatitis B and C.
- A donor can get his semen preparation stored in a semen bank for exclusive use on his wife or on any other woman designated by him in lieu of an appropriate charge.
- A woman donor cannot donate oocytes more than six times in her life, with an interval of at least 3 months between two oocyte pickups.
- Eggs from one donor can be shared between two recipients only, provided that at least seven oocytes are available for each recipient.
- Gametes can be stored only upto 5 years

Record keeping by the ART Banks

- A suitable record of all the gametes received, stored, supplied and the donors should be kept for 10 years after which, or if the bank is wound up during this period, the records should be transferred to the central database of the Department of Health Research, Government of India.
- Unless ordered by a court of competent jurisdiction, all ART banks should ensure that all information about clients and donors is kept confidential and that information about gamete donation shall not be disclosed to anyone other than the central database of the Department of Health Research.

Rights and duties of Gamete donors

- The donor has the right to decide what information may be passed on and to whom, except, if an order is issued from of a court of competent jurisdiction.
- A donor has to relinquish all parental rights over the child which may be conceived from his or her gamete.
- A Donor cannot undergo any assisted reproductive technology procedure on or in relation to his gamete without written consent of his or her spouse.
- The identity of the recipient shall not be made known to the donor.

Rights of a child born through ART technologies

- A child born through ART is presumed to be the legitimate child of the couple, having been born in wedlock and with the consent of both the spouses. Therefore, the child has a legal right to parental support, inheritance, and all other privileges of a child born to a couple through sexual intercourse.
- Children born through the use of donor gametes do not have any right to know the identity (such as name, address, parentage, etc.) of their genetic parent(s). The child, however, should be provided all other relevant medical information as outlined in the previous section about the donor as and when desired by the child or when the child becomes an adult.
- In case of a divorce during the gestation period, if the offspring is of a donor programme be it sperm or ova, the child is considered to be the legitimate child of the couple, provided both the partners had consented to the ART procedure.
- If a foreigner or a foreign couple seeks sperm or egg donation in India, and as a consequence of which a child is born, it will not be given the status of an Indian citizen.

Adultery in the case of ART

ART used for married woman with the consent of the husband does not amount to adultery on part of the wife or the donor. Artificial Insemination Donor (AID) without the husband's consent can, however, be a ground for divorce or judicial separation.

Rights of an unmarried woman to AID

An unmarried woman or an unmarried couple can undergo Artificial Insemination Donor (AID) and a child thus born is deemed to be legitimate.

Posthumous AIH through an ART bank

A child born to a woman artificially inseminated with the stored sperm of her dead husband shall be considered as the legitimate child of the couple.

References

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2. Sharma RS, Bhargava PM. New Delhi: Ministry of Health and Family Welfare, Government of India; Indian Council of Medical Research. Draft The assisted Reproductive Technologies (Regulation) Bill - 2010. Available from: http://icmr.nic.in/guide/ART%20REGULATION%20Draft%20Bill1pdf.
3. Sharma RS. Social, ethical, medical & legal aspects of surrogacy: an Indian scenario. The Indian Journal of Medical Research. 2014; 140(Suppl 1): S13-S16.

Road Map to Adoption ….Getting Baby Home

Deepali Dhingra[1], Sarita Singh[2]
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Department of Obstetrics & Gynaecology, VMMC & Safdarjung Hospital, New Delhi

Documents required for adoption

- Proof of identity(Voter card/PAN card/Passport/Driving License)
- Proof of address indicating residence in India exceeding 365 days
- Marriage Certificate
- Family Photograph
- Health certificate by a registered medical practitioner certifying that the prospective adoptive parents (PAPs) are not suffering from any contagious or terminal disease or any such mental or physical condition, which may prevent them from taking care of the child
- Three recent postcard sized photographs of the adoptive family
- Two letters of recommendation from persons who know the family well
- Income certificate – salary slip / tax returns
- Bank letter
- Undertaking from the relative

Register for adoption -Adoption Coordinating Agency ACA (found in each state capital) or agency certified by Central Adoption Resource Authority (CARA) in New Delhi. The social worker of the agency will guide. Online registration available in CARA

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Waiting period begins once the agency's social worker draws up the home study report within 3 months of the date of registration. When the agency identifies a suitable child, they call the prospective parents to meet the child. The agency's lawyer files a petition to adopt on behalf of the couple with the Court.

