AOGD BULLETIN

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Enlightening the Path for Next Generation of Gynaecologists

Dedicated Issue:
Infertility

AOGD SECRETARIAT
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From the President's Pen

Dear Friends

Second issue of AOGD Bulletin dedicated to "Infertility Management" is in your hands. All of us face an ever increasing number of cases presenting with infertility. Infertility is a problem of not only married couple but whole family. Extremes of anxiety, depression and at times suicidal tendencies are noted in the woman. Not only dealing in medical aspect of infertility but also providing emotional support is the need. Nothing gives more joy than finding a woman who was undergoing your treatment has conceived. Keeping cost of treatment within limits and avoiding unnecessary investigations should be the aim.

Dr Sunesh Kumar
President, AOGD

Vice President's Message

Dear Members,

Namaskar,

'We for Stree- Safer, Stronger, Smarter'

In next few months two major events are happening in Delhi. FOGSI in association with AOGD is organizing a Congress "Breaking Silos Across: Adolescence to Menopause" on 10th-11th August, 2019 at Hotel Lalit and 41st Annual Conference of AOGD is on 28th-29th September, 2019 at Hotel Eros. The preparations are going in full swings.

A regular academic event for postgraduates (once in two months) is being conducted by our resource team for enhancement of their skills and medical information. It helps them in providing quality care.

I congratulate the editorial team for bring out this issue on infertility. Infact, just to keep the sentiments in mind, it is better to use the term 'subfertility'. The bulletin is an opportunity to all of us to keep ourselves updated with the advances in knowledge.

Dr Ashok Kumar
Vice President, AOGD

From the Secretary's Desk

Dear Friends,

Warm wishes from AOGD Secretariat, AIIMS.

The first issue of the AOGD Bulletin on "Urogynaecology" has been received with great enthusiasm. I thank you all.

Continuing with our theme, 'Enlightening the Path of Next Gen Gynaecologists', the next issue is on 'Infertility'. I hope this will be as good as the first one.

Various CME's were organized under the banner of AOGD.

A CME was organized by Breast & Cervical Cancer Awareness, Screening and Prevention Committee on 25th April, 2019. Deptt. Of Obs & Gynae, AIIMS organized a CME on 'Understanding Doppler in Obstetrics' – Third quartly meeting of SFM on 28th April,2019.

'Update on Prenatal and Neonatal Screening' on 4th May 2019, was organized by MAMC. MENSTRUAL HYGIENE DAY was celebrated on 27th & 28th May by Endoscopy committee & Rural Health Committee.

'Pelvic Pain symposium' on 11th May 2019, was organized by Multidisciplinary Committee of AOGD and CME on 'Ovarian Health' on 30th May,2019 was organized by Reproductive Endocrinology Committee, AOGD

We look forward to your support for 41st Annual Conference of AOGD on 28th & 29th September, 2019. The last date for early registration is 31st August and the last date for submitting abstract is 15th August, 2019.

Please visit the Website, www.aogd.org for details.

Dr Vatsla Dadhwal
Hon. Secretary

Please note the change of the venue

Monthly Clinical Meeting

Monthly Clinical Meet will be held at VMMC & Safdarjung Hospital, New Delhi on **Friday, 28th June, 2019 from 04:00pm to 05:00pm**.

From the Editor's Desk

Dr J B Sharma
Editor

Dr Reeta Mahey

Dr P Vanamail

Dr Vidushi Kulshreshtha

Co-Editors

Dear esteemed AOGD members,

We are pleased to bring the second issue of Bulletin from the AIIMS AOGD office with the satisfaction that the first issue of AOGD Bulletin on "Urogynaecology" was appreciated by most members as conveyed through encouraging messages, emails and phone calls.

This issue is dedicated to "Basic Infertility in Gynaecology" and ably edited by Dr Reeta Mahey and her team. The present issue has been dedicated to general initial work-up of infertile couple and treatment strategies based on cause of infertility for the benefit of our esteemed AOGD members in their day to day clinical practice. Infertility affects 1 in every 6 couples and incidence is increasing over the last two to three decades due to delayed marriages, career priorities, stress and to some extent environmental toxins.

We have an interesting and clinically useful article on "Evaluation of female factor infertility" by Prof. Neena Malhotra from AIIMS which will help practitioners to refine their practice by incorporating evidence based guidelines.

Male factor is the sole cause of infertility in 20% patients and a contributory in another 30-40%. Male partner evaluation is cheap and easy and it should be the first step while investigating the infertile couple. We have a very informative article on "Evaluation of male factor infertility" by Prof. Rajeev Kumar and Dr Manoj who successfully run the andrology clinic at AIIMS.

Another controversial topic of unexplained infertility has been detailed clearly by Dr Juhi Bharti and Dr Monica Gupta.

Dr Namrata Bhattacharya and Dr Anupama Bahadur have enlightened us on "Ovarian reserve testing: where do we stand" to better understand the nuances of various tests available to assess ovarian reserve in infertile couples.

Recently there is a surge in patients presenting with premature ovarian ageing which is becoming a difficult entity to manage. Prof Neeta Singh and Dr Yogita Dogra, in her article on "Premature ovarian ageing" has detailed the steps in diagnosing and managing this condition in young females.

Dr Monika Gupta has elaborated on intrauterine insemination and finer details in technique to improve pregnancy outcome in infertile patients.

Although referrals to ART have increased in the last decade, the role of non-ART treatment options and endoscopy cannot be denied. Dr Leena Wadhwa and Dr Lata Singh have clearly outlined in their article on "Role of endoscopy in infertility," that laparoscopy and hysteroscopy still have important role in management of infertility and should be considered whenever indicated.

Sona Dharmendra and Prof JB Sharma have contributed an important article on "Female genital TB and Infertility". Female genital TB is still an important cause of infertility in India affecting approximately 10% of infertile patients in general population and 16-18% in tertiary care hospitals.

Interesting Journal Scans have been done by Dr Reeta Mahey on Important Research Papers or Infertility from World Literature.

We hope that this bulletin will clearly define the management strategies in various causes of infertility and be useful to our colleagues in their day to day practice. We welcome the comments and views of our readers which will help to improve the future editions of the bulletin.

We wish you all a happy reading!

Editorial Team, AIIMS

Evaluation of Male Factor Infertility

Manoj Kumar[1], Rajeev Kumar[2]
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Ten percent of all couples needs evaluation for infertility. Infertility is defined as inability of couple to achieve pregnancy after 1 year or more of regular unprotected sexual intercourse. Infertility is a couple phenomenon requiring both partners to be fertile.[1-3] Although the male partner is involved in half of the infertility cases, social pressure for child bearing is mainly vested on women and the couple often seeks treatment of female partner first and evaluation of male partner begins only after the evaluation of female partner.[4] In developing countries, one in every four couple had been found to be affected by infertility.[5]

Despite the widespread availability of assisted reproduction techniques (ART) that can bypass male factor infertility, evaluation of the infertile male is important for the following reasons:

1. A number of causes of male infertility are reversible.
2. Identification of suitable option of ART.
3. Identify conditions not suitable for ART.
4. Identify any serious medical conditions that may be cause of infertility and require immediate medical intervention.
5. Identify any genetic causes.

Clinical Evaluation of Infertile Male

History:

History plays an important role in evaluation of infertile male. The history is used to identify any risk factors that could be the important cause for the male infertility. A list of important components of male infertility history is summarized in table 1.

Physical examination:

Physical examination should include general and focused examination. Tall, thin patients with poor virilization with bilateral small testis may have Klinefelter's syndrome. Gynecomastia may seen in patients with hypogonadism with low testosterone or increase prolactin. Specific information that should be elicited in examination of infertile male is summarized in table 2.

Abnormalities of penis including bending (chordee) or hypospadias may prevent deposition of sperm in the vagina. Chordee leads to curvature of penis which precludes coitus. Scrotum should be carefully palpated in standing position and in warm environment. Testicular size and consistency should be noted. Soft and small testis may suggest testicular failure. Epididymis should be examined for nodules, a firm and distended epididymis may be seen in patients with obstructive azoospermia. Epididymal nodule may indicate tuberculosis.[6,7]

Table 1: Various components in evaluation of infertility history in male

Reproductive history: • Duration of infertility and previous fertility with current and previous partner (if any) • Past history of infertility treatment • Erection or ejaculation abnormalities • Coital frequency and timing
Medical history: • Recent fever or illness • History of mumps/orchitis • Sexually transmitted diseases • Any systemic disease like diabetes, malignancy • History of chemotherapy/Radiotherapy • Genetic disorders like cystic fibrosis, Klinefelter syndrome
Surgical history: • Undescended/ectopic testis • History of orchiopexy/ vasectomy • Testicular trauma, testicular torsion • Hernia or hydrocele repair • Retroperitoneal or pelvic surgery
Medication history: Anticonvulsants, Arsenic, Ketoconazole, Lead, Mercury, Nitrofurantoin, Sulfasalazine, Tricyclic antidepressants, Cadmium, Medroxyprogesterone, Mercury
Personal and occupational history: • Alcohol, smoking, recreational drugs • Exposure to pesticides • Exposure to chronic heat exposure

Table 2: Physical examination of infertile male

General physical examination
Height, weight, blood pressure, BMI, distribution of body hairs, gynecomastia
Examination of genitalia Penis- Length, meatal opening, chordee, phimosis Epididymis- Nodule, sinus, possible dilatation, cyst Testis- Size, consistency, mass Vas deferens and spermatic cord – Bilateral palpable, varicocele and its grading
Rectal examination Prostatitis, seminal vesiculitis

Spermatic cord should be examined to identify the vas deferens. Congenital absence of vas, unilateral or bilateral (CUAD/CBAVD), is diagnosed by clinical examination.[8] Identification of a varicocele may be associated with testicular atrophy of the same side.

A rectal examination may reveal infection of prostate and seminal vesicles which may contribute to the male factor infertility. Cysts of the prostate and seminal vesicle may be palpable if very large.

Investigations

Semen examination:

Semen analysis forms the cornerstone laboratory investigation for evaluation of infertile male. The World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human semen (2010) presents the detail standard of semen analysis.[9] The WHO values are indicative of normal range and are used to identify men who need further evaluation. However, they are not diagnostic and should be interpreted with clinical information. (Table 3)

Table 3: WHO criteria for a lower reference limits (5th centile) and 95% confidence intervals for semen parameters

Parameter	Units	5th centile Reference limit	95% Confidence interval
Semen volume	ml	1.5	1.4-1.7
Sperm concentration	(10^6 ml)	15.0	12-16
Total number	(10^6 ejaculate)	39.0	33-46
Total motility	(PR+ NP)%	40.0	38-42
Progressive motility	(PR)%	32.0	31-34
Normal forms	%	4.0	3-4
Vitality	%	58.0	55-63
WBC	Million/ml	< 1	
	PR-Progressive Motility (grade a+b)	NP-Non progressive (grade c)	

It is important to give clear instructions to the patients for semen collection. This should include a fixed period of abstinence for 2-3 days, collection in a sterile, wide mouth container. Samples should be analysed within an hour and if produced at home, the sample should be kept at body temperature during transport because sperm motility decreases after ejaculation. A single sample may not be representative, atleast two semen analysis should be obtained after ruling out reversible causes.

Hormonal Evaluation:

Hormonal abnormalities of hypothalamic-pituitary-gonadal axis is seen in less than 5% of all infertile men and detailed hormonal evaluation is rarely required. Hormonal evaluation is indicated if patients have severe oligospermia (<5-10 million sperms/ml), clinical features of hypogonadism and impaired sexual function.

The most common abnormality is elevated FSH secondary to testicular failure. A normal FSH does not ensure normal spermatogenesis but raised FSH level even in upper normal range is indicative of impaired spermatogenesis.

Genetic Evaluation:

About 3% of infertile men have genetic abnormalities. The most common screening involves karyotyping and assays for microdeletion in long arm of the Y chromosome. This region includes the Azoospermia factor (AZF) locus which contains three subregions: AZFa, AZFb, and AZFc. The surgical sperm recovery is good in AZFc microdeletion whereas surgical recovery of sperm is poor in AZFa and AZFb. [10-11]Genetic testing can be offered to patients with non-obstructive azoospermia (NOA) and severe oligospermia (<5 million sperms/ml)

Imaging:

Scrotal ultrasound is usually not required in routine evaluation as most scrotal pathology can be palpated on physical examination. It should be performed if a testicular mass is detected on physical examination. Scrotal ultrasound may be used to corroborate a clinical diagnosis of varicocele. Transrectal ultrasound (TRUS) is indicated in low volume azoospermia to look for dilated seminal vesicles, dilated ejaculatory ducts and midline prostatic cyst which may be the cause for male infertility with low volume. Vasogram as a stand-alone test is almost never required.

Testicular Histology:

Testicular histology can be obtained through fine needle aspiration cytology (FNAC) for diagnostic purpose which requires an experienced cytopathologist. Open testicular biopsies should be avoided as it causes scarring.[12]

Post Ejaculatory Urinalysis:

In men with suspected retrograde ejaculation and low volume (< 1ml), post ejaculate urinalysis is performed to look for sperms. The presence of any sperm is suggestive of retrograde ejaculation. It is important to confirm

before this test that either incomplete collection or short abstinence periods, CBAVD and hypogonadism are not the cause for low volume ejaculate.

