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AOGD BULLETIN

Volume 21 I March 2022 I Monthly Issue 11

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Dedicated Issue:

"Infertility: An Overview"

AOGD SECRETARIAT

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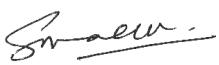
Foreword

It gives me great pleasure to write the foreword for a topic that is so close to my heart- Infertility! The current issue brings forward an update on common problems encountered in infertility management. Hopefully the bulletin resonates with infertility as well as general practitioners alike and benefits our junior and senior residents as well.

Infertility as a diagnosis has increased over the past few decades and its growing significance is mainly due to the negative social impact it has. It greatly affects the lives of infertile couples and particularly women, who frequently experience violence, divorce, social stigma, emotional stress, depression, anxiety and low self-esteem. The growth of ART clinics in India is among the highest in the world, and these are a key part of medical tourism. India does not have standard protocols of ART clinics yet. Amid questions raised on their ethical and legal aspects, Lok Sabha passed the Surrogacy (Regulation) Bill that provides for regulation and supervision of ART clinics and ART banks. With the overwhelming magnitude of COVID-19 and its worldwide prevalence, the associated health burden, and social and economic costs have added to the agony of infertile couples. As the survival rates for adolescents and young adults (AYAs) with cancer increase, there is an expectation that their reproductive health will be preserved whenever possible. Some others experience temporary or permanent infertility as a result of their disease or treatment. This burden of infertility as a cancer complication is a potentially preventable problem. Removing ovarian cysts, unblocking tubes, ovarian drilling for PCOS and other adnexal surgeries are important additive managements that aid in fertility restoration of these couples. Poor responders represent a third of patients undergoing ART. In this group of difficult patients it is clear that to optimize the clinical results in IVF it is not only important to predict the ovarian reserve but also, to tailor the best stimulation protocol to exploit fully the ovarian reserve and optimize the number of oocytes to be retrieved.

You will find all these topics discussed in a comprehensive yet precise manner in this bulletin. The editorial team has done a great job in putting up such an informative bulletin. I hope it gives you the same joy and satisfaction as it gave me when I read it for the first time!

Enjoy !



Dr Sonia Malik
Executive Members

From the President's Pen

Greetings to all AOGDians!

International Women's Day is celebrated every year around the world on March 8 to commemorate the political, cultural, and socio-economic achievements of women. The first gathering of women's day was in 1911 which was supported by over a million people. This year the theme is "Gender equality today for a sustainable tomorrow", to recognise the contribution of women and girls around the world, who are leading the charge of climate change adaptation, mitigation and response, to build a more sustainable future for all. We started this month with a joyous event of talent show by AOGDians. After a long time it was an afternoon full of dance, drama and music with our colleagues and seniors.

Past few years, we have many challenges and various issues to address in management of Infertility. Our editorial team has summed up from basics to advancement of infertility in this issue I am sure our readers will benefit form it.

As our tenure comes to an end with a great sense of satisfaction and gratitude we would hand over the office to MAMC with Dr Asmita as President to carry forward the legacy of AOGD. It had been a wonderful year and I thank all the members for their active participation in the activities of AOGD.

Long live AOGD!

"You educate a man; you educate a man. You educate a woman; you educate a generation."

- Brigham Young

Dr Achla Batra
President, AOGD (2021-2022)

From the Vice-President's Pen

Message from VP

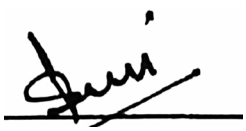
Dear AOGD Colleagues & Friends

Greetings from the pen of Vice President. Hope you have been enjoying the academic activities this past month of which many have been physical. I take this opportunity to invite all of you for the AOGD clinical meet ay Safdarjung Hospital on 1st April, which will be a live meeting and will also witness the handover of the AOGD Secretariat to an extremely competent and enthusiastic Team MAMC!

Coming to the current issue, this time round we are discussing the basics of infertility. With the rising age of marriages and delaying of first childbirth, all of us are seeing a deluge of infertility cases in our practice and essential knowledge about approach towards an infertile couple is something we all need to know. I congratulate the Editorial board under the able leadership of Dr Rekha Bharti for choosing these practical topics and getting them penned by stalwarts in this field.

We are reaching the fag end of our most memorable term at Safdarjung Hospital, but have the privilege of bringing out one more issue of the Bulletin after this one. Hoping to meet you all at Safdarjung Hospital. Thank you for all your encouragement and affection.

With Best Wishes



Dr Jyotsna Suri
Vice President, AOGD (2021-2022)

From the Secretary's Desk

Warm greetings to all!

I write this secretary's message with mixed emotions. As we inch close to handing over the AOGD secretariat to incoming office bearers from Maulana Azad Medical college, I look back upon a much fulfilling year of responsibilities and commitments and look forward for the MAMC secretariat to keep the AOGD flag flying high.

The master trainers for FOGSI-WHO training on 'Respectful Abortion Care' and the have continued to impart training to our AOGD members. FOGSI 'Dheera- No to Violence Against Women' school awareness program had also been collaborated by AOGD and many members have been trained as master-trainers. These master trainers will now collaborate with various schools to spread the awareness.

Feeling proud to present before you the penultimate AOGD bulletin which deals with "**Infertility: An Overview**". It aptly covers all the important aspects viz. Disorder specific infertility management for uterine and adnexal pathologies, Management of poor responders, latest in WHO semen Analysis, ART & Surrogacy Act and Practical aspects of Oncofertility. I am sure these interesting articles with recent advances will be immensely useful for all our AOGD members fulfilling their academic quest, especially the practitioners for helping out in their day to day practice.

Wishing you all a happy reading and the very best for future,

Dr Monika Gupta
Secretary, AOGD (2021-2022)

From the Editor's Desk

Dear Friends,

Greetings from the Editorial Team!

We bring to you the March issue of AOGD bulletin with the theme of **Infertility- An Overview**. We are thankful to Dr Sonia Malik for sparing her time to write foreword for this issue. A word of special thanks to Dr Divya Pandey for being the guest editor for this issue and the hard work done by her to choose and compile all the articles.

All of us face an ever increasing number of cases presenting with infertility. It is a problem of not only married couple but whole family. Nothing gives more joy than finding a woman who conceived while undergoing your treatment. The technological advances in the field of ART have been rather steep, and to keep abreast with them has become a demanding task for the general gynaecologist. This month's AOGD bulletin, a dedicated infertility issue is in tune with the demand.

The present issue covers an interesting and clinically useful article on "**Disorder specific infertility management**: Uterine disorders" by Dr Bindu Bajaj and "Adnexal pathologies" by Dr Garima Kapoor. Poor responders in ART cycles remain one of the greatest challenges that infertility specialists continue to face, and despite all the research, it remains an enigma but Dr Divya Pandey has very elaborately enlightened us on **Management options for Poor responders**.

Male factor is the sole cause of infertility in 20% patients and a contributory in another 30-40%. Male partner evaluation is simple, economical, and should be the first step while investigating the infertile couple. We have a very informative article on "**WHO Semen Analysis 2021-What's new and Why?**" by Dr Pankaj Talwar. There has been lot of discussion and debate over the laws and rights pertaining to surrogacy in India, this has been dealt in detail including the very **recent update on Surrogacy Act 2022** in India by Dr Abha Majumdar.

As the incidence of young cancer is increasing, there is need to discuss about fertility preservation in cancer women so Dr Neeta Singh will discuss the "**Practical aspects of Oncofertility**".

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 wish you all a happy reading!

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Happy Reading!

Dr Rekha Bharti
Editor, AOGD (2021-2022)
editorsaogd2021@gmail.com

From the Guest Editor's Desk

Dear friends

It gives me immense pleasure and happiness to present this dedicated special issue on "the overview of infertility".

The management of infertile couples has been given due importance as per the Sustainable Development Goals (SDG 3.7) which refers to, "Universal access to sexual and reproductive healthcare services". The current issue is dedicated to provide overview of infertility management covering relevant important topics from basics to advanced infertility. I believe that it will help our esteemed AOGD members in improving their practices of infertility management.

I am grateful to Dr Sonia Malik, who is the doyen in the field of infertility for writing the foreword for this issue. I am also thankful to Dr Achla Batra (president AOGD), Dr Jyotsna Suri (vice president AOGD) and Dr Rekha Bharti (Chief Editor AOGD) for believing in me and giving me this task. I thank all the learned authors who are stalwarts in infertility management, for taking out time and contributing intellectual content for the benefit of the practitioners as well as the post graduate residents.

The explicit articles by Prof Bindu Bajaj and Prof Garima Kapoor give an insight into the Disorder specific management of the infertility where the latest evidence based management has been penned down. This will be helpful especially for the postgraduate students.

Poor responders comprise 9-24% females seeking infertility treatment and are a clinical challenge. The article on the current classification and group specific management will be definitely helpful in guiding the patient counselling and to choose single appropriate protocol for them.

This issue encompasses to focus on the two recent important additions in the field of infertility management. First is the sixth edition of WHO Manual for Semen analysis (2021) which has replaced fifth edition of WHO manual (2010). The article by Dr (Col) Prof Pankaj Talwar, is a splendid summary of the exhaustive sixth edition. A precisely summed up salient points of the latest ART and Surrogacy Act (December, 2021) by Prof Abha Majumdar, is the second article. This will apprise the practitioners about the important issues of the two acts.

Prof Neeta Singh has precisely given the highlights of the Practical Aspects of Oncofertility which will be beneficial to not only the infertility practitioners in managing but also the general gynaecologists for appropriate counselling of these patients. The article has made the topic, easy to understand.

The excellent research papers by Dr Ruma Satwik and Dr Alpana Singh add the cherry on the cake.

Without much ado, I hereby wish Happy reading to all of you!!!

Dr Divya Pandey
Guest Editor, AOGD (2021-2022)

Disorder Specific Infertility management: Uterine Disorders

Bindu Bajaj
Professor and Consultant, VMMC and Safdarjung Hospital, New Delhi

Background

The uterus is a thick muscular organ with its inner lining of the endometrium in a state of peristalsis. Uterine factors contribute to 5% of all cases of female infertility. Müllerian anomalies, adenomyoma, adenomyosis, leiomyoma, chronic endometritis, endometrial polyps, thin endometrium and Asherman's syndrome are some notable causes of uterine infertility In this section, we provide a brief overview of some major uterine factors that lead to female infertility.

Adenomyosis and Infertility

Most patients with adenomyosis have symptoms of dysmenorrhea, heavy menstrual bleeding, and dyspareunia. With increasing numbers of women trying to conceive at an advanced age, the incidence of adenomyosis has increased dramatically, with 22% of adenomyosis cases occurring in women under the age of 40. It is known that the the junctional zone in an adenomyotic uterus is hyperplastic; It is this myometrium adjacent to the endometrium that results in endometrial hyper-peristalsis and increased intrauterine pressure. This in turn impairs the normal uterotubal transport and endometrial function and receptivity. There is increasing evidence of an abnormal inflammatory response mediated by increased production of interleukin-6 (IL-6) and tumour necrosis factor- alpha (TNF-alpha) by the endometrial stromal macrophages in an adenomyotic uterus. As levels of IL-6 and TNF-alpha increase, expression of the HOX-A 10 gene (in the secretory endometrium) and Leukemia Inhibitor Factor (LIF) is reduced. LIF plays an important role in the implantation of the blastocyst.

Diagnosis

Diagnosis of adenomyosis is easily made on TVS ultrasound when three or more of the features below are seen:

1. Globular appearance of the uterus.
2. Cystic anechoic spaces in the myometrium.
3. The posterior wall of the uterus is disproportionately thicker than the anterior wall.
4. Sub-endometrial echogenic linear striations or venetian bands- Rain shower appearance
5. Heterogeneous echo-texture of the myometrium.
6. Indistinct endometrial myometrial junction (JZ). While a JZ of 8 to 12 mm thickness on MRI is suggestive of adenomyosis, a thickness of >12 mm is very predictive.
7. Diffused vascularity of the myometrium.
8. Folding of uterus towards the back of pelvis- Question mark sign.

A localized spherical well-defined heterogeneous myometrial lesion with cystic spaces and diffuse blood supply on Doppler indicates an adenomyoma. 3D ultrasound and MRI are particularly useful for diagnosing an adenomyoma and planning surgery.

Pregnancy Outcome in adenomyosis

The pregnancy outcome in women with adenomyosis varies with the grade of the disease. Women usually fail to conceive spontaneously. Intrauterine insemination (IUI) is just as ineffective. Numerous authors have reported negative pregnancy-related outcomes in women with adenomyosis. Chiang et al. reported that women with diffuse adenomyosis were at high risk of spontaneous abortion.[1] Vercellini et al reported poor in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) outcomes with adenomyotic uterus in a meta-analysis.[2] Adenomyosis is associated with recurrent implantation failure in nearly 38% of women.[3] In addition, women with adenomyosis have an increased risk of preterm birth, preeclampsia, and second-trimester abortions.[3]

Medical management

Infertility with adenomyosis can be difficult to treat.