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Once the couple has signed the petition they can take the child in Pre-Adoption foster care

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Court hearing: Attend the court hearing along with the child and follow the judicial procedure till final order is issued.

Adoption agencies in Delhi

Name of agency	Address	Contact number
FOSTER CARE AND ADOPTION SERVICE AGENCY	Nirmal Chhaya Complex, Hari Nagar, Jail Road, New Delhi	No:01128520433, 01128520599
MISSIONARIES OF CHARITY	Nirmala Shishu Bhawan 12, Commissioner Lane, Delhi	23831080
DELHI COUNCIL FOR CHILD WELFARE "PALANA"	Civil Lines Qudsia Garden, Yamuna Marg, Delhi	011-23968907
SOS SOPAN	347 Second Floor Mandakini Enclave Alakhnanda	01126272444
UDAYAN c/o SOS Childrens Village of India	A-7, Nizzamuddin (West) New Delhi	01143357299
ASHARAN ORPHANAGE (Hope Foundation)	A/46 New Multan Nagar, Surya Enclave,Delhi	011-25291672
HOLY CROSS SOCIAL SERVICE CENTRE	Dheer pur DDA Project Near Nirankari Sarovar and ITI, Delhi	01127608765
WELFARE HOME FOR CHILDREN	1-B, Institutional Area, Sarita Vihar, New Delhi	011-26974703
SOS UPVAN	B5/21 Ist Floor Safdurjung Enclave	01145070368

Source: central adoption resource authority www.adoptionindia.nic.in/

Journal Scan

Sunita Malik[1], Deepika[2]
[1]Professor, [2]Senior Resident, Department of Obstetrics & Gynaecology, VMMC & Safdarjung Hospital, New Delhi

Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system

J.A.M. Hamilton, M. Cissen, M. Brandes, J.M.J. Smeenk, J.P. de Bruin, J.A.M. Kremer, W.L.D.M. Nelen and C.J.C.M. Hamilton

Human Reproduction 2015; 30(5):1110-1121

Background: According to the WHO classification system, an abnormal semen analysis can be diagnosed as oligozoospermia, asthenozoospermia, teratozoospermia or combinations of these and azoospermia. This classification is based on the fifth percentile cut-off values of a cohort of 1953 men with proven fertility. Although this classification suggests accuracy, the relevance for the prognosis of an infertile couple and the choice of treatment is questionable. The TMSC is obtained by multiplying the sample volume by the density and the percentage of A and B motility spermatozoa. **Objective:** Does the prewash total motile sperm count (TMSC) have a better predictive value for spontaneous ongoing pregnancy (SOP) than the World Health Organization (WHO) classification system? **Material & Methods:** *Study Design, Size, Duration*: Data from a longitudinal cohort among unselected infertile couples who were referred to three Dutch hospitals was analyzed. Of the total cohort of 2476 infertile couples, only the couples with either male infertility as a single diagnosis or unexplained infertility were included (n = 1177) with a follow-up period of 3 years. *Participants/Materials, Setting, Methods*: In all couples a semen analysis was performed. Based on the best semen analysis if more tests were performed, couples were grouped according to the WHO classification system and the TMSC range. The primary outcome measure was the SOPR, which occurred before, during or after treatments. After adjustment for the confounding factors the odd ratios (ORs) for risk of SOP for each WHO and TMSC group were calculated. The couples with unexplained infertility were used as reference. **Results:** A total of 514 couples did and 663 couples did not achieve a SOP. All WHO groups had a lower SOPR compared with the unexplained group (ORs varying from 0.136 to 0.397). Comparing the couples within the abnormal WHO groups, there were no significant differences in SOPR, except when oligoasthenoteratozoospermia was compared with asthenozoospermia [OR 0.501 (95% CI 0.311–0.809)] and teratozoospermia [OR 0.499 (95% CI: 0.252–0.988)], and oligoasthenozoospermia was compared with asthenozoospermia [OR 0.572 (95% CI: 0.373–0.877)]. All TMSC groups had a significantly lower SOPR compared with the unexplained group (ORs varying from 0.171 to 0.461). Couples with a TMSC of $<1 \times 10^6$ and $1–5 \times 10^6$ had a significantly lower SOPR compared with couples with a TMSC of $5–10 \times 10^6$ [respectively, OR 0.371 (95% CI: 0.215–0.64) and OR 0.505 (95% CI: 0.307–0.832)]. **Conclusion:** The prewash TMSC had a better correlation with the spontaneous ongoing pregnancy rate (SOPR) than the WHO 2010 classification system. We suggest using TMSC as the method of choice to express severity of male infertility.