Other specialized sperm function test:

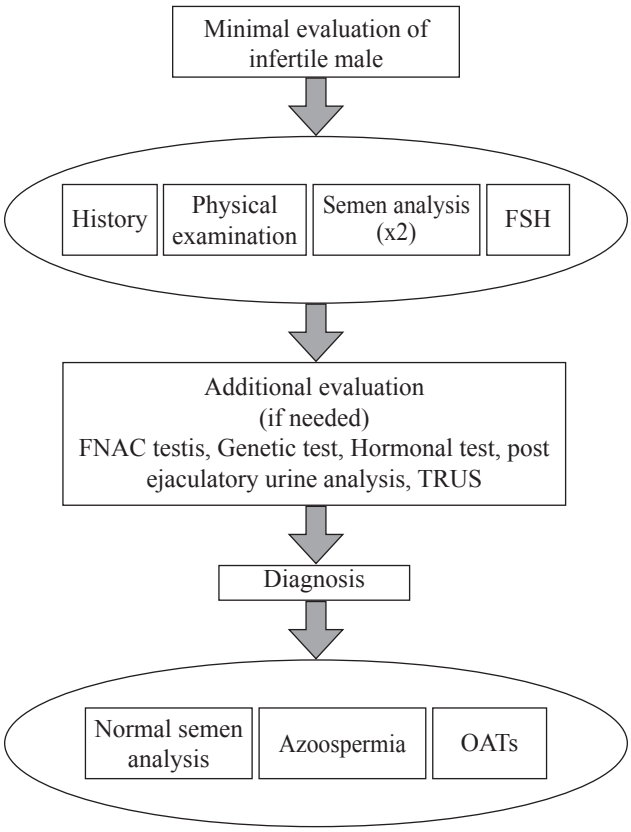
Semen analysis provides very little information about the functional ability of sperm. Sperm function tests include the hemizona assay, sperm penetration assay, post coital test, DNA fragmentation tests and tests for oxidative stress. These tests are not necessary for routine evaluation of male infertility and should be used in specific indications only.

Diagnostic categories:

Based on the semen analysis and minimal hormonal evaluation (figure 1), patients can be categorized into three basic abnormalities and further evaluation and treatment will depend on the identifying causes for these abnormalities. Table 4 describes the main causes of male infertility.

1. Normal semen analysis
2. Azoospermia (Obstructive and Non-obstructive)
3. Oligoasthenoteratospermia (OATS)

Figure 1: Flow chart for minimal evaluation of infertile male.



Normal semen analysis:

Sexual dysfunction like erectile dysfunction and premature ejaculation may prevent normal coitus. Anatomical abnormalities like hypospadias/epispadias/chordee interfere with intercourse or sperm deposition and may cause infertility with normal semen analysis. History and examination can diagnose these problems and no further investigations required. If none of these causes found patient may have unexplained infertility.

Azoospermia:

It is defined as complete absence of sperm in ejaculate. About 1 in 6 men have azoospermia. It is important to differentiate obstructive from non-obstructive azoospermia (NOA) because obstructive azoospermia is amenable to surgical cure while NOA is rarely curable by surgery.

Obstructive azoospermia (OA):

OA is an important diagnostic category since number of these cases can be treated surgically. Obstruction can occur anywhere in male reproductive track from testis to the ejaculatory ducts. CBAVD can be diagnosed clinically on physical examination. If vas deferens is not palpable, further investigations are not required. Some of these men may harbor mutation for cystic fibrosis and partner screening for cystic fibrosis is required before IVF. Vasectomy as a cause can be diagnosed with history and examination, which reveals palpable nodules in both vas at the sit of vasectomy and semen analysis is showing azoospermia. Additional testing is not required. Vaso-epididymal obstruction is a diagnosis of exclusion and is based on normal volume ejaculate, normal spermatogenesis on FNAC and normal palpable vas deferens and is one of the surgically corrected cause.

Iatrogenic injury to vas deferens may occur during hernia/hydrocele/pelvic/retroperitoneal surgery.

In these cases, vasogram can be done at time of reconstructive surgery to identify the site of obstruction. Isolated diagnostic vasography should not be done as it can leads to vasal scarring and injury.[14] Ejaculatory duct obstruction causes low volume azoospermia. TRUS is done to look for dilatation of seminal vesicles, ejaculatory duct dilatation and midline prostatic cyst.

Non obstructive azoospermia (NOA):

Infertile men with impaired spermatogenesis are diagnosed to have NOA. Various causes are listed in table 4. NOA due to reversible causes may be treated through reversal of the insult but in most cases will require ART.

Oligoasthenoteratspermia (OATs):

OATs is used for abnormalities in multiple semen

parameters (number, motility and morphology). Etiological causes overlap significantly with NOA. Various reversible non-surgical causes are infection/ heat/stress/steroids/medications. These can be usually identified with careful history and examination and require no investigations. Varicocele is commonest surgical correctable cause for OATs. The evaluation of varicocele is performed clinically and should not be based on an ultrasound.[15]

Table 4: Main causes of Male infertility[13]:

Normal semen analysis • Sexual dysfunction • Anatomical abnormalities • Unexplained infertility
Azoospermia(Obstructive and non-obstructive) **Obstructive:** • Vasoepididymal junction obstruction • CBAVD • Vasal obstruction/ Vasectomy • Ejaculatory duct obstruction • Inguinal/pelvic/retroperitoneal surgery **Non Obstructive:** • Hormonal abnormalities • Genetic abnormalities • Impaired spermatogenesis • Orchitis/torsion testis • Undescended/ectopic testis • Post Chemotherapy/Radiotherapy • Idiopathic
OATs **Mutiple defects:** • Varicocele • Undescended/ectopic testis • Hormonal causes • Toxins/heat/stress • Drugs/Antibiotic • Idiopathic **Isolated asthenospermia:** • Ultrastructural ciliary defect • Antisperm antibodies • Hypogonadism • Idiopathic

Conclusions

Male infertility is a common problem that requires detailed assessment. Evaluation is based primarily on a good history, careful physical examination and minimal investigations. Investigations can identify conditions and risk factors which, when corrected may results in natural pregnancy and success with ART.

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Evaluation of Female Factor Infertility

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Introduction

Infertility is defined as the inability to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse(1). In India according to WHO estimates, approximately 3.9 to 16.8% couples are suffering from infertility(2). Around 20 to 25 million women seek investigations and treatment for infertility at the present time(3). The evaluation should address the couple and not the individual per se, this section essentially focuses on the female factors and their identification.

An infertility evaluation is initiated after one year of regular unprotected intercourse in women under age 35 years, earlier evaluation is indicated in women beyond 35 years. Also in women with irregular menstrual cycles or known risk factors for infertility, such as endometriosis, a history of pelvic inflammatory disease, or reproductive tract malformations(4).

The basic steps to evaluate the female include a detailed history, thorough examination and diagnostic tests to identify the causative factor for non- conception.

History and Physical Examination

History including the duration of infertility, menstrual history, history of any prior gynecological surgery, any medical disorder (thyroid, DM), sexual history including vaginismus, frequency of coitus, dyspareunia, erectile and ejaculatory problems, Personal history (smoking, alcohol and illicit drugs), Family history, Medication history and allergies- Intake of immunosuppressant drugs(5).

Physical Examination

The physical examination should include height and body mass index (BMI). Look for abnormalities of the thyroid gland, galactorrhea, signs of androgen excess like hirsutism, acne, seborrhea, male pattern baldness. Pelvic examination for uterine size, shape, position, tenderness and any adnexal pathology.

Diagnostic Tests

These should be systematic, expeditious, cost-effective and be least invasive to confirm the etiology and therefore guide treatment. Diagnostic evaluation should always be guided by the age and duration of infertility.(6,7). The most important causes of infertility are:(1) ovulatory dysfunction (20%)(2) Tubal disease (30%)(3) Abnormalities of the uterus and(4) Reproductive aging(5) Male factor (30%)(6) Unexplained (8). Therefore a basic infertility evaluation should include tests aimed at detecting ovulation, tubal patency, uterine architecture and ovarian reserves.

Assesment of Ovulation

Ovulation and menstruation are a well synchronized process governed by the hypothalmic-pitutary- ovarian axis (HPO). Any disruption in HPO axis results in an/ oligo ovulation. In an ovulatory cycle the luteal phase is 14 days and the follicular phase is more variable, with ovulation occurring on day 10 to 21 in a 24-35 day cycle. Anovulation will be identified as a causative factor in approximately 15% of all infertile couples and accounts for up to 40% of infertility in women[8].

Hormone Assays- baseline hormone analysis in the follicular phase around day 2-5 of the menstrual cycle. These include assay for FSH, LH, TSH, PRL, Androgens (free and total testosterone, dehydroepiandrosterone, 17-hydroxyprogesterone)

Urinary LH kits- indirect evidence of ovulation and day of the LH surge and the following two days(9) but may yield false positive and false negative results in about 5 to 10 percent women.

Mid-luteal serum Progesterone- Serum progesterone measured in the mid-luteal phase >3 ng/mL is suggestive of recent ovulation.

Ultrasound- Serial follicular tracking showing progressive follicular growth, sudden collapse of the pre-ovulatory follicle, a loss of clearly defined follicular margins, the appearance of internal echoes, and an increase in cul-de-sac fluid volume(10). This is not a commonly used method for the associated cost and logistics.

Endometrial biopsy (EBM)- secretory changes on histology implies. Earlier used as "Gold standard" to diagnose luteal phase defect (LPD) but lacks both accuracy and precision not used commonly these days(11). It is justified to exclude tubercular endometritis, tissue sent for (histopathology, AFB staining and LJ culture), besides molecular tests (DNA PCR for mycobacterium tuberculosis)(12).

Serial basal body temperature (BBT) measurements provide a simple and inexpensive method, ovulation

indicated by a bi-phasic temperature pattern, while a monophasic pattern indicates anovulation. No longer preferred.

Assessment of Fallopian Tube Patency

The commonly used methods for tubal patency are HSG, saline infusion sonography (SIS), hysterosalpingo contrast sonography (Hy-Cosy) and laparoscopy and chromo perturbation: Most of these tests complement each other and are not mutually exclusive[13]

Hysterosalpingography (HSG) is the standard method for evaluating tubal patency and is conducted in the follicular phase preferably between days 6 to 10 of the menstrual cycle using a water or lipid soluble contrast media.The PPV and NPV of HSG are 38% and 94%, respectively [14]. The sensitivity and specificity for diagnosis of tubal patency with HSG are only 65 and 95 percent, respectively[15]. Specificity and sensitivity is higher for diagnosing distal tubal occlusion, but much lower for proximal tubal occlusion. Proximal tubal occlusion may appear because of tubal spasm or poor catheter positioning leading to unilateral tubal perfusion so it should be confirmed by laparoscopic chromotubation. (Fig 1(A))

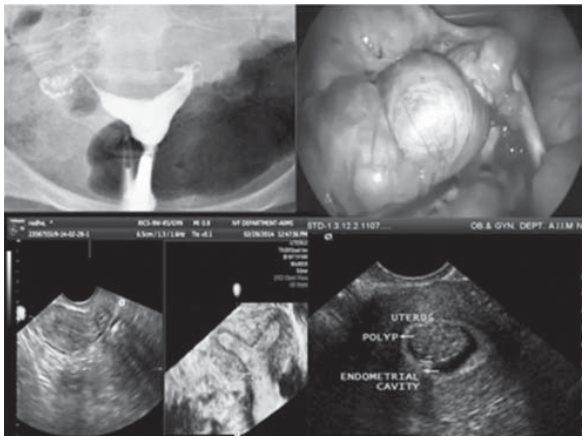

Figure 1(A): HSG-showing beaded appearance of right tube with bilateral distal block, **1(B):** Laparoscopy - endometriotic cysts in both ovaries, **1(C):** 3D image of uterus (right) showing a uterine septum **1(D):** SIS delineating a uterine polyp after the cavity was filled with saline

Also outline uterus and detect submucous fibroids and polyps and intra-uterine adhesions. Therapeutic benefits particularly by flushing the tubes the resulting removal of debris improves the chance of conceiving in the few cycles immediately after HSG[16].

Saline infusion sonography (SIS) – saline instillation under sonographic visualization through tubes is fluid in the cul-de-sac S/O patent tubes. It is useful in detecting a hydosalpinx more readily. The procedure requires expertise and experience in interpreting results besides inability to distinguish patency of a normal from diseased tube. An abnormal test results need an additional tubal testing method and SIS is therefore not a technique of choice to assess tubal patency(fig 1(D)).

Laparoscopy and chromotubation- involves the use of dilute solution of methylene blue or indigo carmine (preferred) introduced via the cervix to check tubal patency or document proximal or distal tubal obstruction. Its advantages include an ability to simultaneously evaluate the abdominal cavity and other pelvic structures (figure 1(B)). It is often combined with hysteroscopy and therefore gives a comprehensive assessment of tubal, peritoneal and uterine defects.

In the era of assisted reproductive techniques (ART) role of laparoscopy as diagnostic modality is controversial only indicated with the intent to offer operative measures[18]. In couples with unexplained infertility its role remains contentious due to lack of randomized trials with its cost-effectiveness[19]. Beneficial in pre-IVF women with hydrosalpinges[20].

Assessment of Ovarian Ageing /Reserve

Ovarian reserve is a term used to describe the quantity and quality of the reservoir of oocytes in the ovary. Diminished ovarian reserve (DOR) can refer to diminished oocyte quality, oocyte quantity, or reproductive potential. Indicated in females with risk of DOR like advanced age, prior surgery, H/o chemotherapy etc. Of the battery of tests available, the most commonly used include day 2 FSH, antral follicle count and serum AMH levels

Cycle-Day 2 Serum FSH - High values (>10–20 IU/L) have been associated with both poor ovarian stimulation and the failure to conceive[21].