- Gonadotropin-Hormone-Releasing-Hormone-Agonist (GnRHa): Use of GnRHa is associated with spontaneous conception in women with adenomyosis.
- Principles of assisted reproductive techniques (ART) in patients with adenomyosis:
  a. Pretreatment with GnRH analogues prior to

IVF is associated with improved pregnancy outcomes. It has been seen that the mean uterine volume reduces significantly from 180 cm3 to 86 cm3 in women pre-treated with GnRH analogues. This leads to an improvement in embryo implantation and clinical pregnancy rates.

b. GnRH analogues have also shown promising results in the two-stage IVF programs. In the first phase, ovarian stimulation precedes oocyte retrieval, fertilization and embryo freezing. This is followed by GnRH suppression for 3 months. In the second phase, frozen embryo transfer (FET) is performed in the first cycle induced by hormone replacement therapy (HRT) with the aim of transferring an embryo before regrowth of adenomyotic lesions.4

c. Mock embryo transfer is particularly useful for assessing the length of the uterus before the actual transfer. A distorted uterine cavity can alert the treating specialist of difficult transfer.

d. It is important to transfer only single embryo to avoid the risks associated with multiple pregnancies.

e. The role of atosiban in relaxing the uterus at the time of embryo transfer has not been established.

- Letrozole 2.5 mg/day, through its aromatase inhibitory activity reduces estrogen synthesis and helps reduce uterine volume and improves symptoms.
- High intensity focussed ultrasound (HIFU): Zhou et al reported conception in 54 of 64 patients after HIFU with only 21 live births.4 Abortion rates after HIFU were high, but there were no reports of uterine rupture. HIFU reduces uterine distensibility and predisposes to uterine rupture. Also, it is unsuitable for diffuse endometriosis.

Surgical treatment of adenomyoma in infertile women

- Adenomyomas larger than 5 cm should be removed. Laparoscopic/open resection of an adenomyoma is difficult but improves infertility outcomes.
- Adenomyosis causes recurrent implantation failure after IVF. For diffuse lesions warranting surgical excision of a significant amount of myometrium, a new technique involving H shaped incision and excision of the adenomyoma has shown better results. It should be considered in patients with IVF and early pregnancy failures. However, with this technique there is an increased risk of uterine rupture in the subsequent pregnancy. This risk can be significantly reduced if a uterine thickness of 9-15 mm is left after the surgery.[5]
- For hysteroscopic removal of the adenomyoma, it is important that it is less than 5 cm in size and protrudes into the uterine cavity. A three-month pre-treatment with a GnRH analogue significantly reduces uterine vascularity in these women. Additionally, intrauterine vasopressin infiltration with an OPU needle contracts the uterus and aids in removal of the adenomyoma after incision of the overlying endometrium and myometrium. The adenomyoma can be removed with a cutting loop or with grasping forceps. This may require repeated attempts. Also, each case of adenomyoma requires individual treatment.

Fibroids and Infertility

Uterine leiomyomas alone are responsible for infertility in <10% of cases.[6] Infertility due to fibroids is attributed to disrupted uterine architecture, abnormal uterine contractility that impedes sperm transport through an elongated uterine cavity, and distortion of uterine vascularity. Submucosal fibroids affect blastocyst implantation through altered expression of the endometrial HOXA-10 and HOXA-11 genes which play an important role in implantation. Intramyometrial fibroids larger than 5 cm, although not distorting the endometrial cavity, are associated with impaired embryo implantation and reduced pregnancy rates.

Diagnosis

Optimal modalities for diagnosing submucosal fibroids are MRI and hysteroscopy. 3D ultrasound can map the exact location of a fibroid in relation to the junction zone. Saline infusion sonography is another modality that has a sensitivity of 92% and a specificity of 89% for the diagnosis of intrauterine submucosal fibroids.

Treatment

1. Only after all other causes of infertility have been ruled out should a fibroid be considered as a cause of infertility. It is therefore important to examine a patient comprehensively and

give her sufficient time, depending on her age. It is also important to determine the total number of fibroids, their size and location in the uterus. Good ultrasound mapping will determine the exact number, size and most importantly the degree of endometrial involvement of the fibroid, as this has a clear impact on planning an optimal treatment approach.

2. All FIGO types 0,1,2 fibroids (submucosal fibroids) should be treated by hysteroscopic myomectomy. For intramural fibroids larger than four centimetres or multiple fibroids, laparoscopic/open my omectomy should be considered in the presence of infertility when all other causes have been ruled out. Myomectomy itself is associated with its share of complications such as excessive bleeding, blood component transfusion, intrauterine adhesion formation, incomplete myomectomy (all fibroids not removed), recurrence, and an uncertainty of conception after surgery. In older women with low ovarian reserve, time is of the essence. In these women, retrieval of the oocytes, followed by fertilization and cryopreservation of the embryo should be followed by FET three months later, after the uterus has adequately healed. Subserous fibroids do not alter fertility outcomes, so their removal is not recommended.
3. Magnetic Resonance Guided Focused Ultrasound (MRg FUS): Magnetic resonance-guided focused ultrasound involves the destruction of uterine fibroids by coagulative necrosis when the leiomyomatous tissue is heated above 70°C. This is achieved by focusing high-frequency ultrasound beams on the target tissue. It's a promising technique, but more randomized controlled trials are needed to validate it. In addition, it is an expensive method.

Müllerian anomalies

Müllerian anomaly is observed in 8.13% of infertility patients, although its prevalence ranges from 0.06% to 38%. This large variation in prevalence rate is due to previous non-standard classification systems.

Congenital uterine anomalies have been classified under the ESHRE-ESGE (2016) and ASRM/AFS classification systems; the latter is universally accepted. Müllerian anomalies are known to be associated with poor maternal and fetal outcomes. Rates of preterm birth, fetal presentations, placental abruption, and caesarean sections are high for all forms of congenital uterine malformations. Regarding pregnancy and miscarriage rates, it has been reported that the septate uterus is associated with low pregnancy rates while the bicornuate uterus is associated with high miscarriage rates. However, this does not apply to Uterus didelphus. In addition, women with an arcuate uterus, a minor Müllerian anomaly, have normal reproductive outcomes. The association of recurrent pregnancy loss with Müllerian anomaly is also well documented. However, its association with infertility is controversial. Although some studies report that resection of the uterine septum reduces the likelihood of spontaneous abortion, others refute this. The surgical treatment of an incidentally diagnosed uterine septa/fusion or unification defect is debatable and unproven.[7-9]

Diagnosis

Diagnosis of Müllerian anomaly can be made by hysteroscopy, hysterosalpingography, and trans vaginal ultrasound (TVS). 3D ultrasound and MRI are confirmatory. Diagnostic laparohysteroscopy is invasive but is considered the gold standard method for diagnosing Müllerian anomalies.

Chronic endometritis (CE)

Chronic endometritis is associated with decreased endometrial receptivity due to insufficient endometrial cytokine secretion. 15% of infertile women undergoing IVF cycles have CE, and the prevalence rate of CE is up to 42% in patients with recurrent implantation failure.[10] Diagnostic hysteroscopy, endometrial biopsy and their careful evaluation by an experienced histopathologist are key to an accurate diagnosis of CE. Treatment of CE requires 14 days of treatment with appropriate antibiotics.

Endometrial polyp

Endometrial polyps are frequently observed in subfertile women. Most clinicians are convinced that they should be hysteroscopically removed prior to an IUI, IVF or FET cycle.

Thin endometrium

Asherman syndrome is an important cause of thin endometrium. It is associated with a high rate of implantation failure. Thin endometrium should be recognized early and its aetiology thoroughly investigated so that it can be treated appropriately.

Conclusion

In summary, uterine causes of infertility deserve as much attention as any other cause. Without an optimally functioning uterus, it is impossible to achieve positive reproductive outcomes. An experienced ART specialist diagnoses uterine pathology from the very first transvaginal ultrasound and directs a series of investigations for its optimal management.

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Disorder Specific Infertility Management: Benign Adnexal Pathologies

Garima Kapoor[1], Bindu Bajaj[2]
[1]Professor, [2]Professor and Consultant, VMMC and Safdarjung hospital

Out of female factors which lead to infertility, benign adnexal pathologies contribute to about 40-45% causes which include endometriosis, tubal abnormalities with or without tubal block, and ovarian cysts. This article will give an overview of current guidelines for basic and advanced evidence based management of infertility due to these adnexal pathologies.

Endometriosis & Infertility

Incidence

Endometriosis is characterized by the presence of endometrial- like stroma outside of the endometrium. It often presents as pelvic pain, dysmenorrhea and infertility. While its prevalence in the general population has been reported to be around 1.3-5%, its prevalence in infertile women is around 21-48%.[1]

Etio-pathogenesis

Several mechanisms have been proposed that may lead to infertility in women with endometriosis (Table 1).

Table 1 Mechanism of infertility in women with endometriosis[2]

Adhesions leading to an altered tubo-ovarian anatomy
Chronic intraperitoneal inflammation
Disturbed folliculogenesis
Luteinized unruptured follicle
Luteal phase defects
Progesterone receptor dysregulation in the endometrium resulting in decreased endometrial receptivity
Dysfunctional uterotubal motility
Association with adenomyosis (90%)
Immune dysfunctions in the form of increased B cell activity, T cell and macrophage dysfunction and the presence of anti-endometrial antibodies

Management of endometriosis in infertility

Due to the heterogeneous nature of the clinical presentation of endometriosis, no standard treatment algorithm can be recommended. Treatment should be guided by the presence or absence of pain symptoms, the patient's age and preferences, previous surgical history, the presence of other infertility factors, ovarian reserve, and estimated endometriotic fertility index (EFI).

Controlled ovarian stimulation and intrauterine insemination (COS-IUI)

ESHRE recommends controlled ovarian stimulation and ovulation induction as the first-line treatment for ASRM stage I/II endometriosis as it offers an increased live birth rate/pregnancy rate versus watchful waiting and outcomes comparable to women with unexplained infertility.[3,4]

Hughes et al. reported in a meta-analysis that COS/IUI conception rates per cycle were reduced by half in women with endometriosis. However, upon further analysis, this failure was attributed to advanced ASRM stage III/IV endometriosis.[5,6]

Despite the lower conception rate, ESHRE recommends that COS & IUI can be considered in women with stage III/IV endometriosis if tubes are patent.

No additional benefit was reported in COS and IUI cycles with aromatase inhibitors or GnRh antagonists.

Endometriosis & Assisted Reproductive Techniques (ART)

ESHRE recommends that assisted reproductive technologies (ART) be used for endometriosis-related infertility when tubal function is compromised or when male infertility is present and/or other treatments have failed.[3]

The impact of endometriosis on the success rate after in vitro fertilization/ Intracytoplasmic sperm injection (IVF/ICSI) is controversial. Implantation failure in endometriosis can occur due to its association with adenomyosis. It has been reported that oocyte count/quality and pregnancy rates after IVF/ICSI are lower in patients with stage III and IV endometriosis than in patients with tubal factor infertility. Omland et al. reported that live birth rates after two-embryo transfer were lower in women with endometriosis than in women with unexplained

infertility (66% vs. 78.8%). Similarly, Kuivasaari et al. reported significantly lower cumulative pregnancy rates after one to four IVF/ICSI treatments in women with stage III/IV endometriosis compared to women with stage I/II endometriosis and a control group of women with tubal infertility alone. In contrast, Suzuki et al. reported that endometriosis affects oocyte count but not embryo quality or pregnancy outcome, regardless of the presence of ovarian endometrioma. Furthermore, Barnhart et al. reported in their meta-analysis that endometrial receptivity and subsequent implantation rate may not be affected by the stage of endometriosis. They estimated an adjusted odds ratio (OR) of 0.56, 0.79, and 0.46 for achieving pregnancy in all patients, stage I/II patients, and stage III/IV patients, respectively, compared to the control group.[7-10]

Role of pre-treatment with GnRH agonists or combined oral contraceptives (COCs) prior to the ART cycle: Clinical pregnancy rates have been reported to increase four-fold in women who received GnRH agonists three to six months prior to IVF- cycle (OR 4.28, 95% CI 2.00 to 9.15).[11] However, due to inconsistencies in the literature regarding the association of ART success rates with GnRH agonists/combined oral contraceptives (COCs) as pre-treatment, neither agent is recommended.[8]

ART Protocol

Both the GnRH antagonist and agonist protocols show comparable results in women with minimal to mild endometriosis and endometrioma.

Pregnancy complications

Endometriosis is associated with increased rates of first trimester miscarriage and ectopic pregnancy.[3] Endometriomas can lead to preterm delivery.[12] However, these complications are rare and routine prenatal monitoring is not warranted in patients with a history of endometriosis.[3]

Role of surgery in infertility with endometriosis

The surgical approach to endometriosis should be tailored to a patient's profile, taking into account her symptoms, fertility preferences, tubal and ovarian status, or the EFI.

ESHREE recommends surgical laparoscopy for infertile women with endometriomas and for women with unrelenting pain. Excision or ablation of the endometriotic lesion and adhesiolys is increases pregnancy rates in stage I/II endometriosis. Diagnostic laparoscopy is not recommended. However, the benefit of surgical laparoscopy is only marginal.

Surgery and ART

While the role of surgery prior to ART is unclear, one study reported that laparoscopy may be considered for the treatment of endometriosis after multiple failed IVF cycles in the absence of tubal occlusion or severe male factor infertility.[13]

Surgical treatment of endometriomas also has no significant impact on IVF pregnancy rates and ovarian response to stimulation.[14] Additionally, it may actually decrease the ovarian reserve.

Cystectomy prior to ART is not routinely recommended except for purposes of pain relief or to allow easy oocyte retrieval. The procedure itself is associated with a loss of ovarian reserve. If a cystectomy has to be performed at all, excision of the endometrioma capsule is recommended instead of drainage and electrocoagulation of the endometrioma wall. This approach results in higher spontaneous pregnancy rates.[3]

Treatment with hormone therapy before or after surgery is not recommended, but postoperative hormone therapy can be used if the patient does not wish to become pregnant immediately.