Cryopreserved embryo transfer is an independent risk factor for placenta accreta

Daniel J. Kaser, Alexander Melamed, Charles L. Bormann, Dale E. Myers, Stacey A. Missmer, Brian W. Walsh, Catherine Racowsky, Daniela A. Carusi.

Fertility and Sterility May 2015;103(5):1176–1184.e2

Objective: To explore the association between cryopreserved embryo transfer (CET) and risk of placenta accreta among patients utilizing in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI). **Material & Methods:** *Design:* Case-control study. *Patient(s):* All patients using IVF and/or ICSI, with autologous or donor oocytes, undergoing fresh or cryopreserved transfer, who delivered a live-born fetus at ≥24 weeks of gestation (n = 1,571), were reviewed for placenta accreta at delivery. *Intervention(s):* Cases of accreta (n = 50) were matched by age and prior caesarean section to controls (1:3) without accreta. The association between CET and accreta was modeled using conditional logistic regression. *Outcome Measure(s):*Placenta accreta. **Result(s):** Univariate predictors of accreta were non-Caucasian race (odds ratio [OR] 2.85, 95% confidence interval [CI] 1.25–6.47); uterine factor infertility (OR 5.80, 95% CI 2.49–13.50); prior abdominal or laparoscopic myomectomy (OR 7.24, 95% CI 1.92–27.28); and persistent or resolved placenta previa (OR 4.25, 95% CI 1.94–9.33). In multivariate analysis, there was a significant association between CET and accreta (adjusted OR 3.20, 95% CI 1.14–9.02), which remained when analyses were restricted to cases of accreta with morbid complications (adjusted OR 3.87, 95% CI 1.08–13.81). Endometrial thickness and peak serum E_2 level were each significantly lower in CET cycles and those with accrete. **Conclusion(s):** Cryopreserved ET is a strong independent risk factor for accreta among patients using IVF and/or ICSI. A threshold endometrial thickness and a "safety window" of optimal peak E_2 level are proposed for external validation.

Proceedings of Monthly AOGD Clinical Meeting held at DDU Hospital on 29th May, 2015

Compiled by Archana Misra[1], Harsha Gaikwad[2]
[1]Assistant Professor, [2]Associate Professor, Obs & Gynae, VMMC & Safdarjung Hospital, New Delhi

Case 1

Perforating Uterine Choriocarcinoma

Dr Poonam Laul, Dr Pinkee Saxena, Dr Niketa Pahuja, Dr V K Kadam.

A 30 years old female G8P4L4A3 presented with irregular bleeding per vaginum and pain in abdomen. Six months back she had amenorrhea for 1½ month for which she took MTP pill. After that she had irregular bleeding for which dilatation and evacuation was done twice in private hospital. On admission she was pale, pulse-112/min, BP- 90/60 mm Hg. Abdominal examination revealed mild tenderness. Minimal bleeding was seen through cervix. On Per vaginum examination uterus was 8weeks size with cervical motion tenderness and fullness in POD.

On investigation- haemoglobin- 6.3gm/dl, Serum β-HCG-2, 11,000IU, rest of blood investigations were normal. Chest X-ray was normal. Ultrasound revealed bulky uterus with 25x23mm lesion on posterior wall with increased vascularity. Adnexa were normal with free fluid in POD.

Patient was taken up for emergency laparotomy. Per operative haemoperitoneum was present, uterus 8 weeks with perforation at fundus and polypoidal mass protruding through it. B/L tubes and ovaries were normal. Hysterectomy was done due to excessive bleeding and friability of the tissues at the perforation site. HPE revealed choriocarcinoma. WHO scoring was < 6. She was given single agent chemotherapy with methotrexate. After completion of two cycle of chemotherapy her Serum β-HCG started to rise. Since it was resistant to methotrexate, patient started on EMACO. Patient is under going treatment and currently under follow up.