Antral follicle count (AFC) - sum of antral follicles (2-8 mm) in both ovaries on day 2-6 of the menstrual cycle. It is a good predictor of ovarian reserve and response but less predictive of oocyte quality, the ability to conceive with IVF, and pregnancy outcome[22].

Anti-Müllerian hormone (AMH) - Produced by granulosa cells of preantral and antral follicles, are gonadotropin-independent and therefore remain relatively consistent within and between menstrual cycles. Overall, lower serum AMH levels (<1 ng/mL) have been associated with poor responses to ovarian stimulation, poor embryo quality, and poor pregnancy outcomes in IVF[23].

Uterine Factor

The uterus with the endometrial layer is crucial for implantation and pregnancy. Following modalities can

be utilized for uterine cavity evaluation

Ultrasound: TVS provides excellent overall depiction of the uterus, endometrial lining, and ovarian architecture. Baseline scan in the follicular phase is mandatory in the evaluation detect adnexal masses, hydrosalpinx, and ovarian architecture including AFC, ovarian cysts, endometrima. 3D and 4D technology has improved the diagnostic ability making the identification of sub-mucous fibroids, polyps and even uterine defects as septum easy obviating the need for further imaging or diagnostic hysteroscopy.

HSG- It has the advantage of not just providing information on tubal patency but delineating uterine pathology as sub-mucous fibroid, intra-uterine adhesions, septum or a bicornuate uterus.

SIS- The delineation of uterine and endometrial defects such as a submucous fibroid or polyp (Fig 1(D)) is readily possible at SIS.

Hysteroscopy- gold standard method for evaluating uterine cavity with few advantages over sonohysterography like it has greater specificity than sonohysterography, it distinguishes between endometrial polyps and submucous myomas and treatment can be done in the same sitting.

Cervical Factors

Abnormalities of cervical-mucus production or sperm mucous interaction rarely are the sole or principal cause of infertility. The post coital test (PCT) tests the cervical mucus around or just before ovulation for the presence of sperms microscopically. Rarely used because of poor reproducibility, inconvenience, rarely changes clinical management.

Conclusion

Infertility evaluation involves a couple approach with the initial evaluation including a detailed history and examination to guide the diagnostic work up. While tests offered need to be individualized, the basic tests should confirm ovulation, tubal patency and uterine and endometrial architecture.

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Ovarian Reserve Testing: Where do we stand?

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Introduction

Ovarian reserve is a complex clinical phenomenon influenced by age, genetics, and environmental variables. A woman is born with about 2 million primordial follicles. By onset of menarche only about 400,000 follicles are left due to natural follicular atresia. On reaching mid-30s pace of oocyte depletion begins to increase and by late 30s, number of follicles declines to approximately 25,000, resulting in a significant increase in miscarriage rate. The term "ovarian reserve" has traditionally been used to describe a woman's reproductive potential specifically, number and quality of oocytes she possesses. Delayed childbearing, voluntary or involuntary, is a common feature in couples visiting fertility clinics. Majority of fertility clinics perform ovarian reserve tests as part of evaluation of women with infertility prior to *In Vitro* fertilization. Diminished ovarian reserve describes women of reproductive age having menses whose response to ovarian stimulation or fecundity is reduced compared with women of comparable age[1]. Decline in a woman's ovarian reserve with time is irreversible and rate at which women lose primordial follicles varies considerably, with wide variation regarding onset of sterility and timing of menopausal transition[2-3].

Ovarian reserve testing (ORT) provide an indirect estimate of a woman's remaining follicular pool. An ideal ORT should be easy to perform, reproducible, and decisions based on their results should help differentiate women with a normal and poor ovarian response thereby identifying couples with negligible chance of conception against any expensive and repeated treatment. However, availability of multiple ovarian markers suggests that none is ideal. Largely, these tests have been used in subfertile women prior to the first IVF attempt to predict a poor ovarian response. More recently, their value in predicting hyper-response and thus using safe stimulation regimes to prevent OHSS is also explored[4]. Initial evidence suggested that various ORTs have a good predictive value for pregnancy. However, in recent years it has been understood that these tests are effective in predicting ovarian response to stimulation and not for prediction of pregnancy or its outcome[5].

Age

It is long established that ovarian reserve reduces progressively with age. Fecundity in both natural and stimulated ovarian cycles declines with maternal age, beginning in late 20s and becoming more abrupt in late 30s. Even though fertility does not decline uniformly in women, age is known to be most important factor determining pregnancy potential in regularly cycling women. Chronological age alone has limited value in predicting individual ovarian responses, which led to development and use of various biochemical and biophysical markers of ovarian reserve.

Basal Follicle Stimulating Hormone (FSH)

Basal Follicle Stimulating Hormone (FSH) levels measured on day 2/3 of menstrual cycle is most widely used test to assess ovarian response to stimulation. An increase in FSH levels occurs due to follicle depletion. Measurement of FSH is easy and inexpensive but it is known to have diurnal, intra- and inter-cycle variability[8]. A wide range in threshold values up to 25 IU/L has been used to define abnormal levels of basal FSH. In regularly cycling women, FSH can predict a poor response adequately only at very high levels, and hence will be helpful only to a small number of women as a screening test, for counselling purposes[9,10]. High FSH levels have not been associated with an increased risk of aneuploidy in pregnancies resulting from IVF[6]. Combined with other markers it can be used to counsel couples regarding a poor response but should not be used to exclude regularly cycling women from ART.

Anti-Mullerian hormone

Anti-Mullerian hormone (AMH) is a dimeric glycoprotein exclusively produced by granulosa cells of preantral (primary and secondary) and small antral follicles (AFs) in ovary. It was first noted to be present in follicular fluid in 1993. Its clinical utility was identified as an ovarian reserve marker and was first reported following studies of AMH deficient mice demonstrating accelerated atresia when AMH gene was deficient. Ovary begins producing AMH in utero at about 36 weeks of gestation, its levels rise in young women beginning in adolescence and peak at about 25 years of age, and then gradually declines until reaching undetectable levels a few years prior to menopause[7]. Production of AMH starts following follicular transition from primordial to primary stage, and it continues until follicles reach antral stages, with diameters of 2-6 mm[8]. AMH levels strongly correlate with basal antral follicle count (AFC) measured by transvaginal

ultrasonography. Unlike other biochemical markers, it can be measured on any day of cycle and does not exhibit inter-cycle variability[15]. Various threshold values, 0.2–1.26 ng/ml, have been used to identify poor responders with 80–87% sensitivity and 64–93% specificity. With better understanding of its clinical implications, AMH is now known to have ability to predict hyper-response as well. A recent study of Society for Assisted Reproductive Technology database found that while women with ultralow AMH (< 0.16 ng/ mL) had 54% cycle cancellation rate, overall live birth rate per cycle start was 9.5% supporting notion that denying infertility treatment solely on basis of undetectable AMH is not advisable.

AMH is a promising screening test and is likely more useful in general IVF population or in women at high risk for Diminished Ovarian Reserve (DOR) than in women at low risk for DOR. Low AMH cut-off points are fairly specific for poor ovarian response, but not for pregnancy.

Inhibin B

Inhibin B is a heterodimeric glycoprotein released by granulosa cells of follicle. Women with a low day 3 inhibin B concentration (< 45pg/ml) have a poor response to superovulation for IVF and are less likely to conceive a clinical pregnancy[9]. Inhibin B is not a reliable measure of ovarian reserve. Inhibin B levels rise with gonadotropin-releasing hormone (GnRH) or FSH stimulation (basis of dynamic tests of ovarian reserve) and therefore exhibit high intra-cycle variability[10]. Inhibin B levels also vary significantly between menstrual cycles.

Basal Estradiol

Basal Estradiol (E2) has been evaluated as a marker of ovarian reserve in women, prior to IVF. An elevated basal E2 level may mask abnormal FSH levels and hence, FSH levels alone may not be predictable of ovarian response in such women. A meta-analysis concluded that as basal E2 does not add to predictive value of other commonly used ovarian reserve tests, its routine use in clinical practice is not recommended[11].

Other tests clomiphene citrate challenge test (CCCT), exogenous FSH administration tests and GnRh agonist stimulation test are not done routinely these days as we have better tests as discussed above[12,13].

Ultrasound Parameters

Antral Follicle Count (AFC)

AFC measured by transvaginal ultrasonography in early follicular phase, by taking mean of two perpendicular measurements. Numbers of follicles in both ovaries are added for total AFC. A count of 8–10 is considered as a predictor of normal response. Repeated measurements have shown that there is only a limited inter-cycle variability. AFC is considered to have best discriminating potential for a poor ovarian response compared to total ovarian volume and basal serum levels of FSH, E2, and inhibin B on day 3 of cycle but lacks sensitivity and specificity to predict non-occurrence of pregnancy. More than 14 AFC are considered to be a good predictor of hyper-response. 3D ultrasound does not have any advantage over 2D ultrasound in assessment of ovarian reserve[14].

Ovarian volume

Ovarian volume is measured by transvaginal ultrasonography applying formula for an ellipsoid (D1 × D2 × D3 × π/6). Volume of each ovary is calculated by measuring in three perpendicular directions. Volumes of both ovaries are added for total basal ovarian volume (BOV). Ovarian volume remains unchanged till perimenopausal period and does not add to predictive value of AFC. A decline in ovarian volume is a late event noticed in women > 40 years.

Ovarian vascularity

Observation of Ovarian Doppler flow during ovarian stimulation has been studied in IVF cycles. Increase in Doppler flow noted during stimulation is considered not to provide additional information to AFC.

Combined Ovarian Reserve Tests

No single measure of ovarian reserve has 100% sensitivity and specificity therefore biochemical and imaging measures have been combined in an effort to improve test characteristics. A prospective analysis of a combination of AMH, inhibin B, and 3D assessment of AFC and ovarian volume concluded that only AFC and AMH predicted poor ovarian response, and prediction was no better than that derived from each test individually or in combination. Notably, none of measures predicted failure to conceive.

In summary, combined ovarian reserve test models do not consistently improve predictive ability over that of single ovarian reserve tests. High-risk scoring systems that combine two or more measures may be clinically useful but require further validation.

Conclusion

Evaluation of ovarian reserve can help identify patients who will have poor response or hyper response

to ovarian stimulation for ART and individualize treatment protocols to achieve optimal response while minimizing safety risks. It may inform patients regarding their reproductive lifespan and menopausal timing, and also aid in counselling and treatment strategy planning of young female cancer patients receiving gonadotoxic therapy.

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Calendar of Monthly Clinical Meetings 2019-20

Months	Name of the Institute
28th June, 2019	VMMC & Safdarjung Hospital
26th July, 2019	AIIMS
30th August, 2019	Army Hospital- Research & Referral
25th October, 2019	ESI Hospital
29th November, 2019	MAMC & LN Hospital
27th December, 2019	Sir Ganga Ram Hospital
31st January, 2020	Dr RML Hospital
28th February, 2020	UCMS & GTB Hospital
27th March, 2020	LHMC
24th April, 2020	Apollo Hospital

Please note there will be no Monthly Clinical meeting on Friday, 27th September 2019

Role of Endoscopy in Infertility

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Hysterolaparoscopy is a minimally invasive surgical procedure that allows to determine and treat cause of infertility. Though pelvic sonography and HSG are good enough for excluding gross intrauterine pathology, subtle changes in the form of small polyps, adhesions and sub-endometrial fibroid seedling, which influences fertility, can be missed. These subtle changes are better picked up on magnification with hysteroscopy. Diagnostic laproscopy can diagnose tubal pathology, tubal patency by chromopertubation, adhesions, inflammatory changes and endometriosis even if HSG is normal[1].

Indications for laparoscopy in infertile women:

- Endometriosis treatment
- Tubal pathology
- Unexplained infertility
- Laparoscopic myomectomy in selected cases
- Chronic pelvic pain
- Mullerian anomaly
- PCOS/Ovarian cyst

Endometriosis and Infertility

Laparoscopy is considered gold standard in the surgical management of endometriosis due to benefits of magnified and illuminated image, shorter hospital stay, faster postoperative recovery, less post-operative pain and less morbidity compared to laparotomy.

Laparoscopic surgery for endometriosis in infertile women includes:

- Adhesiolysis
- Restoring normal anatomy
- Endometriotic implant ablation
- Cystectomy
- Endometrioma removal

Surgical management is warranted for women with symptoms of dysmenorrhea, dyschezia and chronic pelvic pain.

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates[2]. (Level A evidence)

CO_2 laser vaporization of endometriosis instead of monopolar electrocoagulation is associated with higher cumulative spontaneous pregnancy rates. Among energy sources, bipolar is considered safe over monopolar energy source due to less chances of complications by bipolar energy source.

The maximum chances of conception are within 3 to 6 months of laparoscopic surgery of endometriosis. There is no role of pre op and post op medical therapy.

In moderate –severe endometriosis with prior one or more infertility operations, IVF-ET is better therapeutic option than another infertility operation (ESHRE 2013)

Management of Ovarian endometrioma

Treatment of ovarian endometrioma/ chocolate cysts is either excision of the cyst capsule or drainage and electrocoagulation of cyst wall.

Excision of the endometrioma capsule (>3cm), is recommended instead of drainage and electrocoagulation of the endometrioma wall to increase clinical pregnancy rates[3] (ESHRE).

Counsel women with endometrioma regarding the reduction of ovarian reserve following surgery. Malignancy chances are 0.8% in endometrioma cases, so it is to be ruled out.