There is no evidence to recommend surgical excision of deep nodular lesions prior to ART to improve reproductive outcomes. However, it may be necessary for pain relief when all other measures fail.

Hydrosalpinx

It is a collection of watery fluid in the fallopian tube that occurs in the final stages of the pyosalpinx. However, in daily practice, hydrosalpinx is often referred to as any distal tubal obstruction, regardless of the cause. Even a non-tubal infection such as adjacent appendicitis/ abdominal surgery can result in hydrosalpinx.[2]

Diagnosis: It can be diagnosed on ultrasound or on hysterosalpingogram after dye instillation. Laparoscopy is the gold standard for diagnosis but it is invasive. It can also be used to treat hydrosalpinx or any associated pathology.

Fertility outcome

Women with hydrosalpinx have significantly lower

implantation and pregnancy rates than patients suffering from other types of tubal damage. Clinical pregnancy rates and delivery rates are halved and the rate of spontaneous abortion is doubled. A non- significantly increased rate of ectopic pregnancies (OR 1.3) has been reported in these women.[15] Significantly reduced pregnancy rate in the thawing cycles is also seen. Hydrosalpinx when visible on ultrasound or when they are bilateral, are associated with lower pregnancy rates (31% vs 15% and 24% vs 12%, respectively).[16]

Pathophysiology

Several theories have been proposed to explain the poorer fertility outcomes in women with hydrosalpinx.

- Embryotoxic properties of hydrosalpinx fluid
- Oxidative stress (elevation in the steady-state concentration of various reactive oxygen species on a cellular level)
- Inhibition of embryo implantation: The interaction between the embryo and the endometrium is essential for embryo implantation. It is mediated by the secretion and expression of certain cytokines such as interleukin-1 (IL-1), leukemia inhibitory factor (LIF), colony stimulating factor-1 (CSF-1), and integrin during the implantation window. Their expression can be reduced in the presence of hydrosalpinx fluid.
- Mechanical factors: Leakage of hydrosalpinx fluid through the uterine cavity can result in disposal of the embryo and increase endometrial peristalsis.
- Peritubal adhesions impair the ability of normal fallopian tubes to capture an oocyte by mechanically disrupting the anatomical relationship between the distal fallopian tube and the ovary.

Treatment

According to the above theories, which emphasize the damaging effect of hydrosalpinx fluid on implantation and/or embryo development, any surgical procedure that disrupts communication of tubes with the uterus can restore pregnancy rates. Treatment with salpingectomy before IVF is the only surgical method that has been evaluated in a sufficiently large randomized controlled trial (RCT) and has led to the current recommendations.

Distal Tubal Disease: Good Prognosis

When a patient is scheduled for laparoscopic salpingectomy, it is necessary to open the distally occluded tube for mucosal assessment before making a final decision on salpingectomy. If the mucosa is intact, it is appropriate to perform a neosalpingostomy (preferably laparoscopic) and allow time for spontaneous conception rather than proceeding with immediate IVF. Pregnancy rates after these procedures depend on the degree of tubal disease and are more favourable in patients with good- prognosis. In a single-center retrospective study evaluating 434 patients, clinical pregnancy rates differed significantly depending on the stage of tubal disease: 43% stage I, 33.6% stage II, 19.5% stage III and 13.8% stage IV, with half of the patients conceiving within 11 months and 75% within 21 months. The ectopic pregnancy rate ranged from 5.6% to 11.4%.[17,18]

Distal Fallopian Tubal Disease: Poor Prognosis

In the presence of a unilateral hydrosalpinx and a contralateral healthy fallopian tube, unilateral salpingectomy may be recommended. Waiting for spontaneous conception patiently after the procedure.[2]

Only in patients with severe fallopian tube disease (bilateral) which presents as a hydrosalpinx on ultrasound and with a destroyed mucosa on endoscopic examination, IVF is the method of choice. Patient counselling is required prior to laparoscopic salpingectomy as it doubles the patient's chance of having a subsequent birth after IVF.[2] Patients with recurrent miscarriage and unilateral hydrosalpinx may benefit from unilateral salpingectomy or proximal tubal occlusion.[2]

In patients with recurrent implantation failure salpingectomy is not recommended in women with distally occluded fallopian tubes without fluid accumulation.[19] Treatment should be individualised and may be considered in select cases where salpingectomy may not be possible due to adhesions, patient rejection, or detection of a hydrosalpinx during ART cycles. Proximal tubal occlusion and transvaginal aspiration under antibiotic cover at the time of oocyte retrieval can be considered. If fluid accumulates again quickly after aspiration, the chance of conceiving with a fresh embryo transfer is further reduced. Cryopreservation of embryos and surgical correction of the hydrosalpinx prior to freeze-thaw transfer is a better option.

Ovarian Cysts

An ovarian cyst is common in women of childbearing age, including those undergoing fertility treatments. Surgical treatment by laparoscopic cystectomy is often the rule to prevent potential complications such as rupture or malignancy while optimizing fertility preservation.[20]

Dermoid cysts account for 70% of ovarian cysts.[21] A retrospective Korean case-control study found no significant differences in mean AMH levels between women with dermoid cysts and a control group after adjustment for age and body mass index.[22] Therefore, a conservative approach seems appropriate for asymptomatic women with moderately sized dermoid cysts (4 to 6 cm). The risk of secondary intervention is low in these women.

Surgical Techniques of Cystectomy (Excision)

Because preservation of fertility is a priority, surgical management should initially focus on conservative treatment. Cystectomy is preferred and, in suspected cases, the surgeon must await pathological analysis of the lesions before undertaking extensive and irreversible surgical interventions. If a frozen section is not available, they can work in two steps. Laparoscopy is considered the standard. Bipolar energy should be preferred to monopolar, and coagulation should be as sparing and as selective as possible. Coagulation of the cyst walls should be avoided.[23] Laparoscopic cystectomy is preferred for dermoid cysts. One randomized study reported that FSH levels decreased less at 3 months and 12 months when the incision at the cyst was mesial rather than antimesial.[24] Two recent randomized studies found no difference in fertility benefits between bipolar coagulation and hemostatic sutures on the ovaries.[25]

Alternative to excision

Needle aspiration of a dermoid cyst should never be considered because of the risk of chemical peritonitis; only excision is recommended. Likewise, there is no benefit of fine-needle aspiration of a single-chambered cyst. These cysts can be treated with either surveillance or excision, depending on their size. None of the guidelines recommend a precise cut-off size indicating the need for pre-ART treatment. Not enough is known about dermoid cysts to guide their treatment in infertile women, but a conservative approach seems reasonable for asymptomatic women.

Conclusion

Endometriosis is a heterogeneous group of disease and there is no established algorithm for its management. Therefore, treatment must be individualized according to patient preferences, ovarian reserve, tubal factors, and EFI. While salpingectomy remains the gold standard pre-IVF treatment method to optimize reproductive options in women with hydrosalpinx, other procedures to decompress the hydrosalpinx using ultrasound-guided aspiration with or without sclerotherapy are not superior to no intervention. There is little literature on the effects of benign ovarian cysts or their treatment in the ART cycles. Further research is hence, recommended.

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Poor Ovarian response: Classification and management options

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The management and treatment of patients with poor ovarian response is a challenging clinical situation with prevalence estimated to be between 9 and 24%.Importantly, the "poor responder" group of patients constitute a heterogenous population where prognosis depends on age and number of oocytes obtained. Both quality as well quantity seem to be compromised in this group of women.

Cumulative Live Birth Rate (CLBR) per stimulated cycle is very important indicator of IVF, which, in turn depends on the number of oocytes retrieved. Thus, it is important to optimise the number of oocytes retrieved as per the ovarian reserve in each of these patients. In order to manage Poor ovarian response or poor responders, there should be an in-depth understanding of this clinical situation.

Definition

There had been a lack of consensus on the definition of, "poor responders", therefore the ideal management plan has never been defined. Polyzos et al, highlighted 41 different definitions, out of 47 randomised controlled trials.[1]

This posed difficulty in comparing different protocols being used in the management of poor responders, making the condition more confusing. With this background, ESHRE (2011) made the first solid attempt to make an evidence based international consensus to define POR by giving Bologna criteria. As per this, Bologna criteria, at least two of the following points were needed to define poor responder. These were (1) advanced maternal age (>40 years), (2) previous low response (≤3 oocytes after conventional stimulation protocol) and (3) an abnormal Ovarian reserve test (i.e. Antral Follicle count, AFC<5-7 or AMH (<1.1 ng/ml). However, in general terms two cycles with ≤3 oocytes after maximal stimulation are sufficient enough to classify a patient as poor responder even in the absence of the above mentioned criteria. Though this criteria helped to predict IVF outcome and hence couple counselling accordingly, yet it posed problems in clinical trials as it tend to classify women with different biological characteristics (hence different line of management) in one group.

Thus in order to achieve uniformity and improvement in the treatment outcome by suggesting case-based clinical management, definition of POR which was based on heterogenous criteria was shifted to the concept of "low prognosis". The POSEIDON (Patient Oriented Strategies Encompassing Individualise D Oocyte Number) group suggested a new classification of ART in patients with a reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotropins. This classification suggested 4 subgroups based on qualitative and quantitative parameters. They introduced the concept of sub-optimal response to better categorize the sub-groups of patients showing a low prognosis in IVF. The age cut off of 35 years has been taken as more than 50% of embryos tend to be aneuploid after 35 years of age.[2] The embryo euploid rate is about 60% when age <35 years, however it declines to 30% and 20% when age is between 36-40 years and 42-43 years. (Ubardi et al, 2010). The aim of the POSEIDON group was to define the best-suited strategy to optimise the number of the oocytes retrieved to obtain at least one euploid embryo in each patient with different ovarian response to gonadotropins. Table 1 shows the 4 POSEIDON groups

Table 1: POSEIDON Classification

POSEIDON Group	Poor/Suboptimal Response	AGE (years)	Ovarian reserve markers
POSEIDON GROUP 1 Sub gp:1a:<4 retrieved oocytes on conventional COS Sub gp:1b:4-9 retrieved oocytes on conventional COS	**UNEXPECTED** Poor/ Suboptimal Response	< 35	Normal(AMH>1.2ng/ml,AFC>5)
POSEIDON GROUP 2 Sub gp:2a:<4 retrieved oocytes on conventional COS Sub gp:2b:4-9 retrieved oocytes on conventional COS		≥35	Normal(AMH>1.2ng/ml,AFC>5)
POSEIDON GROUP 3	**EXPECTED** Poor/ Suboptimal Response	<35	Poor Ovarian reserve (AMH<1.2ng/ml,AFC<5)
POSEIDON GROUP 4		≥35	Poor Ovarian reserve (AMH<1.2ng/ml,AFC<5)

Strategies used to treat poor responders

Though several strategies have been proposed, yet at present no standard protocol has been defined. The most obvious clinical approach to deal these groups, is to increase the daily gonadotropin dose. However, gonadotrophin can only support the cohort of follicles responsive to stimulation, but cannot generate follicles de novo. Patrizio et al used different protocols in IVF cycles of poor responders (based on Bologna Criteria) like GnRH antagonist regime (in 53%), the short GnRH agonist(in 20%),the GnRH agonist microdose flare protocol(in 15%) and long GnRH agonist regime(in 9%) of the IVF cycles. The live birth rates had been only 6% irrespective of the protocol used. [3,4] Some authors have regarded long agonist and antagonist protocols as better treatment option for Controlled Ovarian Stimulation(COS) in Poor responders. This difference in response is due to heterogeneity in definitions rather than COS protocol used.

Pre-treatment with estrogen or contraceptive pills to achieve synchronised cohort of follicles is also practised. Addition of recombinant LH improves ovarian responsive ness and recruitability. Adjuvants like Growth Hormone, Androgens, and testosterone are also used. **Growth hormone (GH)** modulates, FSH action on granulosa cells, by upregulating the local synthesis of insulin-like growth factor-I (IGF-I). There heterogeneity of the frequency and dosage of GH administered amongst the studies, needs to be investigated. **Androgens**, produced primarily by theca cells, play a critical role for an adequate follicular steroidogenesis and for a correct early follicular and granulosa cell development. They are the substrate for the aromatase activity of the granulosa cells, which converts the androgens to estrogens. Moreover, androgens may increase FSH receptor expression in granulosa cells amplifying the effects of FSH and thus potentially enhance responsiveness of ovaries to FSH. The pre-treatment with androgens such as dehydroepiandrosterone (DHEA) and/or testosterone has been investigated in a few small trials with conflicting results. Nonetheless, the dosage, exact molecule, and the timing of pretreatment need to be further elucidated. Oral administration of dehydroepiandrosterone (DHEA) before ovarian stimulation with gonadotropin could improve the response in poor responder patients. In the last decade androgen receptors (AR) are expressed in the theca cells, granulosa cells, and ova. Expression of AR in follicular cells is critical for normal folliculogenesis and ovulation. Therefore, various androgens, mainly testosterone and DHEA, have been clinically tried as cotreatment before and during COS in patients with POR but the success was very limited and equivocal. **Autologous platelet rich plasma** injected intra-ovarian by transvaginal sonographic guidance, before the IVF COH. The preliminary results suggest a trend toward better implantation rates and LBRs in those POR patients who have received the intraovarian PRP injections. Studies have shown that autologous FSH decreased and AMH increased following the PRP treatment. However, the number of patients used in these studies is insufficient to draw robust conclusions, and additional studies, preferably well-designed RCTs, are awaited to validate this preliminary and optimistic hope. **Antioxidants** are another class of medication with promising prospective in the POR population, especially as they manifest minimal to no adverse reactions and side effects. Recently studies show a significantly higher number of retrieved oocytes and significantly less consumed FSH in the group pretreated for 60 days prior to ovarian stimulation with CoQ10 supplement as compared with controls. Theoretically, CoQ10 would reduce mitochondrial oxidative stress resulting in improved oocyte competence. Further prospective RCTs are needed to validate these findings.