Choriocarcinoma is a rare malignancy with an incidence of 1 in 40,000 pregnancies. It is characterized by absence of villi and presence of areas of hemorrhage and necrosis. These tumor respond well to chemotherapy. Role of surgery is still essential as life saving procedure. Our case, is a rare one with its unusual presentation of uterine perforation and haemorrhage. This case also reiterates the relevance of hysterectomy in management of GTN.

Case 2

Dilemma during Dilation and Evacuation.

Dr Sunita Seth, Dr Rita Ranjan, Dr Ritu Goyal, Dr Harvinder K, Dr Usha Yadav

A 24 yr old G2 P1 presented with 2 months amenorrhea, bleeding per vaginum for 2 days and pain in abdomen for 2 days. On examination her vitals were stable. Abdomen was soft. On per speculum examination slight bleeding through os seen and on per vaginum uterus was 8 weeks size with bilateral fornices free.

Routine investigations sent were normal. Ultrasound showed 7 weeks missed abortion. Patient was taken up for D & E. During the procedure no product of conceptions were obtained. Doubts of perforation were raised and patient was taken up for diagnostic laparoscopy. On re examination under general anaesthesia a longitudinal septum was seen in vagina with two cervices on either side which could not be seen earlier. Laparoscopy revealed uterus didelphys with one uterus enlarged to 8 weeks size and perforation seen in the other smaller uterus. Evacuation was completed under vision, and intestinal injury noticed and repaired.

Uterus Didelphys is seen in 0.5% of healthy fertile population. Often diagnosis is difficult especially in presence of unequal development of two sides or if the septum is displaced. This case highlights the need of high index of suspicion of uterine anomalies if no products of conception are obtained and the need to look for second cervix if there is presence of longitudinal septum in vagina.

Case 3

Spontaneous rupture of unscarred uterus at 20 weeks of gestation

Dr Shashi L Maheshwari, Dr Zipee, Dr Biplap, Dr V K Kadam

22 years old female (G4P3L3) presented with 3 1/2 months amenorrhoea, pain abdomen and bleeding p/v for one day.LMP not known. She had previous three normal vaginal deliveries with no history of any previous surgery. On examination patient was pale, pulse - 100/min, BP-

100mm of Hg. Abdomen was soft. On per vaginum examination 12-14 weeks mass felt through right fornix, firm, tender with restricted mobility, not separate from uterus. Investigation-Hb- 7.2 gm%, Ultrasonography revealed single 15 weeks extra uterine pregnancy in left adnexa, uterus normal size, free fluid in POD. ?ruptured ectopic pregnancy. Patient was taken up for laparotomy. Peroperatively there was a vertical rent on posterolateral wall of uterus extending up to vault, fetus and placenta lying in POD. Repair could not be done as bleeding was uncontrolled. Total hysterectomy was performed.

Rupture of Unscarred uterus is a rare event – 1 in 15,000 to 20,000 deliveries. In India maternal mortality is as high as 30% in rupture uterus. It is a life threatening emergency. USG can help in diagnosis but cannot confirm. Risk factor in our case was multiparity. Repeated child birth makes uterine wall weak. Eden et al and Adanu and Obed reported 83.3% and 75.3 % case of rupture occurring in multipara with unscarred uterus respectively. This case highlights need of proper antenatal care, early referral of high risk patients as grand multipara to higher center. In cases of pain abdomen with h/o amenorrhoea especially with tachycardia and low BP, rupture should be ruled out.

AOGD MONTHLY CLINICAL MEETING

- **Next AOGD Monthly Clinical Meeting** will be held at SHL 3 Auditorium, Army Hospital (Research & Referral), Delhi Cant, on 26th June, 2015. All are cordially invited.