Intraoperative steps to be taken to prevent complications

- Preserving blood supply to the ovary is necesssary to preserve ovarian volume and antral follicular count. It is advised to avoid the procedure near hilum as ovarian tissue is more functional and the plane of cleavage is less visible in this area. Do hydro-dissection/ vasopressin injection beneath capsule to identify plane of cleavage.
- Strict compliance to the principles of microsurgery.
- To remove all visible endometriotic disease.
- During adhesiolysis, take extra precaution to prevent ureter injury during release of ovaries from ovarian fossa.
- Avoid spillage of endometriotic contents to avoid recurrence and adhesion formation

Role of adhesion prevention agents during surgery

Use of oxidized regenerated cellulose (surgicel/ interceed) during operative laparoscopy for endometriosis prevents adhesion formation[4]. Anti-adhesion agents like polytetrafluoroethylene surgical membrane, hyaluronic acid products prevents adhesion in pelvic surgeries but their specificity in endometriosis patients is yet to be proven[3]. (ESHRE 2014)

Laparoscopic Adhesiolysis

Laparoscopic adhesiolysis helps in restoring normal tubo-ovarian anatomical relationship[5].

Shawi et al, performed laparoscopic adhesiolysis on 167 infertile patients with pelvic adhesions[5]. They categorised them to 3 groups: group I- mild; group II- moderate; group III- severe and followed them after 12 months. Pregnancy occured in 70.8% patients in group I, 48.3% in group II, and 21.6% in group III.

Salpingo-ovariolysis is a fertility-enhancing procedure done by separating adhesions with laparoscopic scissors, electrocautery or the laser.

Laparoscopic reproductive surgery reduces peritoneal adhesions and lower chances of postoperative adhesion recurrence and de-novo adhesions formation at surgical sites[5].

Adhesion thin and avascular lyse easily and recurrence is low. Adhesions thick and vascular need energy sources (unipolar/ bipolar/ ultrasonic dissector) and scissors.

Fluid is left in the abdominal cavity to prevent recurrence. Fertility depends on the type of adhesions and how much adhesiolysis was possible.

Laparoscopic surgery follows microsurgical principles to avoid further adhesion formation.

Complications: Injury to bowel and adjacent organs like ovaries, gall bladder and bleeding.

Laparoscopic Myomectomy (LM)

As per ACOG and ASRM, fibroids which need myomectomy are[6]:

- Fibroids causing severe bleeding and anemia
- Pain due to fibroid
- Urinary complaints due to fibroid
- Infertility with associated endometrial cavity distortion and or tubal block.

As per ASRM (2008) myomas that distort uterine cavity and larger fibroids (>5 cm) may have adverse effects on fertility[7].

After myomectomy, conception rate is 53%-70% (submucous fibroid) and 58%-65% (subserosal/ intramural fibroid)[6].

There is fair evidence to recommend against myomectomy in women with intramural fibroids (hysteroscopically confirmed) and unexplained infertility regardless of their size. SOGC (2015)

Procedure of laparoscopic myomectomy: For proper case selection fibroid mapping is to be done. Pre-operativeely fibroid size can be reduced by GnRHa/ ulipristal acetate for proper space and minimising blood loss but it can make fibroid enucleation difficult and missing of small fibroids. Before incision on fibroid, myometrium is injected with vasopressin to reduce blood loss. Incision can be given by monopolar hook/scissor or laser. It helps to find plane easily then incision is increased and with the use of myoma screws, claw forceps or tooth graspers, fibroid can be enucleated by giving traction and counter-traction. Myometrium repair to be done by large curved needles to avoid dead spaces and Serosa is closed with barbed suture and anti-adhesion agents are used on suture line to avoid adhesions. Avoid excessive use of energy sources to prevent uterine rupture in future pregnancy and also weakens suture line. If endometrial cavity is breached, repair it separately. Fibroid to be removed with morcellator. Achieve hemostasis before closing abdomen and irrigate the abdomen[8].

Complications of LM:

- Bleeding
- Adhesion formation
- Bowel injury
- Inflammation
- Risk of uterine rupture during pregnancy and delivery

Concerns associated with LM are regarding adequate reconstruction and healing of myometrial incision to withstand pregnancy and labour. A case report on Uterine rupture post LM has been documented during delivery and labor and also prior to labour onset[5]. It is advisable to avoid excess thermal damage and perform adequate uterine repair to prevent rupture[9].

Infertility and Polycystic Ovary Syndrome

Ovarian drilling: Either GnRH or laparoscopic ovarian drilling(LOD) could be used as in women with PCOS with anovulatory infertility, Clomiphene resistance and no other infertility factor following counselling on benefits & risks of each therapy. It increases sensitivity to GnRH and reduces chances

of multiple pregnancy and ovarian hyperstimulation but has small risk of adhesions and decrease ovarian reserve after LOD.

Electrocautery: 30-50watt, 4-5 punctures, 5-7 mm depth, 4-5 secs each penetration.

LASER: CO2 laser, continuous mode-10-25 W,10-30 holes, 5 sec each.

Infertility and Tubal Disorders

Diagnostic tests like HSG, ultrasonography(USG), chlamydia antibody testing(CAT) for detecting tubal pathology and their efficacy compared to laparoscopy in infertile patients is debatable[1].

Laparoscopy is advocated in infertile patients with suspected bilateral tubal block on HSG as it changed the original treatment plan in 30% of cases[1].

Conditions where tubal surgery is needed:

1. Distal and proximal tubal block (complete or incomplete)
2. Hydrosalpinx
3. Peritubal or periovarian adhesions

Laparoscopic tubal surgery is better than microsurgery by laparotomy as it prevents big scar, less pain, less deformity of tube and prevents adhesions.

Proximal tubal lesions are treated by laparoscopic techniques like tubocornual anastomosis. Tubal preservation surgery for distal tubal lesions includes salpingostomy and fimbrioplasty.

Current guidelines for hydrosalpinx suggest laparoscopic salpingectomy before IVF. Salpingostomy for hydrosalpinx management have high ectopic pregnancy rates while Essure® can be used hysteroscopically in patients with pelvic adhesions/ distorted pelvic anatomy where laparoscopy is difficult. But Essure® use prior to IVF has not shown any improved pregnancy and live birth rates[10].

Due to advancement in the imaging techniques (i.e. 2D/3D USG, CT scan, SIS and MRI) accurate diagnosis of uterine and adnexal disease is possible and it is comparable to diagnostic laparoscopy. So it is advised to take a judicious decision for operative laparoscopy after complete clinical evaluation and investigation.

Hysteroscopy

It is considered gold standard for diagnosing intra-uterine disorders[7].

Indications of hysteroscopy:

- Endometrial biopsy(EB) and polyp removal
- Hysteroscopic myomectomy for submucus fibroid
- Asherman's syndrome
- Cornual block
- Congenital malformations of uterus
- Recurrent miscarriages
- Cervical stenosis

Endometrial Biopsy (EB) and Polyp Removal

EB can be carried out with grasper or biopsy forceps by hysteroscope. It can identify polyp, endometrial infection or rarely malignancy in infertile patient[11]. Polyps can affect the endometrial receptivity and cause implantation failure as it distorts endometrial cavity[7].

Another study concluded that apparently polyps were the only reason for unexplained infertility in patients with menstrual irregularities and their pregnancy rate was 61.4% and delivery rate at term was 54.2%, which was significantly higher after polypectomy[7]. Poylpectomy prior to IUI/IVF increases pregnancy rates[7].

Hysteroscopic Myomectomy

Submucosal fibroid affect fertility and pregnancy rate as it impairs the endometrial receptivity[11]. ASRM[6] published in 2008 that hysteroscopic myomectomy is indicated in intra-cavitary myomas and submucous fibroid with size atleast 50% volume in the uterine cavity. Fibroid size can be decreased upto 50% by using GnRH agonists before hysteroscopic fibroid resection but GnRH agonist also decreases uterus size and changes it to hypoestrogenic phase and so chances of uterine perforation increases.

Procedure: Resection of fibroid is done by slicing at the maximum bulge of fibroid with the loop and it is advisable to remain in pseudocapsule for safety and avoiding perforation. After the procedure, resectoscope is removed and using ovum forceps fibroid fragments are removed. Resected area of fibroid heals itself by covering itself with endometrial tissue[8].

Advantages of hysteroscopic myomectomy:

- Avoids need for laparotomy
- Avoids formation of tubo-ovarian adhesions
- Avoids uterine incision thereby decreasing chances of LSCS[12].

SIS and hysteroscopy are equivalent for diagnosing submucosal fibroid and superior to transvaginal ultrasound[7] while MRI is superior for mapping relationship of submucous fibroid with myometrium and serosa[7]. 3D ultrasound results are comparable to hysteroscopy for diagnosing uterine focal lesion[13].

Asherman's syndrome

It causes recurrrent abortions due to decreased uterine size, scanty endometrium and abnormal placentation[11].

Factors predisposing to adhesions:

- Postabortal/ postpartum
- Infection - tubercular endometritis
- Uterine trauma- curettage
- Congenital anomalies - DES induced

Adhesions causes infertility disrupting sperm migration, blocking fallopian tubes and impairing blastocyst implantation.

Treatment includes hysteroscopic adhesiolysis by using operative hysteroscope, scissors, cautery and Nd-YAG laser. Postoperatively, measure taken to adhesion formation are prophylactic antibiotics, low-dose aspirin, nitroglycerine/sildenafil citrate and postoperative estrogen/progestin therapy. Hormonal treatment stimulates endometrial growth whereas aspirin/ sildenafil/ nitroglycerine improves post-operative endometrial vascular perfusion.

Complications of adhesiolysis:

- Perforation (2%)
- Infection (<2%)
- Adhesion reformation (20-40%)
- Placental complications (2-40%)

Proximal fallopian tube block

It can be diagnosed by HSG and confirmed by hysteroscopy. Hysteroscopic cornual cannulation or catheterization can be performed. Hysteroscopy helps restore tubal patency and avoids major surgery for tube repair or IVF, if procedure is successful[6].

Contraindications to tubal cannulation:

- Active pelvic infection
- Uterine bleeding
- Allergic reaction to local anesthetic agents
- Intra-uterine adhesions
- Submucous fibroid

Hysteroscopic cornual block correction leads to pregnancy approximately 1/3 of the time. Complication rate are also low. Adjunctive Laparoscopy may be required for tubal cannulation.

Complications of this procedure: Perforation, Infection.

Hysteroscopic Metroplasty

HSG is useful for diagnosing uterine disorders but cannot differentiate between type of congenital disorder[7]. 3D ultrasound is very accurate for classification of congenital uterine anomalies. Most accurate diagnosis of congenital uterine anomalies can be made by combining SIS, 3D ultrasound and combined hystero-laparoscopy[7]. Gold standard for diagnosing uterine congenital anomalies is hystero-laparoscopy.

Unicornuate uterus: poor reproductive outcome. Rudimentary horn can be removed by laparoscopy/ laparotomy.

Arcuate uterus: seen in 12.2% RPL cases whereas it is 3.8% in general/infertile population[7]. IVF-ET after septoplasty in infertile patients with incomplete septum/arcuate uterus and normal uterus. Pregnancy and delivery rate post-IVF were higher following septoplasty but there was no significant difference in delivery/pregnancy rates per patient between 2 groups. There was no significant difference in IVF results post-septoplasty between arcuate uterus anomaly and incomplete septum patients with infetility[14].

Septate uterus: Septum can be cut using Collins knife or scissors via operative hysteroscope. HSG cannot differentiate between septate or bircornuate uterus as fundus is not visible[7]. 3D-SIS has 97% sensitivity and 100% specificity for diagnosing uterine anomalies[7].

Metroplasty in unexplained infertile patient with septate uterus can improve pregnancy rate and live birth rate in patients with otherwise unexplained infertility[7].

Office Hysteroscopy (OH)

Office hysteroscopy is a very simple procedure that requires minimal instrumentation.

It can be done in recurrent IVF failure cases for increasing chances of pregnancy rate in subsequent IVF cycles, both in normal and abnormal findings on hysteroscopy[7]. Role of OH before IVF-Embryo Transfer is debatable in improving pregnancy outcomes.

Implantation, pregnancy and clinical pregnancy rates were higher when OH was performed equal to or <50 days before ET. Around 22.9% of IVF population had

endometrial pathology which may have impaired IVF success rates[7]. OH has higher sensitivity than TVS and HSG for diagnosing intra-uterine lesions and should be performed before IVF in all patients even with normal TVS/HSG findings as many of them have undiagnosed uterine disease that affects their fertility treatment[7].

There should be hysteroscopic evaluation of nulliparous patients with complaints of unexplained infertility and one study showed 85% increase in pregnancy rate after 2 years of surgery[12]. Operative hysteroscopy results showed pregnancy rate of 62% post myomectomy, 66% after septal resection, 61% after adhesiolysis[7]. Forty-six percent pregnancy rate was observed after 1 year of treatment of endometrial/tubal pathology[11].

There are no proper consensus on the role of operative hysteroscopy for infertility management as randomised controlled trials does not report that operative hysteroscopy for all intra-uterine disorders improves IVF results and observational studies suggest that operative hysteroscopy improves pregnancy rates. So, more randomised control trials are needed for demonstrating positive role of operative hysteroscopy in unexplained infertility or prior to ART.

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Female Genital Tuberculosis and Infertility

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Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS), alarmed by the high prevalence and mortality and morbidity of the disease[1]. WHO declared TB a global emergency and launched the stop TB strategy as evidence based approach to reduce the burden of TB. According to global TB report 2018, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people and there were an additional 300 000 deaths from TB. Globally, the best estimate is that 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017, 3.2 million TB cases occurs in women in a year with 4, 80, 000 deaths amongst them[1, 2]. Nearly one third of the world population is infected with Mycobacterium tuberculosis (MTB) of whom only 10% are known to progress to clinical disease[3].