Keeping the very important baseline patient's characteristics (age and the ovarian reserve),we hereby summarize the treatment strategies to handle low prognosis women as per the POSEIDON Classification.

Managing the Unexpected poor responders (POSEIDON Group 1 and 2)

Women with normal ovarian reserve parameters (AFC >5 and AMH>1.2ng/ml) but with unexpected poor or suboptimal response were classified in these two groups (group 1<35 years and group 2 ≥35 years).These patients represent 15% of the IVF population. The **main principle of management** here is, "**OPTIMISATION of ovarian response**". They need a higher dose of gonadotropins (>3000 IU) and longer stimulation (>10 days).

The reasons for the hypo-response are as follows. First, the presence of FSH receptor polymorphisms (15%) and/or less bioactive Luteinizing hormone's variants may be responsible for the decrease in ovarian sensitivity to FSH. This may lead to low

follicular output rate (FORT) i.e. ratio between pre-ovulatory follicles after ovarian stimulation and pre-existing pool of small antral follicles. In other words, FORT refers to the follicular response (16-22 mm follicles on the day of trigger) to exogenous gonadotrophins. Low FORT shows the hyposensitivity or hypo-response of granulosa cells to standard gonadotropin dose. In group 1 and 2 patients, the treatment strategy is to identify this hypo-response on time i.e. days 5-8 of COS).The timely identification and increase in FSH dose with addition of LH hormone activity(in the beginning of the cycle or after 4 days) can improve FORT.LH activity helps in improving inadequate levels of endogenous androgens in theca cells. They also improve the ovarian responsiveness by increasing expression of FSH receptors in granulosa cells.

In this group, inter-cycle FSH is also raised leading to asynchrony in the beginning of the cycle. By increasing LH, recombinant LH supplementation can improve reproductive outcome in group 1 and 2 as recommended by the POSEIDON group. But owing to its high cost, HMG can be used as its surrogate in Indian settings. Raised FSH can also be controlled by following long protocol. However antagonist protocol can be used due to its shorter duration.

Follicle-to-Oocyte index (FOI) is the ratio between final number of oocytes retrieved compared with Antral Follicle Count. FOI can be improved by synchronising the follicular cohort, increasing duration of stimulation and triggering strategy. To improve the cohort of follicle, pre-treatment with estrogen (7-10 days before stimulation) can achieve synchronisation. As per the POSEIDON working group, If there is no FSH receptor variance, increase FSH starting dose by 50-75 IU. If FSH receptor variance is there, increase the starting FSH dose by 75-150 IU. After this, they can undergo antagonist cycle. In group 1, add LH in 2:1 ratio from day1, if history of follicular stagnation. While in group 2 (age>35), LH can be added in same 2:1 ratio from day 1 (but higher dose; 300 FSH/150 LH), but never more than 450 IU. Regarding ovulation trigger, **Dual trigger** [GnRH Agonist, 40 hours before OPU and standard dose of HCG 6500 IU, 34 hours prior to OPU] has potential to improve FOI. The GnRh agonist prolongs the interval between trigger and OPU and helps to improve oocyte retrieval rate. The FSH surge elicited, overcomes impairment in Cumulus Oocyte Complex function, oocyte maturation and cumulus expansion and thus improves the number of oocyte retrieved. Every single oocyte retrieved increases the chance of pregnancy by 5%.

In this group, other causes of hypo-response may be, low starting dose of FSH which doesn't reach the FSH threshold (unable to open FSH window) besides the asynchronous development of the follicles.

Managing the Expected poor responders (POSEIDON Group 3 and 4)

Women with poor ovarian response (AFC<5 and AMH<1.2ng/ml) can be classified in group 3 (<35 years) and group 4 (≥35 years). The **main principle of management is, "MAXIMISATION of ovarian response".**

For group 3, the causes are related to genetic, immunologic or acquired like post-ovarian surgery, radio-therapy or chemotherapy. Group 4 is age related ovarian reserve decline. Already here, neither increasing the dose of gonadotropins will compensate for the absence of follicles, nor, co-treatments like Growth Hormone, DHEA, and Testosterone administration have shown to improve ovarian reserve. The intercycle FSH is high in these groups also, which lead to early recruitment of leading follicle causing asynchrony. Raised FSH on day 2 also supresses few smaller antral follicles. Thus, oestrogen pre-treatment (5-7 days before stimulation) supresses the FSH. It has to be remembered that group 3 (younger age) have better oocytes than group 4 (older age group.)

For this group, one of the proposed treatment is the antagonist protocol with gonadotropin (upto 300 IU FSH alongwith LH activity) .Addition of LH increases the recruitment and growth of follicles by synergistic action with IGF-1. Agonist protocol is equally recommended (ESHRE 2019). Agonist protocol is especially important in groups with high intercycle FSH. In well-designed studies, there has been no difference in terms of safety and efficacy between the agonist and antagonist protocol. The antagonist protocol is associated with shorter duration of treatment compared to the long protocol. Dual trigger also helps.

The aim however, remains to increase the number of oocytes retrieved per cycle to enhance the chances of live birth. **CUMULATIVE STRATEGY** is another option. Dual stimulation within same ovarian cycle, can be done. Dual Stimulation is based on the fact, that there is presence of several follicular waves throughout the cycle. Thus follicles can be recruited

anytime in the cycle. This opened new possibilities of COS especially for patient with advanced age and with malignancy. Dual stimulation (DuoStim) refers to double stimulation in same ovarian cycle i.e. combination of Follicular phase stimulation (FPS) and Luteal phase stimulation (LPS) in one cycle. Variarelli et al, reported at ESHRE (2017), the important contribution of LPS in duostim approach to obtain competent embryos. Duostim is a promising alternative approach to improve the number of oocytes retrieved that significantly increased the chance of obtaining atleast one euploid embryo per cycle in this group of patients. But, the cost of cycle goes up. This strategy led to reports of ongoing pregnancy rate that reach 20.7% in POSEIDON group 4 patients. Moreover, according to a recent publication, the oocytes derived by LPS appear to increase the cumulative LBR in a single ovarian cycle in patients fulfilling BC, making this approach a promising option in this difficult setting of patients. Still further studies are required.

Table 2: POSEIDON group wise management and its justification

POSEIDON Group	Issue	Treatment	Justification
Group 1: Young women (<35 years) with normal ovarian markers (AMH >1.2 ng/ml; AFC>5)	Unexpected poor response: - hyposensitivity of granulosa cells to standard FSH doses; - FSH receptor polymorphisms	Synchronise cohort- pre-treatment with E2, or OCP; GnRH Agonist/ antagonist protocol	High FSH leads to asynchronous cohort. Synchronization before starting cycle is a must
Group 2: Old woman (>35 years) with normal ovarian markers (AMH> 1.2ng /ml; AFC >5)		Increasing FSH daily dose Adding LH (75–150 IU once daily)	FSH dose should reach minimum threshold for adequate follicular recruitment To stimulate early stages of follicular growth. To improve FSH receptor expression in granulosa cells To improve the sensitivity to FSH dose and recruitability
Group 3: Young women (<35 years) with poor ovarian reserve markers (AFC <5; AMH <1.2 ng/ml)	Depletion of ovarian reserve in terms of number of antral follicles (post ovarian surgery, chemotherapy/ radiotherapy)	Maximal dose gonadotrophin (300–375 IU once daily) Double stimulation in an ovarian cycle (DuoStim)	Improves follicular recruitment and development. Multiple follicular waves in one menstrual cycle
Group 4: Old women (≥35 years) with poor ovarian reserve markers (AFC <5; AMH <1.2 ng/ml)	Depletion of ovarian reserve in terms of number of antral follicles (age related decline)	Maximal dose gonadotrophin (300–375 IU once daily) Adding LH (75–150 IU once daily) Double stimulation in an ovarian cycle (DuoStim)	Improves follicular recruitment and development. Improves recruitability. Multiple follicular waves in one menstrual cycle

ESHRE(2019) recommendations on management of poor responders.[6]

Clomiphene citrate alone or in combination with gonadotropins and gonadotropins alone are equally recommended for predicted poor responders (strong). The use of modified natural cycle is probably not recommended over conventional stimulation for predicted poor responders (Conditional). A gonadotropin dose higher than 300 IU is not recommended for predicted poor responder (strong). GnRH antagonists and GnRH agonists are equally recommended for predicted poor responders (conditional). The addition of Letrazole to gonadotropins is probably not recommended for predicted poor responders (conditional). Use of Growth Hormone before and/or during stimulation,use of testosterone before stimulation, use ovarian stimulation, use of DHEA before and/or during ovarian stimulation and use of Sildenafil is not recommended for poor responders.

Conclusion

Many strategies have been proved to manage poor responder patients, but consensus on most effective one is still awaited. POSEIDON classification have helped in identifying different classes of poor responders and helped in directing class specific management. It's a clinical management guide, which focusses on optimising FOI to achieve pregnancy. The management of poor responders should thus be based on age and ovarian reserve and should aim at increasing CLBR per cycle.

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WHO Semen Analysis: What is New and Why?

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The WHO lab manual for the examination of human semen and cervical mucus interaction was first published in 1980. It has been revised four times since then, is widely read, and has become a recognized standard used by clinical and research labs throughout the world. The 5th edition published in 2010 has been the most popular edition. The sixth manual has come out in 2021.[1-5]

Background of Previous Editions

The First Edition

It was published in 1980 and had 43 pages. The main contributors-Dr R Eliasson (Sweden), K S Moghissi (USA), CA Paulsen (USA). The main components of the manual were: a) Semen Analysis - Sperm density, motility, morphology Semen Analysis report form. b) Stains and plates for morphology. c) Sperm cervical mucus interaction.

The Second Edition

It was Published in 1987, had 67 pages and was translated into 8 languages. This manual targeted on: a) Evaluation of an infertile couple. b) Assessment of men whose sperm was suppressed by potential male contraceptive or toxic agents

The second edition also introduced the normal Values of Semen Variables which were as follows

- Volume >2ml
- Sperm Concentration >20 million spermatozoa/ml
- Total Sperm Count >40 million spermatozoa/ml
- Motility >50% with forward progression
- Morphology >50% with normal morphology
- Viability > 50% viable

These suggest each laboratory develop a "normal range" from men who achieve a pregnancy within the past 12 months

The Third Edition

The version introduced in 1992, was translated into 8 languages and had 107 pages. This included a) Standardized procedures for objective measurements b) Semen Analysis for infertility diagnosis and treatment including ART, male fertility regulation, environmental pollution and fertility. A controversy was introduced with defining normal range. The normal morphology of sperm was given as >30% (empirical reference value introduced without clinical studies to support this value).

The Fourth Edition

It was published in 1999, had 128 pages. The procedures were divided into three parts:a) Standard b) Optional: added multiple sperm defects index, hypo osmotic swelling test, computer assisted sperm analysis, free hamster oocyte test. c) Research -reactive oxygen species, human zona pellucida binding, acrosome reaction.

The quality control was expanded to include: a) Practical methods for implementing quality control in an andrology lab. b) Statistical consideration of counting errors. The Reference Range was not to be used as the lowest semen values were compatible with fertility in vivo or vitro. The Percent normal morphology using strict criteria was <15% (but no data provided).

The Fifth Edition

The most extensive and comprehensive revision of the manual was published in 2010 and had 271 pages. It provided the following: a) Greater detail of procedures, the rationale for alternative methods with examples, notes, comments, and boxes b) Included total sperm/ejaculate as an important parameter c) Provided methods to estimate very low sperm count and errors when reporting no sperm in the ejaculate (azoospermia).

It described the new morphology plates, new procedures for sperm preparation from-semen, testis and epididymis, Cryopreservation of sperms and gave updated methods of quality control and assurance. The reference range and limits were based on samples (400 to 1900) from fertile men whose partners had a time to pregnancy <12months. The conventional statistics use the threshold of 2.5th centile (2-sided reference) below which values are considered to come from a different population. Manual utilized one-sided 5% as the lower reference limit.

The Sixth Edition

WHO and UN-sponsored HRP (Human Reproduction Program) research for impact have issued the sixth edition. This supports country's efforts to attain **SDG 3.7** (Universal access to sexual and reproductive health care services including family planning).

Though many authors have contributed to this edition noteworthy is a contribution by Editor in chief **LARS BJORNDAHL,** who has been formerly coordinator of SIG Andrology. **IAN ASKEW**, Director of WHO, Department of Sexual and Reproductive Health and Director of UNDT, UNPA-UNICEF-WHO-World Bank Special Program on Human Reproduction gave the foreword. Some others are **CHRISTINA WANG** who has a significant association with all the manuals, Prof Oleg Apolikhin, Prof Elisabetta Baldi, Prof Mario Philip, Dr. Kirkman Brown, Dr. Igor Toskin, etc.