FORTHCOMING EVENTS

- **Women's Comprehensive Health Camp** organised by VMMC & Safdarjung Hospital, co-ordinated by Dr Rupali Dewan under aegis of AOGD on 10th June, 2015 under outreach activities.
- **Session on 'Adolescent PCOS'** by South Delhi Gynae Forum at Madhuban Hotel, Greater Kailash on 11th June, 2015
- **AOGD Endoscopy and Endometriosis Subcommittees** hands on courses in Hysteroscopy Laparoscopy and Vaginal Surgery on 11th,12th,13th June, 2015 and 9th,10th,11th July, 2015 and endometriosis video workshop on 22nd June, 2015 and 18th July, 2015 at Fortis Flt Lt Rajan Dhall Hospital,Vasant Kunj. Dr UP Jha M: 9811029310, Dr Neema Sharma M: 9911057456, Dr Ramandeep M: 9810605842 for registration.
- **'Tips & Tricks in Endometriosis Management'** on 24th June, 2015, 7.30pm at India Habital Centre in association with DGES, GESI & AOGD. Speaker- Dr Camran Nazhat.
- **Eighteenth PG practical course and CME**, to be organized by the Department of Obstetrics and Gynaecology, Maulana Azad Medical College, New Delhi, will be held on 9th, 10th and 11th October, 2015 at MAMC auditorium, Bahadur Shah Zafar Marg, New Delhi. For details please visit MAMC website: www.mamc.ac.in
- **Sixth MICOG-MRCOG Part 1** examination will now be conducted in September, 2015. Last date for receiving the application is 1 June, 2015. Sixth Refresher Course for Sixth MICOG-MRCOG Part 1 examination, September 2015 exam will be held in 20-22 July, 2015 at FOGSI Office, Mumbai between 9.00am to 6.00pm under the able guidance of Dr Neelanjana Mukhopadhyay from RCOG. For details and form contact, ICOG Secretary at icogoffice@gmail.com.
- **22nd Annual conference of NARCHI Delhi** Branch on 22nd & 23rd August 2015 at Scope Complex Lodhi Road, Delhi. Theme topics: 1. Medical Disorders in Pregnancy, 2. Quality Maternity Care, 3. Recent Advances in Operative Gynecology, 4. Miscellaneous. PG quiz on "Contraception". Last Date of Registration & Abstract Submission is 31stJuly, 2015. For details contact website www.narchidelhi.org Contacts no. - 9868399724, 9868399730
- **'FENIX-2015'- Annual Conference of Delhi Gynaecological Endoscopists Society with theme Fertility and Beyond: Inception to Xcellence.** Department of Obstetrics and Gynaecology, AIIMS, New Delhi is organizing 'FENIX-2015', the Annual Conference of Delhi Gynaecological Endoscopists Society from 28th to 30th August, 2015, at J L N Auditorium, AIIMS, New Delhi in collaboration with Gynae Endocrine Society of India (GESI).
- **Annual AOGD Conference** will be held at India Habitat Centre on 31st October and 1st November, 2015. For further details contact website www.aogd.org

Brain Teasers

Dr Monika Gupta
Assistant Professor
Dept. of Obs & Gynae, VMMC & Safdarjung Hospital, New Delhi

The correct answers will be published in the next issue and winner (after luckydip of all correct entries) will be given an attractive prize in next AOGD monthly meeting.

1. Which of the following is not a criteria for prediction of poor response to In-Vitro Fertilisation:
   a. Antral follicle count less than 5-7
   b. Follicular Stimulating Hormone less than 10
   c. Anti-Mullerian Hormone less than 1.35
   d. Shortened menstrual cycles

2. Best suited ovarian stimulation protocol for a PCOD patient is:
   a. Step down protocol
   b. Step up high-dose protocol
   c. Step up low-dose protocol
   d. Mild stimulation protocol

3. Which of the following is not a high risk factor for hyperstimulation:
   a. Age > 35 yrs
   b. Thin built female
   c. Anti-Mullerian Hormone > 3.5 ng/L
   d. Polycystic Ovarian Disease

4. According to CONSORT study which of the following does not influence gonadotropin dose for ovulation induction
   a. Poor responders
   b. Hypergonadotropic hypogonadism
   c. PCOS patients
   d. Unexplained infertility

5. Which of the following is not true regarding Corifollitropinalfa:
   a. Presence of carboxy terminal peptide of beta-subunit of HCG
   b. Can replace 7 days of daily injections of FSH
   c. Its action mimics step-up protocol
   d. Always causes multifollicular development

6. Percentage of normal morphological sperms acceptable according to WHO guidelines 2010 is:
   a. >30
   b. 20-30
   c. 10-14
   d. 3-4

7. Genital tuberculosis in male partner is associated with
   a. Obstruction Azoospermia
   b. Teratozoospermia
   c. Non-obstructive Azoospermia
   d. Oligozoospermia

8. In hypogonadotropic hypogonadism exogenous testosterone should be co-administered with which of the following to maintain intra testicular level (ITT)
   a. LH
   b. FSH
   c. HCG
   d. N-Acetyl-L-Cysteine