FGTB is a common disease which is caused by Mycobacterium tuberculosis (rarely M bovis or atypical mycobacteria). It is an important cause of significant morbidity, short and long term sequelae especially infertility whose incidence varies from 5-15% cases in India[4,5].

Genital tuberculosis has been described as a disease of young women, with 80–90% of patients being first diagnosed between the ages 20 and 40 years especially in developing countries while in developed countries, the mean age is 40 years[6].

Revised National TB Control Program (RNTCP) of India has also achieved high success of 71% case deletion rate and 87% treatment success rate with a seven fold reduction in death rate (from 29%to 4%) in all cases of TB including FGTB[7].

Most frequently affected genital organs include fallopian tubes (95%-100%), endometrium (50-60%), ovaries (20-30%), cervix (5%), and rarely vulva and vagina (1%). It causes menstrual dysfunction and infertility through the damage of genital organs[8].

The diagnosis is made by from proper history taking of TB including family history, in contacts or past, thorough clinical examination[3,4]. Endometrial sampling should be performed for detection of acid fast bacilli on microscopy or culture or on histopathological detection of epithelioid granuloma on biopsy[5]. Polymerase chain reaction (PCR) may be false positive and alone is not sufficient to make the diagnosis[2,8].

WHO-recommended rapid diagnostic test for detection of TB and rifampicin resistance as Xpert MTB/RIF assay. It has emerged out to be useful in detecting TB both in pulmonary and extra-pulmonary cases[9]. Newer diagnostic techniques like LAMP (Loop isothermal mediated amplification process) and LAM (Lipoarabinomannan: secreted in urine in HIV infected cases in TB) has been under review but has shown positive results[10, 11].

Use of radiological modalities like ultrasound, CT scan, MRI, PET scan is more in adnexal masses[3].

Laparoscopy and hysteroscopy is the gold standard for the diagnosis of the disease [2-5]. Diagnostic hysteroscopy shows features like pale endometrium, tubercles and intra-uterine adhesions of varying grades. There may be a constricted cavity[3,4]. Laparoscopy is more useful in abdomino-pelvic TB with features like tubercles on peritoneum, shaggy areas, peritoneal blebs, caseous nodules, encysted ascites, tubo-ovarian masses, varying grades of pelvic adhesions and perihepatic adhesions (Fitz Hugh Curtis Syndrome), hydrosalpinx, pyosalpinx, beaded tubes, tobacco pouch appearance and inability to see tubes due to adhesions[2-4].

Another clinical signs like Sharma's Hanging Gall Bladder Sign (due to severe perihepatic adhesions, position of gall bladder changes and it hangs vertically showing hanging gall bladder sign), Sharma's Ascending Colonic Adhesion (5×4cm large ascending colonic adhesion at junction of lower 2/3rd and upper 1/3rd of ascending colon, below the hepatic flexure, between ascending colon and anterior abdominal wall), Sharma's Blue Python Sign (partial or complete blockage of tubes at cornual ends, multiple constrictions and dilatations of fallopian tubes and partial or complete blockage of fimbrial end of tubes. During chromotubation, tubes may be distended with alternate constriction and dilatation resembling blue python), Sharma's Kissing Fallopian tube sign (sometimes caseous material may come out from the fimbrial end of one or both fallopian tubes and make an adhesion between the two fimbrial ends causing their fusion (kissing fallopian tube sign) can be seen during diagnostic laparoscopy[3,6].

Treatment

Medical treatment

Treatment of latent genital TB detected only on positive polymerase chain reaction (PCR) is controversial due to high false positivity[3,5,8]. Many assisted reproductive technology (ART) experts routinely treat positive PCR patients with better pregnancy outcome in those women treated with anti tubercular therapy (ATT) than without treatment. The logic of treating later TB is that in early

stage, it can be treated without causing permanent damage to endometrium and other genital organs with much better outcome[2,3].

Jindal et al[12] observed 30.8% pregnancy rate an TB PCR positive women with ATT, whereas Kulshrestha et al.[13] also obtained 31% pregnancy rate on ATT in TB PCR positive women. Latent genital TB has been found to be associated with repeated IVF failure in Indian clinical setting[3- 4,8].

Short course chemotherapy of 6 months has been found to be effective treatment for FGTB[2].

In a randomized controlled trial, we observed 6 months antitubercular therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol to be as effective as 9 months therapy confirming that 6 months therapy is adequate for FGTB[14].

Directly Observed treatment short course therapy DOTS under RNTCP (Revised National Tuberculosis Control Program)

The Revised National TB Control Programme (RNTCP) of India has incorporated the DOTS strategy all over India by the end of 2005 diagnosing about 71 per cent cases and curing above 87 per cent cases with a seven-fold reduction in mortality[7]. Treatment is daily therapy of rifampicin(R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) for 2 months followed by daily 4 month therapy of rifampicin (R) and isoniazid (H). Alternatively 2 months intensive phase of RHZE can be daily followed by alternate day combination phase (RH) of 4 months. Three weekly dosing throughout therapy (RHZE thrice weekly for 2 months followed by RH thrice weekly for 4 months) can be given as directly observed treatment short course (DOTS)[2,3,7].

Treatment of chronic cases, drug resistant and multi drug resistant (MDR) FGTB can be treated with Category IV drugs for long duration (18-24 months)[4,8].

Surgery is rarely required only as drainage of abscesses. There is role of in vitro fertilization (IVF) and embryo transfer (ET) in women whose fallopian tubes are damaged but endometrium is healthy[3-6]. Surrogacy or adoption is needed for women whose endometrium is also damaged[6].

Hence, there has been a renewed interest in research in TB at global level. New and improved BCG vaccines which are effective against strains, resistant to conventional drugs and requiring a shorter treatment regimen are being developed[9,14]. Research on the role of epigenetics in the regulation of immune response in relation to TB infection can give answer regarding host susceptibility but limited studies have reported the interaction between *Mtb* infection and changes in host epigenetic machinery, however, the precise molecular mechanism is yet to be studied[15].

By controlling TB, FGTB can also be kept at bay and treated early to prevent development of short term and long term sequelae of this menace.

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26th September 2019

Ist Trimester USG - Quality Control
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Optimizing success of IUI Cycles

Monika Gupta[1], Divya Pandey[1]
Associate Professor, Department of Obstetrics and Gynaecology, VMMC and Safdarjung Hospital, New Delhi

Introduction

Infertility is a very common condition which affects about 13-14% of reproductive aged couples. The demand for infertility services has increased substantially over past few decades. Assisted reproductive technologies (ART) are considered as an established therapy for the treatment of infertility in a multitude of clinical conditions. It embraces a wide scope of techniques of which intrauterine insemination (IUI), in-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) are most popular. IUI is often used as an intermediate level and cost-effective intervention prior to proceeding to in vitro fertilization (IVF).

IUI is a simple and non-invasive technique which can be performed without expensive infrastructure with a reasonable success rate. It is a safe and easy treatment with minimal risks and monitoring. Also, IUI has a good couple compliance (low drop-out rate) and a very low risk for complications such as OHSS (ovarian hyperstimulation syndrome).

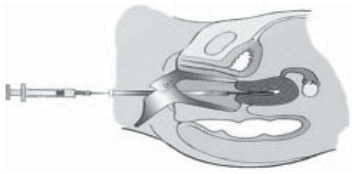
Clinical Use

Clinical use of intrauterine insemination (IUI) is based on the hypothesis that likelihood of conception is enhanced by placing a large number of sperm high in the reproductive tract. The minimum requirements to be ensured before this procedure are ovulation in the IUI cycle, patency of at least one fallopian tube, an adequate number of motile sperms in the inseminate, and absence of documented or suspected active cervical, intrauterine, or pelvic infection.

Evidence suggests IUI must be a first-line treatment option for most couples except in cases of bilateral tubal blockage and severe oligozoospermia.

IUI is particularly useful in the following situations:

- Couples with some types of severe sexual dysfunction (eg, severe vaginismus, ejaculatory dysfunction)
- Discordant for sexually transmitted disease carriage (eg, HIV, hepatitis).
- Donor semen IUI in cases of azoospermia
- In cases of cervical factor infertility mild male factor infertility, the potentially hostile cervical factors can be avoided by IUI and thus increasing the number of sperm can gain entry to the uterine cavity (and oocyte).



Optimizing the Success of IUI

The significance of IUI, especially in relation to IVF remains controversial. There have been divergent opinions regarding the benefits obtained from IUI. The success of IUI is judged in terms of the pregnancy rate achieved after one or more IUI cycles for a particular candidate. Further, the pregnancy rate after IUI depends on male factors, female factors, and technical factors.

As per the literature review over past 15 years, there has been a wide range of variation in the clinical pregnancy rates predicted after successful IUI cycles. An estimation of 0 - 26% pregnancy / cycle for different indications has been suggested. The take home baby rate is a matter of further controversy for which no evidence-based infertility data is available. Various factors such as choice of patients, clinical management of patients, the type of stimulation regime, timing and the management of sperm usage have significant bearing to whether IUI will succeed.

Success rates of IUI cycles are contingent upon the procedure being performed with correct indication and avoiding performance of IUI when contraindicated. It also depends on whether woman is ovulating normally on her own or requires induction of ovulation. There exist, wide variations in indications, protocols of ovarian stimulation, semen preparation, timing, number & technique of insemination. Various aspects affecting the IUI procedure, its determinants of success and possible areas for future improvements are enlisted in table 1.

Table 1: Factors influencing IUI pregnancy rate:

Female Factors	• Age • Cause of Infertility • Type of Ovarian Stimulation • Response of Endometrium • Number of Preovulatory Follicles
Male Factors	• Age • Semen Collection • Semen Parameters • Semen Processing methods • Cryopreservation of Semen
Common Factors	• Duration of Infertility • Number of IUI cycles • Technique of Insemination • Number of Insemination per cycle • Type of catheter used

Patient Selection

Age

Age of the women is single most important factor determining the success of IUI. The pregnancy rate decreases after 35 years and further drastically falls after 40 years of age presumably related to oocyte quality. Older women have associated issues like fewer oocytes per cycle, low E2 on day of hCG, lower implantation rates, increased risk of miscarriage and increased chances of chromosomal abnormalities.

For the male partners, age does not seem to hamper pregnancy rate much but there are higher sperm abnormalities observed after age of 50 years. Oxidative stress-induced mtDNA damage and nuclear DNA damage in aging men may put them at a higher risk for transmitting multiple genetic and chromosomal defects.

Cause and duration of Infertility

Infertility type – Primary or secondary does not significantly affect outcome of IUI. Female factors like anovulation and unexplained infertility have better results compared with other etiologies like endometriosis, tubal factor infertility, severe male factor and other combined factors. Duration of infertility, if greater than four years, has a negative impact on success of IUI.

Ovarian Parameters

Controlled Ovarian Stimulation

Various studies have shown that controlled ovarian hyperstimulation (COH) in combination with IUI results in significantly higher pregnancy rates than natural cycle or timed IUI alone. This is most important for patients with mild male factor, early stage endometriosis, or unexplained infertility.

Optimum ovarian stimulation should result in

- 1 - 3 follicules (18 – 20 mm)
- E2 is 150-250 pgm /ml per dominant follicle >/= 15 mm
- Endometrium >/= 8 mm thick & is trilaminar

Cancellation of IUI cycle is warranted when:

- >/= 6 follicles >/=15 mm irrespective of E2 level
- Estradiol >/= 1500 pg/ml

Ovulation Induction Protocols & Preovulatory follicles

Stimulation with gonadotropin gives better results compared with clomiphene citrate (CC). Letrozole produces comparable results to CC. Addition of COH to IUI especially with gonadotropins increases its efficiency with cost of higher expenses and risk of multiple pregnancies.

- Clomiphene citrate 50-100mg per day from day 2-6 of the cycle (can be started upto 5th day of cycle)
- Letrozole 2.5mg per day from day 3-7 of cycle
- Gonadotrophins can be added along with oral agents starting from day 7-8 of cycle in case of inadequate response
- Gonadotrophins can be started from day 2-3 of cycle

Patients on ovulation induction especially when gonadotrophins are added require regular follicular monitoring starting from 7-8th day of cycle.

Perifollicular flow & Endometrial receptivity

In an IUI cycle, if there is poor perifollicular blood flow (Perifollicular flow velocity (PSV)< 3 cm/sec) when the follicle is mature, consideration should be given to canceling the cycle. If more than three follicles have strong perifollicular flow (>10 cm/sec), IUI should be canceled because of high risk of multiple pregnancy.

Ultrasound parameters that indicate a good receptive endometrium are:

- Endometrial thickness of 8 – 14 mm
- Endometrial morphology – “triple line” pattern
- Uterine Vascularity – Mean uterine artery PI between 2 - 3
- Endometrial perfusion – presence of subendometrial and endometrial flow

Luteal phase support should be added to IUI cycles mildly stimulated with gonadotrophins in couples with unexplained subfertility.

Semen Parameters

Semen Collection & Processing

Semen processing for IUI is not difficult to learn and can be adapted to use in clinical offices. Environment in laboratories and consumables should be contamination free and regular microbiological screening of work environment necessary. Maintenance of equipments and use of good quality consumables & media is essential for optimizing the success of IUI. Care must be taken to ensure that adequate quality measures are in place.

IUI outcomes showed to be optimal after 2 days of ejaculatory abstinence. Semen processed within 30 minutes of collection and IUI performed within 90 minutes of collection results in higher pregnancy rates. IUI should be done at setup of sperm processing & preferably not transported to different place. If the prepared spermatozoa are to be stored after the sperm preparation before the IUI, it is advised to use a sperm buffer (e.g., HEPES medium).