To introduce to the world, the launch of the sixth WHO manual was done on 27th July 2021 where an August constellation of WHO manual torchbearers delivered keynotes. Here our accomplished **IAN ASKEW** delivered the introductory note. Then **Christina Wang** spoke about the past editions, **James Kiarie** enlightened about the context of fertility care in this manual, **Lars Bjorndahl** informed about the key elements and what is new. The distribution of semen examination, new findings, way forward was spoken by **Christopher Baratt**.

The WHO Manual Sixth Edition (2021) encompasses 3 main components: 1) Semen Examination; 2) Sperm preparation and cryopreservation; 3) Quality assessment and quality control.

The clinical assessment plus semen analysis is crucial to guiding the investigation and management of a sub-fertile couple. The experts from 43 countries in all 6 WHO regions participated and contributed to this edition. For declaring the various semen parameters, the semen samples were collected from a wider geographical region (3500 subjects, 12 countries and 5 continents allowing more global representation of the fertile men.

What is Retained in the 2021 WHO Manual (6th Edition)

- Basic Semen Examination-recommends ONE procedure, if scientific evidence for clinical value is weaker than tradition moved to Extended Examination
- Extended Analysis
- Research tests

A. Basic Examination
   - Concentration
   - Motility
   - Vitality (only if a few motile sperms)
   - No replicate assessment is required
   - Morphology
     - WHO /Tygerberg strict by sperm adapted Papanicolaou
     - No replicate assessment required

1) Sperm Concentration
   - Use of hemocytometer chambers with improved NEUBAUER ruling is RECOMMENDED.
   - Labs should not stop assessing if the number of sperms is as low as 2 million/ml.
   - LOWEST reference range -16 million/ml
   - In order to increase the prognostic value of routine Semen Analysis, the sperm count have been combined to provide

TOTAL SPERM COUNT=Sperm Conc x Volume of semen

TOTAL MOTILE SPERM COUNT=Total sperm in ejaculate x % motility or MOTILE SPERM/ml (sperm/ml x % motility)

2) Sperm Motility

The extent of progressive sperm motility is related to pregnancy rates
   - Obtained by multiplying the total number of spermatozoa in the ejaculate by the percentage of progressively motile sperms.
   - Back to 4 pointer system:
     1. Rapidly Progressive≥25 micrometers/sec or at least half tail length per sec.
     2. Slow Progressive- 5 TO 25 micrometers per sec or at least one head length to less than half tail length/sec
     3. Non-Progressive -<5 micrometers/sec or less than one head length
     4. Immotile-no tail movement
        -Lowest Reference Value: total motility-42%; Progressive motility-30%

3) Sperm Morphology

The lowest reference value of morphology: 4%. In this more and better quality micrograph of spermatozoa from unprocessed semen samples

considered normal, borderline, or abnormal are included, accompanied by explanations of why each spermatozoon has been classified the way it has.

4) Sperm Vitality

The recommended test for diagnostic use is the Eosin-Nigrosin test
Alternative vitality is also described.
Lowest reference value: 54%

B. Beyond Basic Exam-Extended Analysis

1) Sperm DNA damage
2) Markers for genital tract inflammation
3) Sequence of Ejaculation
4) Semen biochemistry
5) Anti Sperm antibodies
6) Indices of multiple sperm defects
7) Sperm aneuploidy assessments

C. Research Procedures

1) Oxidative stress
2) Acrosome reaction
3) Sperm chromatin structure and stability
4) CatSper channels
5) CASA

Table 1 shows the comparison between fifth and sixth edition. Table 2 shows the semen parameters in different WHO editions. Table 3 and 4 shows distribution of semen parameters for the fertile men an analysis 1(2010-2020 data) and analysis 2(2020 data) respectively.

Table 1. Semen Analysis Components – Fifth Edition Versus Sixth Edition.

Standard	**Basic Examination**
Sample Collection	Main Methods, examples and explanations separated:
Initial Microscopic Investigation	Concentration
Sperm Motility	Motility
Sperm Numbers	Vitality
Routine counting Procedures	Only if few motile
Sperm Morphology	No replicate assessment required
Sustaining methods	Morphology
Assessment of Leukocytes in Semen	WHO / Tygerberg strict by sperm adapted Papaniclaou
Optional	**Beyond Basic Exam Extended Analysis**
Indices of multiple sperm defects	Sperm DNA damage
Panleukoyte Immunocytochemical Staining	Markers for genital tract inflammation
Interaction between sperm and cervical mucus	Sequence of Ejaculation
Biochemical Assays for accessory sex organ function	Semen biochemistry
Computer aided Sperm analysis	Anti Sperm antibodies
	Indices of multiple sperm defects
	Sperm aneuploidy assessments
Research Procedures	**Research Procedures**
Reactive Oxygen Species	Oxidative stress
Human Zona Pellucida binding tests	Sperm chromatin structure and stability
Assessment of acrosome reaction	CatSper channels
Zona free hamster oocyte pentration Test	CASA

Table 2: Reference for semen characteristics as published in consecutive WHO manuals:

Semen Parameter	**WHO 1980**	**WHO 1987**	**WHO 1992**	**WHO 1999**	**WHO 2010**	**WHO 2021**
Volume (ml)	ND	≥2	>2	≥2	1.5	1.4
Sperm Concentration ($x10^6$) / ml	20-200	≥2	≥2	≥2	15	16
Total motiolity (%)	≥60	≥50	≥50	≥50	40	42
Progressive Motility (%)	≥2[3]	≥25	≥25 (grade a)	≥25 (grade a)	32 (a+b)	30
Vitality (%)	ND	≥50	≥75	≥75	58	54
Normal morphology (%)	80.5	≥50	≥30	14	4	4

Table 3: Distribution of semen parameters for the fertile man and the 95% confidence intervals(CI) for the 5th centile, collated from published sources used in Analysis 1:2010-2020 data.(source: WHO sixth edition)

		Centiles									
	N	2.5th	5th	(95% CI)	10th	25th	50th	75th	90th	95th	97.5th
Semen volume (ml)	1789	1.0	1.2	(1.1-1.4)	1.5	2.0	2.8	3.8	5.0	5.5	6.0
Sperm concentration (10^6 per ml)	1789	14	18	(15-20)	22	31	60	104	157	203	243
Total sperm number (10^6 per ejaculate)	1789	30	36	(33-40)	50	88	168	288	467	573	679
Total motility (PR + NP, %)	1789	35	43	(40-45)	50	59	67	78	90	92	94
Progressive motility (PR,%)	1789	22	27	(26-30)	34	44	54	64	75	80	84
Non-progressive motility (NP, %)	1789	0	1	(1-1)	2	6	12	20	32	37	40
Immotile spermatozoa (IM, %)	1101	10	15	(12-17)	20	27	35	43	50	57	66
Vitality (%)	1337	45	54	(50-56)	60	69	78	88	95	97	98
Normal forms (%)	1621	3	4	(3.1-4.0)	5	7	12	19	30	32	34

The 5th centile is indicated above, of fertile men from published sources, from 01/01/2010 – 30/04/2020.

Table 4: Distribution of Semen Parameters for the fertile man and the 95% CI for the 5th centile,Analysis 2:WHO 2020. (Source:WHO Manual, sixth edition)

		Centiles									
	N	2.5th	5th	(95% CI)	10th	25th	50th	75th	90th	95th	97.5th
Semen volume (ml)	3586	1.0	1.4	(1.3-1.5)	1.8	2.3	3.0	4.2	5.5	6.2	6.9
Sperm concentration (10^6 per ml)	3587	11	16	(15-18)	22	36	66	110	166	208	254
Total sperm number (10^6 per ejaculate)	3584	29	39	(35-40)	58	108	210	363	561	701	865
Total motility (PR + NP, %)	3488	35	42	(40-43)	47	55	64	73	83	90	92
Progressive motility (PR, %)	3389	24	30	(29-31)	36	45	55	63	71	77	81
Non-progressive motility (NP, %)	3387	1	1	(1-1)	2	4	8	15	26	32	38
Immotile spermatozoa (IM, %)	2800	15	20	(19-20)	23	30	37	45	53	58	65
Vitality (%)	1337	45	54	(50-56)	60	69	78	88	95	97	98
Normal forms (%)	3335	3	4	(3.9-4.0)	5	8	14	23	32	39	45

The 5th centile, is indicated above, and provides the lower reference values, of the fertile man.

What Is Discarded?

1) Sperm cervical penetration tests
2) Hamster egg penetration test

Limitations of the Manual

For interpretation of results limits between **normal** and **pathology** are essential. There is a problem that **there are no distinct limits.** It does not represent limits between fertile and sub fertile men[7].The distribution of data is from reference men. But, the reference population is mixed.

The Time to Conception (TTC) is ≤12 months. It

includes men with semen quality issues but were lucky as a couple to conceive. It excludes men with longer TTC and good semen.

Semen Examination has Different Goals

1) Assessment of male reproductive organ function.
2) Follow up of andrological treatment of the man.
3) Assessment of male contraceptive treatments.
4) Choice of Assisted Reproductive treatment modality.
5) Epidemiological and environmental studies.

A better prognostic value can be obtained from using the combination of several semen examination parameters**.**

Decision Limits are More Useful Than Reference Limits

1) When clinical investigations are essential to discover endocrine or genetic disorders.
2) To decide if clinical interventions are sufficient .
3) To choose the optimal ART treatment modality.
4) To understand when external factors influence sperm production and function.

Matter of Standardization

Global standardization is necessary for the development of Andrology and Reproductive Medicine to generate new diagnosis and treatments. Without robust data, any scientific investigation will not reveal true pathology and the misinterpreted "limits" will not disclose factors of importance for infertility.

Conclusion

The basic Examination focused on stepwise procedures and evidence-based techniques. It's supported by a new formal ISO standard. The decision limits need to be developed. Standardization is needed for the development of Andrology and Reproductive Medicine.

Suggested Reading

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ART and Surrogacy Act 2022: Essentials to be known

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The *Assisted Reproductive Technology (ART) (Regulation) Act, 2021* and *The Surrogacy (Regulation) Act, 2021* have been passed by parliament in December 2021, gazetted on 25th January 2022 and a notification has been issued in March, 2022

The objectives of the ART regulation act are as follows–

1) Regulation and supervision of the assisted reproductive technology (ART) clinics and assisted reproductive technology banks.
2) Ensuring safe and ethical practice of ART services
3) Regulation and supervision of research and development in the field of ART

Definitions

(a) "Assisted reproductive technology" with its grammatical variations and cognate expressions, means all techniques that attempt to obtain a pregnancy by handling the sperm or the oocyte outside the human body and transferring the gamete or the embryo into the reproductive system of a woman.

(b) "Assisted reproductive technology bank" means an organisation which shall be responsible for collection of gametes, storage of gametes and embryos and supply of gametes to the assisted reproductive technology clinics or their patients.

(c) "Commissioning couple" means an infertile married couple who approach an assisted reproductive technology clinic or assisted reproductive technology bank for obtaining the services authorised of the said clinic or bank.

Authorities to Regulate Assisted Reproductive Technology

The National Assisted Reproductive Technology and Surrogacy Board will be constituted under this act. The State Assisted Reproductive Technology and Surrogacy Board will be constituted at the state level.

Procedures for Registration

- Registration of assisted reproductive technology clinic or assisted reproductive technology bank:

(1) All the ART clinics or banks have to be duly registered under this Act.

o Levels of ART Clinics

a. Level 1 ART Clinic

These would be ART clinics where preliminary investigations are carried out and only IUI is carried out as part of treatment.

b. Level 2 ART Clinic

These would be ART clinics where all/ advanced investigations, diagnostic and therapeutic procedures in ART such as IVF are carried out. Such clinics may also undertake research.

(1) Every application for registration shall be made to the National Registry through the appropriate assisted reproductive technology and surrogacy authority .

(2) An application for registration shall be made by the ART Clinics accompanied by an application fee of:

i) Rupees 1,00,000 for Level 1 ART Clinic

ii) Rupees 5,00,000 for Level 2 ART Clinic

iii) Rupees 1,00,000 for ART Bank

(3) Every clinic or bank which is conducting assisted reproductive technology, partly or exclusively shall, within a period of sixty days from the date of establishment of the National Registry, apply for registration.

(4) Renewal should be carried out every 5 years with the same registration fee.

(5) No clinics or banks shall be registered under this Act, unless the appropriate authority is satisfied that such clinics and banks are in a position to provide such facilities and maintain such equipment and standards including specialised manpower, physical infrastructure and diagnostic facilities as may be prescribed.

The National Board, the National Registry and the State Board shall have the power to:

(i) Inspect, any premises relating to assisted reproductive technology; or

(ii) Call for any document or material, exercise of their powers and discharge of their functions.

- **Staff requirements for ART Clinics/Banks**

The staff requirements given below will be mandatory for all ART Clinics/Banks.

Level 1 ART Clinic - minimum staff requirement

- o 01 Gynecologist
- o 01 Counselor

Level 2 ART Clinic - minimum staff requirement

- o Director
- o 02 Gynecologist
- o 02 Embryologist One Senior and one Junior Embryologist)
- o 01 Andrologist
- o 01 Anesthetist
- o 01 Counselor

ART Bank - minimum staff requirement

- 01 Registered Medical Practioner trained in preparation and storage of semen sample
- 01 Counselor

Duties of Assisted Reproductive Technology Clinic and Assisted Reproductive Technology Bank

- **General duties**

(a) The clinics and banks shall ensure that commissioning couple, intending woman and donors of gametes are eligible to avail the assisted reproductive technology procedures

(b) The clinics shall obtain donor gametes from the registered banks and such banks shall ensure that the donor has been medically tested for such diseases as may be prescribed;

(c) The clinics shall—

(i) Provide professional counselling to commissioning couple and woman about all the implications and chances of success of assisted reproductive technology procedures in the clinic.