9. Which of the following is not a cause for poor endometrial growth during ovulation induction:
   a. Blood flow impedence in uterine- radial artery
   b. High FSH levels
   c. Damage to basal endometrium
   d. Decreased estrogen receptors in endometrium

10. Best sperm function test to denote the ability of sperm to withstand harsh vaginal environment and oxidative stress is:
    a. ROS test
    b. HOS test
    c. DNA fragmentation test
    d. Fructose test

Key to the Quiz in May issue: 1. **b; 2. b; 3. c; 4. a; 5. b; 6. b; 7. b; 8. b; 9. b; 10. b**

Winner of the Quiz: Dr Pancham Preet Kaur
Senior Resident, VMMC & Safdarjung Hospital, New Delhi

Royal College of Obstetricians & Gynaecologists-AICC- Northern Zone India

Website: **www.aiccrcognzindia.com**

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UK Conveners - Dr John Duthie, Dr Moshen Iskander and Dr Sanjeev Sharma

India Conveners and Contacts for details - Dr Saritha Shamsunder (shamsundersaritha@gmail.com/ 9313826748)
Dr Sweta Gupta (swetagupta06@yahoo.com/8130140007)
Dr Puneet Kochhar (drpuneet.k20@gmail.com/9953001628)

Registration Guidelines (Online registration available on website)

- **Eligibility Criteria: Atleast 70% pass marks for screening test before the online lessons. Only those who pass the screening test can register**
- Bank Transfer or Demand Draft must be made in favour of "RCOG NZ 2012 Plus" payable at New Delhi. (cheques not accepted).
- There will be no refunds on cancelation
- Registration request along with Demand Draft to be posted to the Secretariat mailing address as given below:-

Mailing Address: **RCOG North Zone Secretariat**
Hostel Complex- Basement, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110076
Tel No - 91-11-29871616/2146/2199, 09716801190/09810116623
Email: rcog_nz2012@yahoo.com/drsohaniverma@gmail.com

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For Bank Transfer:

Account Name: "Society of Fetal Medicine" **Account No.:** 91111010002044

Bank Name & Address: Syndicate Bank, Sir Gangaram Hospital, Rajinder Nagar, New Delhi-110060,

IFSC Code: SYNB0009111

Forthcoming Activities of the Society of Fetal Medicine

1. 30th-31st May 2015: Society of Fetal Medicine 3D/4D Ultrasound Simulator Program in Obstetrics & Gynecology, Kolkata. Course faculty: Ashok Khurana. For participation contact Khushboo Srivastava at +919717775817
2. 14th June 2015: Society of Fetal Medicine, Mumbai Regional Chapter Inaugural Program. Contact: Mohit Shah at +91 8108300086.
3. 5th July 2015: Society of Fetal Medicine, Patiala Regional Chapter Inaugural Program. Contact: Chander Mohini at +91 9814087891
4. 11th-12th July 2015: Society of Fetal Medicine 3D/4D Ultrasound Simulator Program in Obstetrics & Gynecology, Bhubaneshwar. Course faculty: Ashok Khurana. For participation contact Khushboo Srivastava at +919717775817
5. 11th August 2015: Society of Fetal Medicine Delhi Chapter Quarterly Meeting. Contact Vivek Kashyap at +919811116050
6. 23rd August 2015: CME on "Ultrasound in Fetal Medicine" in association with GGSMC, Faridkot. For details contact Deepak Bansal at +91 9815020649.
7. 30th August 2015: Society of Fetal Medicine Comprehensive Course in Fetal Neurosonography, New Delhi. For details contact Vivek Kashyap at +919811116050
8. 25th October 2015: Society of Fetal Medicine Fetal Day Celebration in Jabalpur. For details contact D'Pankar Banerjee at +919826166952.
9. 31st October-1st November 2015: Society of Fetal Medicine Midterm CME, Hyderabad. Foreign faculty includes Bosky Thilaganathan who is the editor of the ISUOG Journal of Ultrasound in Obstetrics and Gynecology. For details contact Chinmayee Ratha at +919885348600.
10. 20th November 2015: Society of Fetal Medicine Delhi Chapter 2nd Quarterly Meeting. For details contact Rajeev Choudhary at +919810615454 and +919310615454.

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