It has been proven in literature that there is no significant difference between pregnancy rates for Swim–up vs. density gradient and centrifugation techniques.

Semen Quality

IUI should be used as a first-line treatment in case of moderate male subfertility provided more than 1 million motile spermatozoa are available after washing and at least one tube is patent. The success rate of IUI is improved with a morphology score of more than 4% normal forms, a Total motile Sperm count of more than 5 million and an initial total motility of more than 30%. The influence of sperm parameters on IUI outcome is influenced by other parameters such as female age and number of follicles obtained after ovarian stimulation

Semen Cryopreservation

Cryopreservation of sperms lead to 30-40% decrease in sperm motility and 10-15% decrease in pregnancy rates compared with fresh semen.

Procedural Issues

Number of IUI Cycles

The pregnancy rate per cycle is highest in the first three treatment cycles. Couples with mild male subfertility, unexplained fertility problems, or mild endometrioses show acceptable cumulative ongoing pregnancy rates after six cycles of IUI with OH, so should be offered 4-6 cycles of IUI.

Timing & Number of Insemination

Rationale is that viable sperms should be present at the time of ovulation. Detection of ovulation can be done by

- Serum or urinary LH - IUI 24 hrs later
- TVS - leading follicle >18 – 20 mm (hCG 5000 - 10000 IU / Rec hCG - 250 mcg SC/ GnRha 300 - 500 mcg)---IUI 36 – 42 hrs later

A single IUI procedure is recommended as when compared with double IUI, single IUI has the same efficacy with fewer visits and lower cost. In couples with mild male subfertility, double IUI should be performed in research setting. The frequency of insemination should not depend on multi-follicular growth

Technical aspects

- IUI success increases with use of abdominal USG with partially filled urinary bladder.
- No touch to fundus technique is desirable.
- About 0.3-0.5 ml of processed semen should be slowly injected and the catheter should be slowly withdrawn.
- The choice of catheter (soft or firm) does not seem to have a detrimental effect on success of IUI.
- An easy and atraumatic transfer is an essence of successful IUI.
- Open ended/rounded tip-Teflon catheters are least traumatic & most efficient.
- A 10 minutes bed rest after IUI has a positive effect on pregnancy rates.

Media supplements

Platelet activating factor (PAF) has been primarily used to effectively improve sperm motility. Exposure of sperm to PAF during semen washing might significantly increase IUI pregnancy rates in couples with unexplained subfertility receiving OH/IUI. Although the exact mechanisms of PAF action remain unclear, the importance of PAF for normal reproductive function is clear. Exposure of sperm to PAF significantly improves sperm motility, capacitation, and the acrosome reaction.

Suggested Reading

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Unexplained Infertility

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Introduction

Unexplained infertility can be described as infertility without any identifiable cause. It has been defined as inability to conceive despite unprotected intercourse for one year after exclusion of causes such as anovulation, tubal blockage, poor semen parameters or other known causes of infertility. This comprises around 10-30% of couples seeking fertility treatment(1).

Diagnosis of unexplained Infertility

The diagnosis of unexplained infertility is made after no cause has been identified after a standard infertility work up. The investigations for evaluation of infertility has gradually evolved over time and there is difference in opinion among practitioners for labelling a couple as having unexplained infertility. Traditionally basic infertility work up included semen analysis of the male partner and assessment of ovulation and tubal patency of the female partner. But it is also important to assess other identifiable causes like ovarian reserve and uterine cavity assessment. Sometimes patients having mild endometriosis can be misdiagnosed and treated as unexplained infertility. Unexplained infertility can also be considered a type of subfertility due to subtle abnormalities. Infact, Gleicher opined in a paper in 2006 that this term really does not exist and that should be abandoned as it very much depends on quantity and quality of tests(2) however, so far overlooked the fact that one of the most frequently made diagnosis, so-called unexplained infertility (UI.

Prognostic Factors

The prognosis in these couples depend on duration of infertility and of course, age of female partner. Various prediction models have been proposed to prognosticate chances of natural conception in patients with unexplained infertility. It is worse if duration of infertility exceeds 3 years and age of female is more than 35 years(3).

Possible Explanations

Couples with unexplained infertility may have subtle abnormalities in the male or female partner for which there are no specific tests available. The possible reasons in males could be mild defects in the sperm parameters, acrosome reaction or ability to bind to zona pellucida. In the females, there could be abnormalities in cervical mucus, defective oocyte quality, tubal motility, defect in endometrial receptivity, subtle alterations in follicle development and luteal phase.

Management

Treatment options and their success depends on cause of infertility. Therefore, in the absence of any unidentifiable cause, it is empirical. The treatment has to be individualized based on age, duration of infertility and ovarian reserve. Also, the couple should be counselled about lifestyle modifications like achieving body mass index between 19 to 25 kg/m^2 , smoking cessation and minimizing caffeine (250 mg/day) and alcohol consumption(4).

a) Expectant management

There is variable spontaneous pregnancy rate in couples with unexplained infertility. In one randomized trial (253 patients), there was 27% ongoing pregnancy rate in expectant management group(5). One to 3 percent of couples with unexplained infertility followed prospectively without active treatment become pregnant each month(6). The success rate depends on the age of the female partner and duration of infertility. Thus, expectant management may be an option for a couple with unexplained infertility in whom the female partner is young (less than 30 years of age) with good ovarian reserve.

b) Role of Intra-uterine insemination (IUI)

The rationale of performing IUI in unexplained infertility is concentrated motile sperms when placed directly into the uterine cavity close to the oocyte will bypass the cervix thereby taking care of the cervical factor as a hypothesized cause of infertility. But IUI has to be performed around the time of ovulation and hence to correctly time the procedure ovulation monitoring needs to be done either with urinary LH kits or ultrasound monitoring.

c) Superovulation

The most commonly used drugs for superovulation are clomiphene citrate (CC) and aromatase inhibitor, Letrozole which are available as oral preparations

and injectable preparations like gonadotropins. They can be used alone with timed intercourse or combined with IUI. The purpose of superovulation is to increase the number of oocytes available for fertilization and for accurate timing of IUI thereby increasing chances of pregnancy.

There is controversial evidence in literature regarding effectiveness of IUI with or without superovulation compared to expectant management and in addition the increased risk of multiple pregnancy with ovulation induction is a matter of concern. In a recent Cochrane review consisting of 14 trials and 1867 women with unexplained infertility, there was no difference in live birth or multiple pregnancy between those treated with IUI with or without ovulation induction and expectant management or timed intercourse[7]. In a randomized trial it was shown that there was no significant difference in per cycle pregnancy rates between CC/IUI and gonadotropins/IUI (7.6% and 9.8% respectively)[8]. Gonadotropins have been the mainstay of pharmacological therapy for unexplained infertility but the huge costs involved and treatment risk like medication side effects, ovarian hyperstimulation and multiple pregnancy cannot be overlooked.

d) In vitro fertilization (IVF)

The European Society of Reproductive Medicine and National Institute of Clinical Excellence on infertility management have emphasized that all infertile couples should be given information regarding their chances of natural conception and should not be exposed to ineffective treatment with additional risks[9],[10]. It is estimated that infertility affects about one in seven heterosexual couples in the UK. Since the original NICE guideline on fertility was published in 2004 there has been a small increase in the prevalence of fertility problems and a greater proportion of people now seeking help for such problems. The main causes of infertility in the UK are (percentage figures indicate approximate prevalence. It is theorized that IVF can bypass several in vivo steps and biological defects like ovarian and sperm dysfunction and cervical factors which may be a hindrance to conception in unexplained infertility.

First line treatment: IUI or IVF

Four dimensions to treatment needs to be considered when deciding the first line treatment: treatment burden, effectiveness, safety and financial expenses. Treatment burden with IUI and ovarian stimulation includes recurrent visits to clinic and emotional burden of failed cycle. IVF on the other hand can lead to more pain and medication side effects as well as poor outcome. Treatment effectiveness is measured in terms of clinical pregnancy and live birth which is approximately 8% per cycle for IUI and 29% for IVF[11]. However no difference was found in cumulative pregnancy rates in patients with unexplained infertility who were treatment naïve in a randomized trial. The safety concern with treatment is risk of multiple pregnancy which is approximately 7% after IUI and 19% with IVF[11]. Also additional concerns of ovarian hyperstimulation with IVF and minimal risk with IUI cannot be ignored. IVF is significantly more financially daunting than IUI. Hence taking all these into account it seems that IUI with ovulation induction may be considered the first line treatment. Moreover despite the recommendation by NICE that patients with unexplained infertility should be advised for IVF after two years trying, only 26.72% of UK specialists planned to change their practice according to the above guideline[12].

Conclusion

Diagnosis and management of unexplained infertility still presents a dilemma to the clinicians. There is a need for more advanced tests and new biomarkers for detection of subtle causes of infertility. Management of these patients needs to be individualized based on age of female partner, duration of infertility and ovarian reserve.

Practice Points

- Unexplained infertility is a diagnosis of exclusion
- Both partners should modify their lifestyle to optimize reproductive health
- Empirical treatment algorithm for unexplained infertility in order of preference:
  - 3 cycles CC/Letrozole plus IUI
  - 3 cycles gonadotrophin plus IUI
  - IVF

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Forthcoming Events

- CME on 26th June 2019 at Hotel City Park Pitampura, Delhi, organized under aegis of Breast Committee FOGSI, DGF North, NARCHI and Breast and Cervical Cancer Awareness Screening and Prevention Committee AOGD: Contact: Dr Susheela Gupta
- "Legends Go Live" by Sunrise Hospital on 20th & 21st July, 2019 at Hyatt. Contact : 9643404061.
- Next Monthly Clinical Meeting on 28th June, 2019 (4:00-5:00 pm) at VMMC & Safdarjung Hospital
- Breaking Silos Across: Adolescent to Menopause on 10th & 11th August, 2019 at Hotel Lalit, New Delhi. Org Chairperson – Prof Sudha Prasad
- "Masterclass in Gynaecologic Oncology' on 11th August, 2019, at India International Centre in collaboration with AGOI, AOGIN India, FOGSI and AOGD oncology Committee organized by Department of Obstetrics and Gynaecology, UCMS and GTB Hospital. Contact Dr Rashmi.

Answer: May Issue

Crossword

Across:

1. TVTO
2. Cooper Ligament
3. Pentosan Polysulphate
4. Indigo Carmine

Down:

5. Groin Pain
6. Fowler Syndrome
7. Interstim
8. Botulinum

Pictorial Quiz

1. Tape erosion in urethra
2. Perineometer
3. SUI

Premature Ovarian Ageing

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Background

Diminished ovarian reserve (DOR) is a natural outcome of ageing. However, this age-related decline ovarian function begins much earlier in life in approximately 10 per cent of women, who are considered to suffer from premature ovarian ageing (POA). Similar to older women with age-related DOR, women with POA have a tough time conceiving on their own and even with fertility treatments, as they are often misdiagnosed and given unfitting treatments for their ovarian reserve status. It is certain with DOR that it is irrevocable and that these women are at peril of poor ovarian response to ovarian stimulation in Assisted Reproductive Technologies (ART). DOR is a poor prognostic factor because of a decline in the quantity and quality of the oocyte. It is different from menopause or premature ovarian insufficiency. The diagnostic criteria for DOR remain poorly defined, although its diagnosis is increasing.[1,2]

Aetiology

Apart from the "natural" age-related decline, factors that may further diminish the ovarian reserve during reproductive years are diverse.

a. Idiopathic - involves accelerated oocyte apoptosis. According to Barkers hypothesis, maternal endocrine disturbance during in utero life may result in DOR in the female fetus.[3]
b. Chemotherapy
c. Radiotherapy
d. Genetic mutations - Turner's, Fragile X, FSH receptor and Inhibin B mutations
e. Smoking
f. Ovarian surgeries
g. Uterine artery ligation
h. Autoimmune - Polyglandular syndrome, lymphocytic oophoritis, Addison's disease, Hashimoto thyroiditis, celiac disease
i. Mumps oophoritis
j. Metabolic - Galactosemia
k. Tubal surgery

Ovarian surgery, certain pelvic infections, endometrioma, all can reduce the ovarian reserve. Such etiological factors are assumed to provoke impairment of intrafollicular endocrine and other regulatory mechanisms, reduced aromatase activity, the reduced biological activity of gonadotropin surge-attenuating factor, and altered blood flow.[4-7] Genital tuberculosis, even in its latent form, is increasingly being recognized as a cause of diminished ovarian reserve in Indian women.[8]

Diagnosis

Although oocyte quantity and quality wane with age, fertility varies considerably among women of a similar age. Several tests involving biochemical measures and ovarian imaging, collectively known as ovarian reserve tests (ORT), have been suggested to help foresee ovarian reserve and reproductive potential. Ovarian reserve testing aims to augment further prognostic information to the counselling and planning process in infertile couples to help them choose among treatment options. However, it is imperative to emphasize that ovarian reserve tests are not surefire and should not be the sole criteria used to deny the patient's access to ART or other treatments. Evidence of DOR does not inevitably parallel with an inability to conceive.[9]

Elevated basal FSH is one of the earliest ORTs found to be associated with inadequate response. However, a normal FSH does not exclude inadequate response, as an increase in FSH occurs somewhat late in the course of declining ovarian reserve. Therefore, basal FSH is not an idyllic test to identify poor responders.[10] Antral follicle count (AFC) and anti-Mullerian hormone (AMH) are the most sensitive markers of ovarian reserve recognized to date and are the epitome for planning personalized ovarian stimulation protocols.