(ii) Inform the commissioning couple and woman of the advantages, disadvantages and cost of the procedures, their medical side effects, risks including the risk of multiple pregnancy.

(iii) Help the commissioning couple or woman to arrive at an informed decision on such matters that would most likely be the best for the commissioning couple.

(d) The clinics shall make commissioning couple or woman, aware of the rights of a child born with assisted reproductive technology.

(e) The clinics and banks shall ensure that information about the commissioning couple, woman and donor shall be kept confidential.

(f) The clinics shall provide assisted reproductive technology services keeping in mind the following:

(i) The woman must be above the age of twenty-one years and below the age of fifty years.

(ii) The man should be above the age of twenty-one years and below the age of fifty-five years.

(g) The clinics shall issue to the commissioning couple or woman a discharge certificate stating details of the assisted reproductive technology procedure performed on the commissioning couple or woman.

(h) All clinics and banks shall provide all information to the National Registry periodically, in such manner as may be prescribed—

(i) Enrolment of all the commissioning couple, woman and gamete donors.
(ii) Procedure being undertaken.
(iii) Outcome of the procedure, complications, if any.

Written informed consent

(1) The clinic shall not perform any treatment or procedure without—

(a) The written informed consent of all the parties seeking assisted reproductive technology.

(b) An insurance coverage of such amount as may be prescribed for a period of twelve months in favour of the oocyte donor by the commissioning couple or woman from an insurance company

(2) The clinics and banks shall not cryo-preserve any human embryos or gamete, without specific instructions and consent in writing from all the parties seeking assisted reproductive technology, in case of death or incapacity of any

of the parties.

- **Record keeping**

The records shall be maintained for at least a period of ten years, upon the expiry of which the clinic and bank shall transfer the records to a central database of the National Registry.

- **Using human gametes and embryos**

(a) While retrieving oocytes, efforts should be made to retrieve not more than seven oocytes during one cycle from the **oocyte donor**. However, all formed follicles may be retrieved.

(b) Not more than three embryos may be placed in the uterus of a woman during the treatment cycle.

(c) A woman shall not be treated with gametes or embryos derived from more than one man or woman during any one treatment cycle.

(d) A clinic shall never mix semen from two individuals for the procedures specified under this Act.

(e) The embryos shall not be split and used for twinning to increase the number of available embryos.

(f) The collection of gametes posthumously shall be done only if prior consent of the commissioning couple is available.

- **Pre- implantation Genetic Diagnosis.**

Subject to the provisions of the Pre-conception and Pre-natal Diagnostic Techniques (Prohibition of Sex Selection) Act, 1994, the clinic shall not offer to provide a couple or woman with a child of a pre-determined sex.

- **Sourcing of gametes by assisted reproductive technology banks.**

(1) The screening of gamete donors, the collection, screening and storage of semen; and provision of oocyte donor, shall be done only by a bank registered as an independent entity.

(2) The banks shall—

(a) Obtain semen from males between twenty-one years of age and fifty-five years of age.

(b) Obtain oocytes from females between twenty-three years of age and thirty-five years of age.

(c) Examine the donors for such diseases, as may be prescribed.

(3) A bank shall not supply the sperm or oocyte of a single donor to more than one commissioning couple.

(4) An oocyte donor shall donate oocytes only once in her life.

(5) All unused oocytes shall be preserved by the banks for use on the same recipient, or given for research to an organisation registered under this Act after seeking written consent from the commissioning couple.

(6) A bank shall obtain all necessary information in respect of a sperm or oocyte donor.

Storage and handling of human gametes and embryos.

1) **The gamete of a donor or embryo shall be stored for a period of not more than ten years** and at the end of such period such gamete or embryo shall be allowed to perish or be donated to a research organisation registered under this Act for research purposes with the consent of the commissioning couple or individual, in such manner as may be prescribed.

2) The sale, transfer or use of gametes, zygotes, and embryos within or outside India shall be prohibited except in the case of transfer of own gametes and embryos for personal use with the permission of the National Board.

Offences and Penalties

- **Sex selective assisted reproductive technology.**

(1) The clinic or bank shall not issue, publish, distribute, communicate any advertisement in any manner including internet, regarding facilities of sex selective assisted reproductive technology. Whoever contravenes the provisions shall be punishable **with imprisonment for a term which shall not be less than five years but may extend to ten years or with fine which shall not be less than ten lakh rupees but may extend to twenty-five lakh rupees or with both.**

(2) Any medical geneticist, gynaecologist, registered medical practitioner or any person shall not—

(a) Cause to be abandoned, disowned, or

exploited in any form the child or children born through assisted reproductive technology.

(b) Sell human embryos or gametes, run an agency, a racket or an organisation for selling, purchasing or trading in human embryos or gametes.

(c) Import or help in getting imported in whatsoever manner, the human embryos or human gametes.

(d) Exploit the commissioning couple, woman, or the gamete donor in any form.

(e) Transfer human embryo into a male person or an animal.

(f) Sell any human embryo or gamete for the purpose of research, or use any intermediates to obtain gamete donors or purchase gamete donors.

Whoever contravenes the provisions shall be punishable with a fine which shall not be less than five lakh rupees but may extend to ten lakh rupees.

Where an offence under this Act has been committed by any clinic or bank, the executive head of such clinic or bank shall be deemed to be guilty of an offence and shall be liable to be proceeded against and punished accordingly unless he proves that the offence was committed without his knowledge or that he had exercised all due diligence to prevent the commission of such offence.

The Surrogacy (Regulation) ACT , 2021

This act was passed by Parliament in December, 2021 with the objective of regulating surrogacy practices in India. As per this act, surrogacy should now be performed for "altruistic" purposes which means the gestational surrogacy in which no charges, expenses, fees, remuneration or monetary incentive of whatever nature, except the medical expenses and such other prescribed expenses incurred on surrogate mother and the insurance coverage for the surrogate mother, are given to the surrogate mother or her dependents or her representative.

Regulation of Surrogacy Clinics & Practices

1) No surrogacy clinic shall conduct, offer, undertake, promote or associate with or avail of commercial surrogacy in any from.
2) Surrogacy procedures should be conducted at a place registered under this Act.
3) Advertising commercial surrogacy in print or electronic media or in any other form is prohibited
4) Surrogacy procedures shall only be conducted for an intending couple of Indian origin having medical indication necessitating gestational surrogacy or an intending woman who intends to avail surrogacy, after obtaining certificate of recommendation from the board.
5) **Surrogate mother shall be insured for a period of 36 months covering post-partum delivery complications from an authorised insurance company.**
6) The surrogacy clinic shall maintain all records under this Act, and they shall be preserved for a period of twenty-five years, or such period as may be prescribed

Eligibility to act as Surrogate

An ever married woman having a child of her own and between the age of 25 to 35 years on the day of implantation, who willingly agrees to act as a surrogate mother and has never acted as a surrogate in her lifetime.

Eligibility for intended parents:

1) The intending couple are married and between the age of 23 to 50 years in case of female and between 26 to 55 years in case of male, who have a medical indication necessitating gestational surrogacy
2) The intending couple have not had any surviving child biologically or through adoption or through surrogacy earlier.
3) "Intending woman" means an Indian woman who is a widow or divorcee between the age of 35 to 45 years and who intends to avail the surrogacy.

Offences and Penalties

1) As per this act, there is a strict prohibition of commercial surrogacy, exploitation of surrogate mothers and children born through surrogacy as well as conducting sex selection in any form of surrogacy. Any contraventions by any person or surrogacy clinic shall be punishable with imprisonment for a term which may extend to

ten years and with fine which may extend to ten lakh rupees.

2) Any contravention of provisions of Act, other than those listed in section 38 (as mentioned above) of the act shall be punishable with imprisonment for a term which may extend to five years and with fine which may extend to ten lakh rupees.
3) In case of subsequent or continuation of the offence, the name of the registered medical practitioner shall be reported by the appropriate authority to the State Medical Council concerned for taking necessary action including suspension of registration for a period of five years.
4) Any intending couple or intending woman or any person who seeks surrogacy procedures for commercial purposes shall be punishable with imprisonment for a term which may extend to five years and with fine which may extend to five lakh rupees for the first offence and for any subsequent offence with imprisonment which may extend to ten years and with fine which may extend to ten lakh rupees.
5) Every offence under this Act shall be cognizable, non-bailable and non-compoundable.

Overall, this draft leaves little scope for unregulated practices or malpractice. However, there are certain things which may need to be modified especially for doctors who do not intend harm to patients but may get caught up in situations which may jeopardize their sanctity as doctors.

There was a scope to voice one's opinion on this document which was to be done before 2nd April 2022. One could voice their opinion on https://dhr.gov.in/whatsnew/public - opinion or email to mohite.saxena@gov.in.The registration fee appears very steep and more manpower for all the paperwork will be required, all of which will increase the cost of treatment to the patient. The penalty is very harsh in terms of finance and imprisonment both and is nonbailable and non compoundable.

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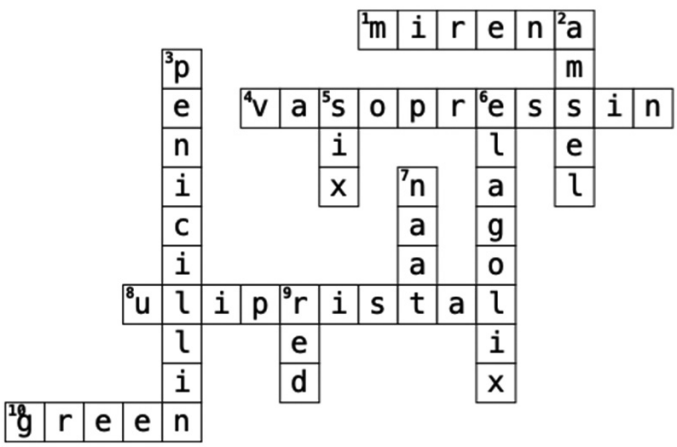
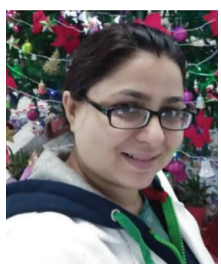
February Cross Word Puzzle





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Practical Aspects of Onco-fertility

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Scope of Onco-Fertility

Cancer incidence has been steadily increasing, with approximately thousands of men and women being diagnosed each year. However, with the advent of more effective multimodal therapies, cancer survival rates have continued to improve over the past 40 years, with >80% of childhood cancer patients now surviving into adulthood. Preserving fertility has become an important quality of life issue for many cancer survivors. Therefore, preservation of male and female fertility is important in prepubertal, adolescent, and adult patients.[1]

A multidisciplinary approach is required, with a team consisting of an oncologist, a reproductive medicine specialist, an andrologist, an embryologist and a consultant. The subject of gonadal toxicity and fertility preservation (FP) is an intimidating one and should be discussed as early as possible in the diagnostic process so that the patient and family can understand her condition.

These patients need timely referral to reproductive medicine specialists for detailed advice. They may or may not opt for FP.[2] Many female patients have a shortened fertility window after therapy, so ongoing education and discussion about FP options is important in this setting. Unfortunately, most patients with malignancy do not opt for FP because of malignancy setback and the need for an early cancer treatment Additionally, the majority of patients in India and other developing countries do not have the time or financial means to undergo FP and should therefore be counselled on the options of egg/sperm donation or adoption once they have recovered and are in remission. In this chapter, we elaborate on the current status of fertility preservation in men and women in all age groups.

Indications of Fertility Preservation

Malignancies like

1. Lymphomas
2. Leukaemia
3. Hematological disorders requiring bone marrow transplantation (mainly thalassemia and immunodeficiency disorders)
4. Sarcoma
5. Breast cancer
6. Solid tumours (carcinoma)
7. Central nervous system and neuroendocrine malignancies
8. Gynaecological Malignancies

Most chemotherapy drugs lead to a significant reduction in the ovarian follicle pool and sperm cells. It is therefore of the utmost importance that fertility preservation is offered before starting chemotherapy or radiotherapy. The **risk of fertility loss is classified** as high, moderate and low risk depending on the type of chemotherapy drug used, as shown in Table 1. One of the most important long-term side effects of cancer treatment (chemotherapy or radiation) is ovarian failure. Loss of ovarian function due to chemotherapy depends on which and what dose of chemotherapy drug is administered.[1] Similarly, the effect of radiation therapy on ovarian or uterine function depends on the radiation dose, radiation field, and fractional dosing regimen. Alkylating agents lead to DNA breaks and thus damage both dormant and dividing ovarian cells. They also lead to ovarian cortical fibrosis and vascular damage.[4] The most important prognostic factors for the extent of fertility decline are the patient's age and ovarian reserve at the time of treatment.