Whom to test: With the present scenario of many women lingering childbearing, this matter may be of concern since it means many more women will end up in an inadequate ovarian response.[11] In the West, 25% of women do not attempt pregnancy until 35 years of age.[12] Azhar E et al. concluded that the knowledge of ovarian reserve would lead women to modify their reproductive decisions and make alternative decisions.[13]

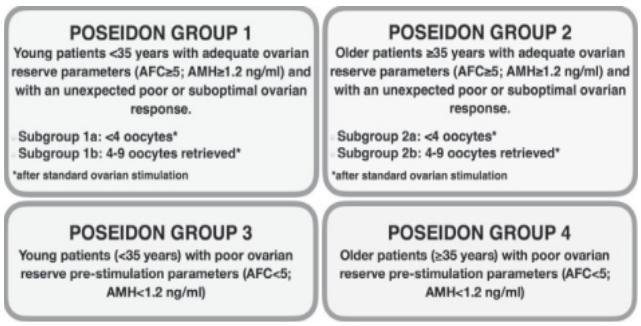
Due to want of universality in the definition for poor ovarian reserve, Bologna criteria was introduced following the consensus meeting of "ESHRE working group on poor ovarian response definition" held in

2011.[14] The presence of at least two of the following three features is required for the diagnosis of POR:

- Advanced maternal age (≥40 years) or any other risk factor for POR
- A previous POR (≤three oocytes with a conventional stimulation protocol)
- An abnormal ORT (i.e. AFC < 5–7 follicles or AMH < 0.5–1.1 ng/ml)

Two episodes of poor ovarian response after maximal stimulation are sufficient to define a patient as a poor responder in the absence of advanced maternal age or abnormal ORT. Bologna criteria were critiqued mainly because of the diversity of the risk factors included such as pelvic infection, endometrioma, ovarian surgery, and extensive periovarian adhesions, as the effect of each of these factors on the ovarian reserve is highly variable.[14]

The POSEIDON group (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize **D** **O**ocyte **N**umber) was recently established to focus specifically on the diagnosis and management of low prognosis patients. [15] Four subgroups have been suggested based on quantitative and qualitative parameters-



While live birth rate is more appropriate for counselling purposes and designing RCTs, the POSEIDON concept is based on (i) a better stratification of women with "low prognosis" in ART, and (ii) customized therapeutic approaches in each group, having as endpoint the number of oocytes required to have at least one euploid embryo for transfer in each patient.[15]

Management

The management of DOR can be infuriating despite extensive studies and approaches. All strategies are aimed at a higher oocyte yield. Several treatment regimens have been designed which are as follows-

1. *Synchronizing early follicle development:* The stimulation and synchronization of earlier follicles before traditional ovarian stimulation may improve IVF outcomes, particularly for poor responders.[16]
   a. Androgen supplementation: It is hypothesized that, in some patients, the diminished ovarian reserve may essentially be an androgen deficiency state and, in these women, androgen supplementation via testosterone or dehydroepiandrosterone (DHEA) may help stimulate early follicle development and improve functional ovarian reserve.[17,18] Notably, DHEA supplementation has been associated with lower miscarriage rates[19] and higher pregnancy and live birth rates[20] in some studies. Patients should be informed of the probably undesirable side effects such as acne, oily skin, deepening of the voice, hirsutism and hair loss.[17] A small percentage of patients do not respond to DHEA and instead require testosterone administration.[21] The follicles require about 6–8 weeks after the initiation of androgen supplementation to achieve synchronization and become mature enough to respond to ovarian stimulation with gonadotrophins.[17] Based on this, many patients could potentially benefit from androgen supplementation beginning weeks or months before starting their IVF cycle.
   b. Estradiol priming in luteal phase*:* Estradiol priming in the luteal phase with or without the concurrent use of GnRH antagonist was found to decrease the risk of cycle cancellation and increase the chances of clinical pregnancy in a meta-analysis of 8 studies.[22] It improves follicle synchronisation. However, more studies are desirable to establish its role.
2. *IVF protocols for poor responders:* Each patient's clinical characteristics (e.g. basal antral follicle number, luteal synchronisation), treatment history and past stimulation outcomes should be judiciously considered when selecting stimulation protocols for poor responders.[23] A protocol that complements her natural cycle should be selected as far as possible; avoiding high-dose gonadotrophins and suppressive treatments (e.g. GnRH agonists and oral contraceptive pills).[24] High dose of gonadotropins may not profit the patient beyond a particular dose and may also increase the likelihood of poor oocyte quality, patient discomfort and side effects. Furthermore, overwhelming stimulation has an unfavourable effect on luteal endocrine milieu and in turn, affects endometrial receptivity.[25] Premature luteinisation frequently occurs in the older patient and some poor responders. In these patients, earlier ovulation trigger (i.e. when the leading follicle is 16 mm) may improve the

number and quality of embryos, as well as clinical pregnancy rates.[26]

a. Low-dose (or 'mild') stimulation protocol: The low-dose gonadotrophin protocol involves initiating HP-HMG 150 IU/day and rFSH 150 IU/day on Day 2 for nine days; inclusion of HP-HMG is essential to provide some LH activity. A GnRH antagonist is administered when the lead follicle is ≥12 mm in diameter, followed by ovulation trigger with leuprolide or HCG 10,000 IU when the lead follicle is 16–17 mm.[24]

b. The low-dose clomiphene/gonadotrophin protocol involves administration of clomiphene citrate 100 mg/day for five days beginning on Day 2 to obtain the pituitary output. A low dose of HP-HMG (150 IU/ day) is given on Days 2, 4 and 6, followed by daily dosing until the follicle reaches maturity. A GnRH antagonist is administered when the lead follicle is ≥12 mm in diameter, which is intentionally a little early to help avoid breakthrough ovulation; if the patient's LH level begins to rise, the GnRH antagonist can be given twice a day. Ovulation is triggered with HCG 10,000 IU or leuprolide when the lead follicle is approximately 18–19 mm.[24]

c. Augmented natural cycle protocols are designed to provide continued gentle cycle support for women who have slow follicle development. Patients are observed for oestradiol production >20 pg/ ml and/or the presence of 3- to 4-mm sized basal antral follicles; in these patients, it may take 7–10 days for these characteristics to be observed. Once the follicles are present, ovarian stimulation is initiated with a low-dose combination of HP-HMG and rFSH 75 (e.g. 75 IU/ day of each) and continued for approximately 6 days, depending on continued follicle development; a GnRH antagonist is added when the lead follicle reaches ≥12 mm. ovulation is triggered with HCG 10,000 IU or leuprolide. This protocol may particularly benefit patients who have not had a positive response (no mature follicles) to past stimulation protocols.[24]

Objectively determined optimal stimulation protocols for poor responders do not exist in the literature. A Cochrane Review published in 2010 concluded that 'There is insufficient evidence to support the routine use of any particular intervention in the management of poor responders to controlled ovarian stimulation in IVF' [27]

d. Segmentation of the IVF cycle through embryo cryopreservation and deferred (i.e. cryopreserved) embryo transfer has been proposed as a possible strategy to accumulate more significant numbers of embryos over several stimulation cycles in poor responders. This is supposed to mend clinical outcomes in poor responders by letting for the selection of only high-quality embryos for transfer and ensuring that the embryos are transferred to a more receptive endometrium[28]

e. Dual stimulation/double stimulation (follicular and luteal phase): This has unbolted a new sphere of opportunities to utilize ovarian stimulation in the luteal phase following oocyte retrieval with follicular phase stimulation in the same cycle.[29] Typically, a luteal phase stimulation starts 2–7 days after oocyte retrieval in the same cycle. Either Gonadotropins or CC or Letrozole are used followed by a trigger at lead follicle size of ≥18 mm. Embryo freezing is recommended because of anticipated endometrial asynchrony.

3. *Use of adjuncts:* Human growth hormone (HGH), either directly or indirectly via insulin-like growth factor 1 (IGF-1), also regulates oocyte maturation by increasing the sensitivity of the ovaries to gonadotrophins and promoting early follicle development. A Cochrane Review demonstrated improved clinical pregnancy (odds ratio [OR] = 3.28 [95% confidence interval (CI), 1.74–6.20]) and live birth rates (OR = 5.39 [95% CI, 1.89–15.35]) in poor IVF responders who received HGH supplementation.[30] However, minimal side effects, such as peripheral oedema and joint pain, have been reported with HGH supplementation.[31]

4. *Oocyte donation:* Egg donation may be the final effectual remedy to offer any prospect to these patients. However, the decision of egg donation is often difficult to make. Moreover, the facilities for egg donation, acceptability and adequate counselling may not be available worldwide.

5. *Embryo handling:* The use of PGS should be limited in these patients with very few available embryos; consider Day 3 embryo transfer to limit the culture time.[24]

Conclusion

Time is the most crucial factor with DOR, and the

chances of pregnancy will be higher if sooner, the treatment can be started. Meager responders are a heterogeneous population of IVF patients with irreplaceable needs. Rather than intervening them with high doses of exogenous gonadotrophins, IVF protocols for poor responders should complement the patient's natural cycles, and suppressive hormonal treatments should be avoided. Counseling and support, both before and during IVF cycles, can aid in optimal outcomes for poor responders and cope up with concomitant distress and anxiety. In light of limited researches on the optimal management of poor responders, robust studies to support evidence-based clinical recommendations are needed.

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Journal Scan

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1. **Endocrine (2018) 59:30–38**

Effectiveness of Myoinositol for Polycystic Ovary Syndrome: A systematic review and meta-analysis

Liuting Zeng, Kailin Yang

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age group with a prevalence of 6-14%. Insulin resistance (IR) and the consequential hyperinsulinemia are considered primary triggers, both in obese and in lean women with this syndrome. Hyperinsulinemia caused by the IR occurs in roughly 80% of obese PCOS women and in 30–40% of lean PCOS. Obesity, IR and compensatory hyperinsulinemia trigger androgenization leading to features of hyperandrogenism. Among the insulin sensitizers, metformin has been widely studied and has been shown to improve clinical pregnancy rate but it is associated with gastro-intestinal side effects.

Lately, there has been literature on myo-inositol in improving insulin resistance in PCOS women. Evidence shows that it may decrease the hormonal profile, oxidative abnormalities, as well as the metabolic factors in patients with PCOS, probably due to the amelioration of insulin resistance in these patients. The present systematic review and meta-analysis was done to compare the effects of myoinositol (MI) on women with PCOS.

Methodology: The authors searched the Cochrane Library and other publication sites from their inception to June 2017. The search terms included myoinositol and PCOS. Studies meeting the inclusion criteria were included in this review: (1) randomized controlled trials (RCTs), which assess the effects of MI for the treatment of PCOS (2) women with a diagnosis of PCOS; (3) interventional therapy was MI; control therapies included blanks, placebo, and conventional western medicine.

Results: When compared to placebo or alternate medicine, MI showed significantly better improvement in fasting insulin and insulin resistance (HOMA-IR). MI showed more increase in E2 levels as compared to placebo. There was no difference in testosterone levels in MI and placebo groups. Similarly, the improvement in BMI was also comparable among MI and placebo groups. No adverse events were reported by any of the authors.

Discussion: The present meta-analysis (10 trials) showed that MI can improve insulin resistance (HOMA-IR) and causes improvement in hypothalamic-pituitary-ovarian axis (HPO-axis) in terms of increase in E2 levels. It did not show any improvement in BMI and androgen levels. Based on current evidence, MI may be recommended for the treatment of PCOS with IR.

Conclusion: MI may be recommended for the treatment of PCOS with insulin resistance, as well as for improving symptoms caused by decreased estrogen in PCOS. However, current RCTs have limitations, including small sample sizes and short duration. The benefits from long-term treatment of MI beyond 6 months remain to be defined by future studies. Meanwhile, more randomized, double-blind, large sample size trials of MI for PCOS are needed in the future to confirm or modify the result of this work.

Editor's comments: Insulin resistance is an integral part of PCOS pathophysiology. Due to gastro-intestinal side effects associated with metformin, compliance is an issue. MI is a novel insulin sensitizer which causes improvement in insulin resistance and HPO axis dysfunction without any side effects. The present meta-analysis has shown that MI can be used as first line insulin sensitizer in PCOS women and further research is warranted to evaluate its long term effects.

2. **Gynecol Endocrinol. 2019 May 12:1-4.**

Comparison of Endometrial Receptivity of Clomiphene Citrate Versus Letrozole in Women with Polycystic Ovary Syndrome: A randomized controlled study

Li Wang, Xinqiang Wen, Shulan Lv, Juan Zhao, Ting Yang & Xiaofeng Yang

Background: PCOS is the most common cause of anovulatory infertility affecting about 70-75% PCOS women. Clomiphene citrate (CC) is the most commonly used oral ovulation induction agent but poor clinical pregnancy rate is an issue due to negative effect on endometrial thickness and receptivity. Letrozole is an aromatase inhibitor that is thought to promote FSH release from the hypothalamic-pituitary axis in response to decreased estrogen feedback from decreased peripheral conversion of elevated circulating androgens, especially in women with PCOS. The present study aimed to assess the endometrial receptivity between CC and letrozole ovulation induction in patients with PCOS by 3-D power Doppler ultrasound.

Methodology: Total 239 infertile PCOS were randomized. Among them 119 patients received CC of 50 mg/day on cycle days 3–7 (1cycle) and 80 patients with successful ovulation were assigned to the CC group. 120 patients were given 2.5mg/day of letrozole (1cycle), among them 80 patients with successful ovulation were assigned to the letrozole group.