Table 1: Chemotherapeutic drugs/Radiotherapy and the risk of fertility decline associated with it

Risk of fertility decline/ Gonadotoxicity	Chemotherapeutic drugs/Radiotherapy	Common Malignancies
High Risk	**Alkylating agents (cyclophosphamide, chlorambucil, busulfan, and mechlorethamine)** **Post-pubertal girls** - pelvic or whole abdominal radiation dose >10 Gy **Adult women-** pelvic or whole abdominal radiation dose >6 Gy or total Body Radiotherapy	Cancers of the lung, breast, and ovary as well as leukemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma

Intermediate Risk	**Platinum-based compounds (carboplatin and cisplatin), doxorubicin, and bevacizumab Post-pubertal girls-p**elvic radiation or whole abdominal dose of 5–10 Gy or **Craniospinal irradiation-** > 25 Gy	Lung, Breast, ovarian, colon cancers and other gynaecological malignancies
Low Risk	**Antimetabolites (methotrexate and 5-fluorouracil); vinca alkaloids (vincristine and vinblastine); anthracycline antibiotics except doxorubicin** Low dose radiation in areas other than craniospinal, pelvic or abdomen fields	Combination chemotherapy regimens for acute lymphoblastic leukemia, myeloid leukemia, and non-Hodgkin lymphoma

According to the literature, cyclophosphamide and other alkylating agents, particularly used in childhood cancer, can lead to decreased ovarian reserve, premature ovarian failure, premature menopause and poor obstetric outcomes, such as small for gestational age neonates.[3] Monitoring AMH at baseline, during, and after chemotherapy can help predict loss of ovarian function.

Similarly, radiation therapy leads to ovarian damage, decreased vascularity of the uterus, subsequent decrease in endometrial volume and thickness, and endocrine insufficiency.[4] Pelvic radiation therapy also leads to poor obstetric outcomes such as miscarriage, premature birth, and SGA babies. Estrogen hormone replacement therapy can improve endometrial volume and thickness in patients who have received whole-body radiation therapy, but this has not been demonstrated in the literature.[1]

Radiation therapy is sufficient to destroy more than half of the primordial follicles in humans at a dose less than 2 Gy. Total abdominal radiotherapy (approximately 25 Gy) can result in ovarian failure in 97% and 67% of patients respectively, when received during childhood and adolescence.[5] There is limited data on the effect of newer cancer drugs on fertility. The literature suggests that 34% of patients who received bevacizumab will have POI.[1]

Fertility Preservation in Prepubertal Females

Ovarian tissue cryopreservation (OTC) is the FP method of choice in premenarchal or postpubertal women for whom IVF is either contraindicated or chemotherapy cannot be postponed due to the IVF/ICSI cycle.[6]

ASRM states that cryopreservation of ovarian tissue is experimental.[7] A study by Van der et al. showed that approximately 100 live births were reported after transplantation of cryopreserved ovarian tissue.[8] OTC is the removal of all or part of an ovary, followed by retrieval of tissue sections of the ovarian cortex for cryopreservation. Nowadays, experiments are being conducted with cryopreservation of the entire ovarian tissue for orthotopic (inside the pelvis) or heterotopic (outside the pelvis) transplantation after the end of cancer therapy. The main limitation in ovarian cortex transplantation is ischemic injury, which results in the loss of two-thirds of its follicular reserve and thus a shortened graft lifespan. If the entire ovary is transplanted, with expert surgical skills and best cryopreservation protocols that ensure diffusion of the cryoprotectant throughout the entire ovary, the post-transplant ischemic injury can be prevented.

The literature indicates that the possibility of live birth in orthotopic transplantation is greater when the ovary is transplanted into the ovarian fossa or near the infundibulopelvic ligament. In heterotopic transplantation, the ovarian tissue is transplanted subcutaneously to different sites, in the lower abdomen under the rectus sheath or the brachioradialis fascia of the forearm. The advantages of heterotopic transplantation are that ovulation monitoring becomes easier and the risk of pelvic adhesions in patients who have received pelvic radiation therapy is avoided. It restores the endocrine function of the ovaries and can also undergo ovarian stimulation. The eggs obtained from heterotopic ovaries can be fertilized.[9] Studies report that orthotopic transplantation showed better outcomes in terms of reproductive and endocrine function. The clinical pregnancy rate and live birth rate were about 30% and 20%, respectively, and hormonal function was present in about 65% of cases.[8] A meta-analysis by Pacheco et al. comprised 19 studies involving approximately 300 orthotopic ovarian tissue transplant cases, showing cumulative live birth rates and ongoing

pregnancy rates of almost 40% per woman and recovery of hormone function in almost 65% of patients. The literature also reports that the median ovarian transplant survival is almost 27 months.

The controversies surrounding OTC are the possibility of malignant cells being reintroduced into the patient after the completion of cancer therapy. Some studies suggest that in vitro maturation can be performed in immature oocytes obtained from ovarian tissue prepared for OTC. This is a new area of research and this will help eliminate the possibility of reintroduction of malignant cells.

Vitrification vs. Slow Freezing of the Ovarian Tissue for Cryopreservation

Vitrification is the standardized method of cryopreservation of embryos and oocytes. For ovarian tissue, slow freezing is well established and widely used for cryopreservation, but vitrification is an emerging and interesting area of research.[10] There is conflicting data on slow freezing versus vitrification, with some studies suggesting that there may be higher follicular survival rates and better preservation of ovarian tissue and follicular structures after ovarian tissue vitrification. In contrast, few studies report that slow cooling is better, while other studies report similar results between the two techniques. A recent meta-analysis included 14 studies and found that both slow freezing and vitrification had similar results in terms of primordial follicle number and follicle density. Nonetheless, they found that vitrification is better in terms of less DNA damage and better preservation of stromal tissue. Larger RCTs are needed to compare the two cryopreservation techniques, with the main outcome for the comparison being the live birth rate (LBR).

Fertility Preservation Options in Post-Pubertal Females

Oocyte and embryo cryopreservation are the standardized methods for FP that can be offered to post pubertal women.[1] Oocyte cryopreservation is preferable when patients do not have a partner or do not wish to use donor sperm, or have religious or ethical objections to embryo cryopreservation. Table 2 shows fertility preservation options in women with cancer.

Table 2: Fertility Preservation Options in Women with cancer

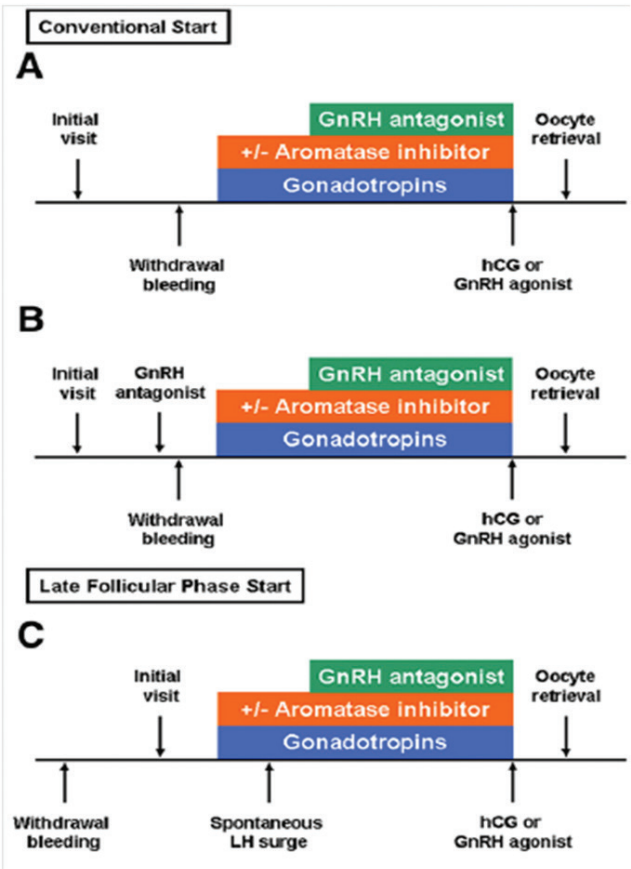
Method	Advantages	Disadvantages
Embryo Cryopreservation	• Established in post-pubertal females.	• Needs a male partner. • Controlled ovarian stimulation for 10-14 days. • Postpones cancer treatment for atleast 2 weeks.
Oocyte Cryopreservation	• Established in post-pubertal females. • Does not need male partner to provide reproductive autonomy to the females.	• Controlled ovarian stimulation for 10-14 days. • Postpones cancer treatment for atleast 2 weeks.
Ovarian Tissue Cryopreservation (OTC)	• Only available option for pre-pubertal girls. • Promising literature on future reproductive and hormonal function. • No delay in cancer management and no need for hormonal stimulation.	• Experimental model. • Requires laparoscopic ovarian tissue procurement with later orthotopic or heterotopic transplantation. • Requires surgical expertise. • Risk of reintroduction of cancer cells at the time of transplantation.

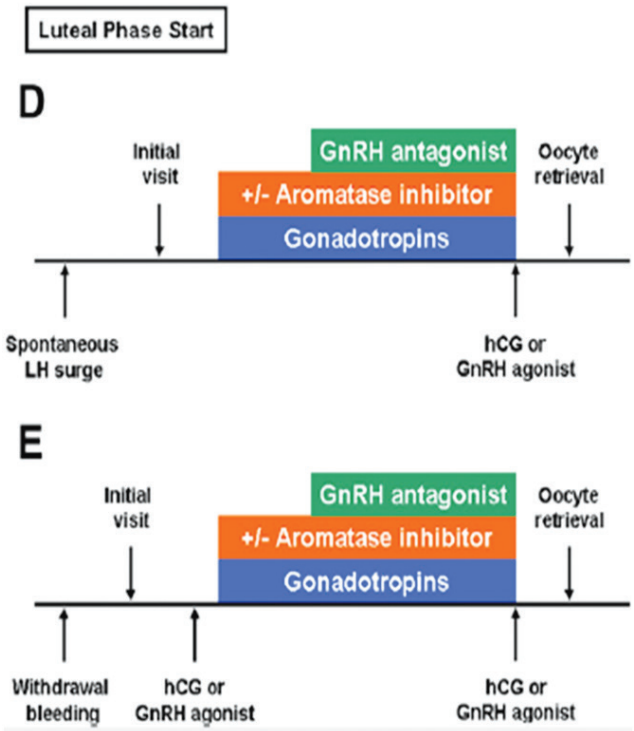
Ovarian stimulation protocols for Fertility Preservation:

In patients undergoing FP, the GnRH **antagonist protocol** is the preferred choice for controlled ovarian stimulation. **Dual stimulation** during the follicular and luteal phases can be used in these patients for better oocyte recovery or embryo pooling, saving time and causing fewer delays in cancer therapy. The **random start protocol** is also useful because the patient can be randomly started on ovarian stimulation regardless of her menstrual cycle phase. It is particularly useful in patients who require immediate initiation of gonadotoxic cancer treatments. Studies show that the number of oocytes retrieved in the same when controlled ovarian stimulation (COS) is started in different phases of the menstrual cycle. However, there is

no concrete data on oocyte quality, pregnancy rate and LBR in these randomly started COS cycles. Supraphysiological levels of estradiol during COS protocols can be detrimental to patients with hormone-sensitive malignancies. In these patients, use of letrozole, an aromatase inhibitor, or tamoxifen, a selective estrogen receptor modulator, will lower serum estradiol levels. Studies show that the risk of breast cancer recurrence is not increased when letrozole is used during COS. GnRH agonist trigger is preferred in GnRH antagonist protocols because of its shorter half-life and lower likelihood of ovarian hyperstimulation syndrome (OHSS). Minimizing the risk of OHSS is a crucial factor in patients undergoing FP as cancer therapy should not be delayed. Figure 1 illustrates protocols for controlled ovarian stimulation to preserve fertility in postmenarchal women.

Figure 1: Controlled Ovarian Stimulation protocols for fertility preservation in post-menarchal women





A- COS can be started with spontaneous menses or
B- with menses following luteolysis induced by GnRH antagonist
C- Late follicular phase
D- Luteal phase following spontaneous LH surge
E- after ovulation induction with hCG or GnRH agonist

Embryo and Oocyte Cryopreservation

Embryo vitrification has been an established method for preserving fertility for decades. The literature reports similar pregnancy outcomes between cancer patients using frozen embryos and their age-matched controls. Patients with a male partner or those who are ready for donor sperm may choose to have the embryos frozen.

For other patients, oocyte cryopreservation is the primary option for FP. Oocyte vitrification has now been proven effective and safe and is no longer considered experimental but can be offered to patients outside of research facilities. Recent studies report that the cryo-survivability of vitrified oocytes is better than that of slow-frozen oocytes; it is almost 80%. In addition, pregnancy rates with vitrified oocytes are comparable to fresh oocytes with no adverse obstetric consequences. More research on neonatal outcomes using frozen oocytes has negated any risk of chromosomal abnormalities or congenital anomalies.

Age at the time of oocyte vitrification is an important factor in successful pregnancy outcomes. The literature shows that pregnancy rates were approximately 40%, 35%, 30%, and 15% in patients under 35, 35–37, 38–39, and >40 years of age, respectively. Therefore, in patients aged 38-40 or <38 years, 25-30 or 15-20 oocytes should be cryopreserved. Despite this reassuring data, currently only five percent of women receiving cancer therapy actually use their frozen eggs/embryos.