TVS monitoring of follicle and endometrial thickness and pattern was done. Pulsatility index (PI) and resistance index (RI) of the uterine arteries were calculated by color Doppler. The averaged uterine PI and RI of the right and left sides of uterine artery were obtained. Sub-endometrial blood flow was obtained at the strongest point in the dark zone of the junction of endometrium and muscular layers in a longitudinal plane. The endometrial volume and vascularization parameters included vascularization index (VI), flow index (FI) and vascularization flow index (VFI) using 3-D mode power Doppler.

The primary outcome was USG markers of endometrial receptivity which included endometrial thickness and pattern, uterine PI and RI, sub-endometrial region PI and RI, endometrial volume, endometrial VI, FI and VFI. The secondary outcomes were pregnancy rates.

Results: Baseline parameters were comparable among the two study groups. Mean measurements of the PI/RI of uterine artery and sub-endometrial region calculated on day of hCG administration and 7–9 days after ovulation did not differ between the two groups. The ratio of multilayered endometrial pattern was significantly higher in letrozole group compared with CC group on day of hCG administration ($p < 0.05$). The endometrial thickness, volume, VI, FI, and VFI were significantly higher on day of hCG administration and 7–9 days after ovulation in letrozole group compared with CC group. The biochemical pregnancy rate, clinical pregnancy rate and ongoing pregnancy rate in letrozole group were significantly increased compared with CC group ($p < 0.05$).

Discussion: Evaluation of endometrial receptivity continues to be a challenge in reproductive medicine, which cannot be well predicted using serum hormone levels, and methods such as histologic and molecular studies are invasive. The present study used non invasive (USG) parameters to evaluate endometrial receptivity among patients undergoing ovulation induction and reported better endometrial parameters in letrozole group.

Conclusion: Letrozole increased pregnancy rates by improving endometrial receptivity as compared with CC in patients with PCOS. However, the mechanism studies are inadequate and thus require further exploration.

Editor comments: The overall prevalence of PCOS and related infertility is increasing and ovulation induction is the first line of management for infertile PCOS women. Letrozole, an aromatase inhibitor, acts by reducing the peripheral conversion of androgen to estrogen. Main reason for low pregnancy rate in CC is because of poor endometrial thickness. The present article shows that in addition to endometrial thickness, other endometrial parameters including endometrial volume, vascularization flow index (VFI) are also affected in CC cycles. Letrozole can be used as first line of ovulation induction agent in any patient where ovulation induction is indicated.

Clinical Proceedings of AOGD Clinical Meeting held at Sitaram Bhartia Institute, New Delhi on 31st May, 2019

Unusual findings at laparoscopy for infertility

Renu Misra, Priya Sindhwani

Case 1:

Mrs SG 30 years, nulliparous, presented with primary infertility for one year. HSG showed right tubal block and left restricted spill, in view of which she was admitted for diagnostic laparoscopy with hysteroscopy. Routine blood tests were normal. Ultrasound (TVS) showed a normal uterus, para-ovarian anechoic cyst adherent to left ovary with a focal nodule 2 x 1.8 cm. Right ovary was normal. Hysteroscopy was unremarkable. Laparoscopy revealed a normal size uterus with ~2 cm fibroid at the left cornua. Bilateral ovaries and right tube were normal. A 2-3 cm cauliflower growth was seen arising from the fimbrial end of left tube. The tumour was excised completely, histopathology showed borderline serous tumour of fallopian tube. Patient was taken up for definitive surgery and laparoscopic left salpingectomy with left ovarian biopsy with multiple peritoneal biopsies with partial omentectomy was performed. There was no residual tumour seen on laparoscopy, and histopathology of all biopsies was also normal. She conceived after an IUI and delivered a healthy baby, who is 2 years old, alive and well. Follow up ultrasound and CT scan are all normal on follow up.

Case 2:

Mrs KR 29 years old presented with primary infertility for 11 years. During the last 9 years patient had received three courses of anti-tubercular treatment. She underwent laparoscopy and hysteroscopy in 2010 for tubal block on HSG. Hysteroscopy was normal. Laparoscopy showed bilateral tubal block, on the basis of which she was prescribed ATT. She received two more courses of ATT for ? bone TB and fever in 2014 and 2018 respectively. She was planned for IVF but ultrasound showed bilateral hydrosalpinx with calcific foci. Laparoscopic bilateral salpingectomy was performed. Histopathology revealed endometriosis in both tubes, and no evidence of TB.

Case 3:

Mrs RK 36 years presented with primary infertility for 11 years. She had undergone laparoscopy in 2011 for which no details were available. She was taken up for diagnostic laparoscopy which showed normal uterus, ovaries and tubes. Liver was nodular and fibrotic suggestive of cirrhosis. Patient was referred to gastroenterologist. An ultrasound showed coarse echotexture of liver with minimal ascites. A CT scan confirmed the diagnosis of Budd Chiari syndrome. IVC recanalization and ballooning of hepatic vein was done and she was discharged on oral anticoagulants (Acitrom). Patient conceived spontaneously after 6 months, and was switched over to low molecular weight heparin. She had an uneventful pregnancy and delivered by elective caesarean at 37 weeks.

Hysteroscopy and beyond - our experience

Swati Sinha, Panchampreet Kaur

Background: Retrospective study of women 45 years and above who underwent diagnostic hysteroscopy and hysteroscopic polypectomy in SBISR in last 2 years.

Method: Data for 126 women were obtained and medical and per-operative details and histopathology were collected.

Results: Fifty-three women in perimenopausal age underwent hysteroscopy for AUB. Among postmenopausal age group, 57 women underwent hysteroscopy for postmenopausal bleeding or spotting and 16 for asymptomatic thickened endometrium.

In perimenopausal group, 11/53 women who had polypoidal endometrium on hysteroscopy had histopathology of benign endometrial hyperplasia, 1 woman had hyperplasia with atypia who was later managed with panhysterectomy. Other women were managed with medical therapy.

In postmenopausal group with bleeding, there were 4 (7 %) malignancy cases - 2 had well differentiated endometroid cancer, 1 had keratinizing squamous cell carcinoma and one was rare malignant mixed mullerian tumour. Benign endometrial hyperplasia was present in 5 out of 57 women and atrophic endometrium in 6. Polyps were present in 33/57 patients and rest 9 had proliferative endometrium. Caseating nodules in endometrium were seen in 1 patient amidst atrophic endometrium, her AFB culture came positive and HPE showed benign endometrial hyperplasia, and

she underwent panhysterectomy after two months for persistent bleeding.

In the asymptomatic postmenopausal group with thickened endometrium, 62.5 % had polyps, 2 patients had endometrial hyperplasia and 1 had endometroid cancer.

Discussion: Endometrial biopsy is a reasonable approach for first episode of bleeding in postmenoapusal women, especially with risk factors for endometrial cancer. Office biopsy with pipelle has sensitivity of 99.6%, if the disease is global and involving more than 50% of cavity. As per ACOG, 2018 guidelines, endometrial thickness of < 4 mm on TVS has a 99% negative predictive value for endometrial cancer and can be offered as first line investigation to these women. However, if bleeding is persistent, Hysteroscopy with D&C should be done even with thin endometrium. Hsyteroscopy involves visualization and biopsy always. Evaluation of incidental finding of thickened endometrium should not be a routine but individual assessment to be made.

Foetal Distress - Different Perspectives

Rinku Sen Gupta Dhar, Neeru Jain

Introduction

Foetal distress is an abstract term which could be interpreted in many different ways by obstetricians. As low as 14% of Caesarean sections that we do for foetal distress have babies delivered with a poor apgar or need a nursery stay. One of the many causes of an alarming rise of caesarean sections is over-diagnosis of fetal distress due to increasing use of cardiotocography (CTG). CTG requires regular training for optimum use. Although CTG was initially developed as a screening tool to predict fetal hypoxia, its positive predictive value for intrapartum fetal hypoxia is approximately only 30%. Even though different international classifications have been developed to define combinations of features that help predict intrapartum fetal hypoxia, the false- positive rate of the CTG is high (60%). Existing guidelines employ visual interpretation of CTG based on 'pattern recognition', which is fraught with inter- and intra-observer variability. Therefore, clinicians need to understand the physiology behind fetal heart rate changes and to respond to them accordingly, instead of purely relying on guidelines for management.

Case Studies

Labour is dynamic and to understand the implications of the ever-changing CTG in labour, we have to interpret the CTG in its entirety.

Case strips representing acute hypoxia warranting immediate management like rupture uterus, transient hypoxia like mechanical stimulation due to vacuum cup and cord compression were presented. It was emphasised that in such cases despite CTG changes we need to be conservative and do intrauterine resuscitative measures first. Cases of subacute hypoxia; psuedosinusoidal pattern with varying duration and contrasting perinatal outcome; possible chronic hypoxia with CTG showing a deep sleep pattern for more than an hour were discussed.

Second stage is a critical time as both the mother and baby are undergoing maximum stress due to reduced venous return, cord compression and head compression. Hypoxia at this time could be rapidly evolving without giving time to the fetus to cope. Physiological adaptations by the baby will be represented by intermittent variable decelerations but baseline and variability need to interpreted appropriately to detect a decompensating fetus.

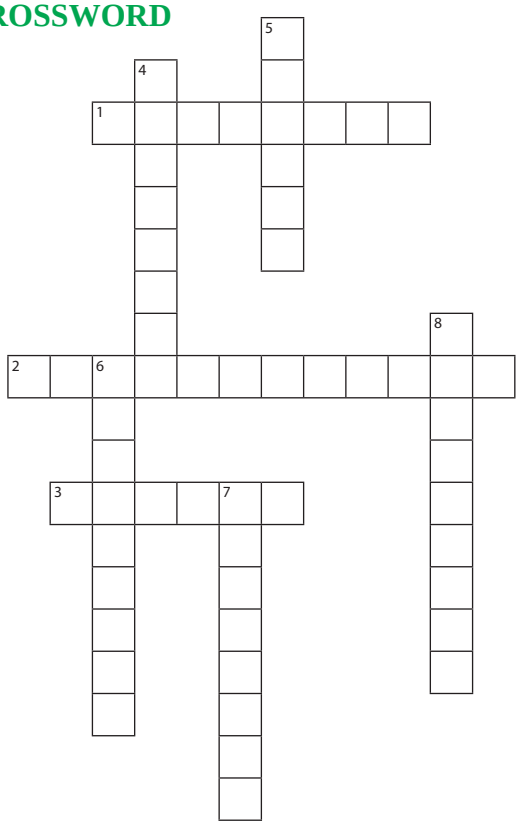
Discussion

Obstetricians should understand fetal response to stress based on the features observed on CTG trace before instituting any intervention. The aim of management is to identify a fetus that is unable to maintain a successful compensatory response to the ongoing hypoxic stress, or that has exhausted all its resources. If appropriately interpreted, the CTG trace will provide information regarding the nature of ongoing hypoxic and mechanical stress and fetal compensatory mechanisms. However, clinicians need to incorporate the wider clinical picture (meconium, intrapartum bleeding, maternal pyrexia or clinical chorioamnionitis), regardless of the classification of the CTG at a given time.

The Maze of Knowledge

Vidushi Kulshrestha, Monica Gupta
Department of Obst. Gynaec. and Urogynaecology, AIIMS, New Delhi

CROSSWORD



ACROSS

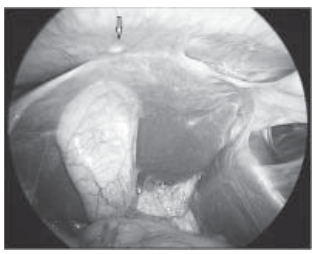
1. Absence of semen in ejaculation
2. Most common genetic syndrome associated with non-obstructive azoospermia or severe oligospermia
3. Testicular cells producing the male hormone

DOWN

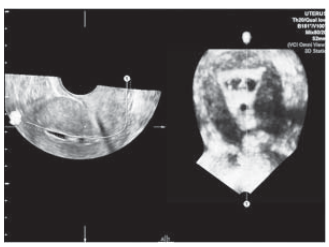
4. Cause of amenorrhoea due to tuberculosis
5. A karyotypic abnormality causing POF in adolescence
6. Adhesion barrier used during surgery
7. Low follicular level of this hormone secreted by granulosa cells is a marker of poor ovarian reserve
8. Letrozole inhibits which enzyme

PICTORIAL QUIZ

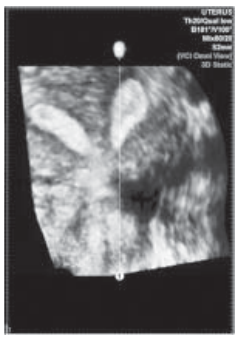
Q1. What is this sign called and it is seen in which condition ?



Q2. What is the intrauterine pathology shown in the USG picture ?



Q3. Identify the uterine pathology and what is the gold standard for diagnosing this condition ?



Watsapp your answers to **9211656757.**

Names of first three correct entries will be mentioned in the next issue

Refer page 38 for previous answer key.

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MULTIDISCIPLINARY MANAGEMENT PATHWAYS: EVIDENCE BASED MEDICINE IN OBGYN

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HIGHLIGHTS

- **The transgender population: Improving awareness for Gynaecologists and their role in the provision of care**
- **Management of a pregnant women with Solid organ transplant (Kidney and liver transplant patients)**
- **Approach towards women in reproductive age groups with ovarian tumors**
- **Management of women with Bad obstetrical history with Non Immune Hydrop fetalis**
- **Care of women with pelvic organ prolapse – Performing concomitant continence surgery**
- **Multidisciplinary care and surgical planning for women with suspected placenta previa/ accreta**

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