Minimizing the Effect of Cancer Treatment on Fertility in Females

Shielding and Ovarian Transposition

Women receiving pelvic or abdominal radiation therapy can use a lead shield to protect their gonads from the side effects of radiation therapy. Shielding is not useful if the patient requires total body radiation or if the ovaries are in the radiation field. In these patients, surgical ovarian transposition or oophoropexy outside of the radiation field makes sense.[11] Ovarian transposition is considered feasible and safe as normal endocrine and reproductive functions have been reported after the procedure. ASCO and NCCN recommend oophoropexy as fertility preserving in patients receiving pelvic radiation therapy. It is a minimally invasive procedure using laparoscopy that can be performed before radiation therapy for gynaecologic cancers and non-gynaecologic pelvic malignancies. It is reported that ovarian function is preserved in 60% to 90% of patients after ovarian transposition. However, only 10% of patients scheduled for radiation therapy undergo oophoropexy because oncologists, gynaecologists, counsellors, or women undergoing cancer therapy are not sufficiently informed.

Gonadotrophin-Releasing Hormone Agonist

When GnRHa is administered continuously, it leads to ovarian suppression. There is conflicting data on the benefit of GnRH agonists (GnRHa) in preventing chemotherapy- induced ovarian failure in women with malignancy. However, a recent review reported the beneficial effects of GnRHa in preventing chemotherapy-induced ovarian damage. The use of GnRHa is also routinely recommended by many societies as an adjuvant to breast cancer therapy. In premenopausal women with hormone receptor-positive breast cancer, the tamoxifen and exemestane study (TEXT) found good results with GnRHa ovarian suppression plus tamoxifen or aromatase inhibitors.

Male Fertility Cryopreservation

The success of sperm cryopreservation depends on whether the patient has reached puberty, which usually begins between the ages of 12 and 14. For male FP prior to the onset of cancer therapy, collection of ejaculated sperm is the preferred method because it is safe, simple, and non-invasive in all post pubertal males and has success rates approaching 90%.

The pre-requisites are

- Tanner Stage II development,
- Testis volume more than 10 ml
- Seminal emission at night/ nightfall

If the pubescent male does not meet these criteria, he cannot produce an ejaculated semen sample for cryopreservation.[12]

Indications for surgical sperm retrieval for male FP includes:

- Azoospermia
- Anejaculation
- Neuro-stimulatory techniques are unsuccessful or not available

Finally, the currently available methods for male FP require mature sperm for IVF/ICSI cycles. In prepubertal boys, immature testicular tissue (ITT) is the only option because sperm cannot be collected or spermatogenesis has not yet started. ITT is obtained through Testicular sperm extraction (TESE) but is an experimental technique. Under research conditions and after appropriate patient counselling, some institutions allow ITT cryopreservation.

Even before the start of cancer therapy, men with malignant diseases often have disturbed spermatogenesis,. In addition, iatrogenic effects of cancer therapy through chemotherapy, radiotherapy and surgery further impairs spermatogenesis.

Sperm cryopreservation is the best method for FP in men. After cancer therapy, men with ART can become fertile with cryopreserved sperm or a freshly collected semen sample. For prepubertal men, the use of cryopreserved testicular stem cells and auto transplantation or in vitro maturation of ITT is an interesting alternative in the future.

Conclusion

- FP is an emerging area of paramount importance that holds promise for young cancer patients who can enjoy post-cancer life and become future parents if fertility preservation has been offered in a timely manner prior to the start of chemotherapy.
- A multidisciplinary approach is important in the management of patients with cancer, where FP options should be discussed prior to initiating gonadotoxic therapy.
- Gamete cryopreservation is currently the only ASRM- recommended female fertility preservation method for postpubertal women. Although ASRM states OTC as experimental, it shows promise for premenarchal women.
- Sperm cryopreservation is the best method of male fertility cryopreservation for postpubertal men. The use of immature testicular tissue cryopreserved testicular stem cells and auto-transplant or in vitro maturation is an interesting alternative but experimental presently.

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Effect of Antioxidant Therapy on Semen Parameters in the Male Infertility

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Abstract

Introduction: Half of infertility cases are secondary to male factors and in a quarter of these cases no cause is identified. Oxidative damage to the sperm membrane can reduce its function and concentration and antioxidants may have a role in improving semen parameters. **Material and Methods:** In this prospective interventional study, male partners of thirty-seven women with infertility and abnormal semen parameters were evaluated for improvement in semen parameters before and after combination therapy with antioxidants consisting of ubidecarenone, zinc, lycopene, astaxanthin and L-carnitine. **Results:** A total of 37 men were included in the study. Of 37 men, 6 men had oligospermia only, 29 had oligoasthenozoospermia, and 2 had oligoasthenoteratozoospermia. None of them had asthenospermia alone. The increase in mean sperm count after antioxidant therapy was statistically significant at $p < 0.001$ (10.91 versus 12.61 million/mL before and after therapy, respectively). The proportion of motile sperms increased significantly from 28.63% to 38.2% ($p < 0.001$). Sperm movement and counts also increased significantly after three months of therapy. **Conclusion:** Antioxidant therapy with ubidecarenone, zinc, lycopene, astaxanthin and L-carnitine is highly effective in improving semen parameters in affected men and should be used routinely in management of male infertility.

Introduction

Infertility is defined as the inability to conceive after one year of unprotected intercourse. It has important psychosocial and health implications for society. The average incidence of infertility is reported to be around 15%. Of all causes, male factors account for 50% and female factors for 50% of infertility. Twenty-five percent of male infertility cases have no identifiable cause.

Oxidative stress is an important factor in male infertility. Numerous authors have reported 25% higher levels of semen reactive oxygen species (ROS) in infertile men compared to their fertile counterparts.[1,2] Oxidative stress occurs when the production of ROS overwhelms the body's natural antioxidant defense mechanism. Although controlled production of ROS is essential for normal sperm physiological function (hyperactivation, capacitation and acrosome reaction of sperm) and for fertilization, excessive production of ROS by abnormal sperm and leukocytes causes sperm dysfunction.[3,4] The structure of a sperm plasma membrane is unique. It contains high amounts of polyunsaturated fatty acids (PUFAs), which play an important role in sperm membrane flexibility. However, this also makes the sperm susceptible to oxidative stress. The lipid peroxidation cascade compromises the functional integrity of a sperm membrane and reduces its motility. It also affects the acrosomal response, sperm-ovum fusion and fertility.[5]

Antioxidants such as carnitine, carotenoids, vitamins C and E, folic acid, selenium and zinc are known ROS scavengers. They have been studied as treatment options to reverse the adverse effects of high levels of ROS in semen. Zinc, a trace mineral used as an antioxidant, has membrane-stabilizing activity, which in turn destroys hydrogen peroxide molecules. Carnitine is involved in transporting long-chain fatty acids into the mitochondrial matrix for beta-oxidation. It exerts its antioxidant activity by increasing the expression of the antioxidants heme oxygenase and endothelial nitric oxide synthetase. Astaxanthin, a carotenoid extract from seaweed, has a large number of conjugated double bonds that make it a powerful antioxidant. Ubidecarenone works by inhibiting the formation of hydrogen peroxide in semen. Lycopene, a powerful antioxidant, inactivates hydrogen peroxide and nitrogen dioxide.

The literature on the effect of antioxidants on semen parameters is not robust. In addition, a large proportion of them come from the western world. We therefore conducted this study with the aim of investigating the effectiveness of various antioxidant therapies in improving semen parameters in infertile Indian men.

Materials and Methods

This was a prospective interventional study conducted from December 2018 to April 2020 at the Infertility Clinic in the Department of Obstetrics and Gynecology of the hospital. Male partners of women with infertility and abnormal semen parameters were included in the study after their written informed consent and the approval of the Institute's Ethics Committee. Abnormal sperm parameter was defined as two abnormal sperm analysisreports,performed2-3weeksapart, reporting oligozoospermia and/or asthenozoospermia according to the 2010 WHO guidelines for semen parameters (sperm density <15 million/mL, motility <32). Men with severe oligospermia, asthenospermia, and azoospermia were excluded from the study. A total of 37 men were included in the study. They were asked to submit their semen samples at enrollment and after three months of antioxidant therapy. Antioxidant therapy was administered twice daily for three months. A single dose of antioxidant therapy contained ubidecarenone - 50 mg, zinc - 5 mg, lycopene -3 mg, astaxanthin - 8 mg and L-carnitine - 300 mg. Semen samples from infertile males were obtained by masturbation without the use of lubricants after an abstinence of 3-5 days. The sample was collected in the hospital's semen collection room in a wide-mouth sterile plastic container. After liquefaction, 0.5 ml of sample was taken for standard semen analysis. All samples were processed and semen parameters analyzed within one hour of sample receipt according to conventional World Health Organization (WHO) guidelines for human semen testing. The following parameters were noted: volume, sperm density, motility, morphology, and the presence of pus cells.

Data were tabulated in an Excel spreadsheet and analyzed using SPSS software version 21.0. Mean and standard deviation were used to summarize continuous variables. Proportions and percentages for categorical variables. Pearson's correlation coefficient between the quantitative variable and its t-test p-value was calculated using the two-tailed significance t-test. T-test for equality of means or Wilcoxon-Mann-Whitney tests were used for continuous variables. Qualitative variables were compared using the chi-square test/Fisher's exact test. A value of $p<0.05$ was considered statistically significant.

Results

A total of 37 men were included in the study. Of 37 men, 6 men had oligospermia only, 29 had oligo- asthenozoospermia, and 2 had oligo-astheno- teratozoospermia. Neither of them had solely asthenospermia. The mean sperm counts before and after antioxidant therapy were 10.91 and 12.61 million/ml, respectively. This increase in sperm count was statistically significant ($p<0.001$). The proportion of motile sperm also increased significantly from 28.63% to 38.2% after three months of therapy ($p < 0.001$) (Table 1). A significant improvement in sperm movement and counting after therapy was also observed. None of the patients had any side effects with the therapy.

Table 1 : Sperm Count and motility before and after treatment

Variables			P-value
Sperm count (before) in million/mL	Mean 10.91	Mean (SD) 1.69±1.44	<0.001
Sperm count(after)in million/mL	Mean 12.61		
Sperm motility (before) %	28.63%		<0.001
Sperm motility(after)%	38.20%		

Discussion

Taking into account the 90-day spermatogenesis cycle, this study was conducted to evaluate the effect of antioxidant therapy on semen parameters for 3 months. The study showed a significant improvement in sperm count and motility after antioxidant therapy. The antioxidants especially L carnitine participate in the transportation of long chain fatty acids to mitochondrial matrix, providing energy for beta-oxidation of spermatozoa in epididymis. Thus playing important role in sperm motility, spermatogenic process and maturation by increasing energy metabolism.

Lenzi et al conducted a double blind controlled trial to evaluate the effect of L-Carnitine on male infertility and observed a positive relationship between carnitine and sperm motility in infertile women.[6] Similarly, Balercia et al evaluated effect of antioxidants(L-carnitine) on semen motion kinetics and total oxygen radical scavenging capacity and showed increased sperm motility. They also found that spontaneous pregnancy was achievable in 9 couples.[7]

This finding was similar to another study that reported an improvement in sperm concentration

and motility after 6 months of vitamin E administration. However, they used only vitamin E as an antioxidant.[8] In another study by Scott et al. an improvement in sperm motility was observed after three months of intake of vitamin A, vitamin E, vitamin C and selenium.[9]

In contrast to the studies mentioned above, Greco et al. found no significant differences in semen parameters after 3 months of antioxidant therapy.[10] Appropriate combination of antioxidants in our study stopped sperm damage at different stages of spermatogenesis. However, large-scale randomized controlled trials are needed to validate this finding because treatment regimens vary widely and results of inconsistent improvement in semen parameters have been reported with non-standard doses of antioxidants in the treatment of male infertility.

Conclusion

The antioxidant therapy is very effective in oligoasthenoteratozoospermia. It should be used routinely in the treatment of male infertility.

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Factors affecting live births after a single completed In-Vitro Fertilization cycle in women with low ovarian reserve

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Abstract

Introduction: Anti-Mllerian hormone (AMH) is a marker of ovarian reserve and shows good sensitivity and specificity for predicting ovarian response to exogenous ovarian stimulation.

Material and Methods: In this retrospective observational study, demographic, stimulatory, and embryological variables of women with low ovarian reserve (AMH levels 1.1 ng/mL) undergoing IVF were examined in terms of IVF live birth rates (LBR) and pregnancy rates. **Results**: 220 completed cycles were included in the analysis. 62 (28.2%) cycles resulted in live births. A total of 196 cycles of embryo transfers (fresh+frozen) occurred with embryos developed from 176 cycles. Age (OR: 0.89 95% CI = 0.82-0.97), duration of infertility, unexplained infertility (OR: 0.31, 95% CI = 0.13-0.78) significantly affected LBR. Cycles with unexplained infertility were less likely to result in live births than cycles with male infertility. The LBR for women aged <35 and > 35 years was 43% and 16%, respectively. Blastocyst transfer instead of day 2/3 embryo transfer was associated with significantly higher live births in women younger than 35 years. **Conclusion: W**omen with low ovarian reserve under 35 years of age, regardless of the cause of infertility, and over 35 years of age with brief and known cause of infertility have a good prognosis for IVF live birth. An antagonistic protocol, use of hMG instead of recombinant FSH and performing fresh embryo transfer is associated with better IVF outcomes.

Introduction

A woman is born with a fixed pool of ovarian follicles, and this pool shrinks as a woman ages through puberty, pregnancy, lactation, premenopause, perimenopause, and menopause. The number of follicles remaining in a woman's ovary has been linked to her cumulative hypothetical fecundability, or ability to produce children over the years.[1] This pool of follicles is divided into the non-growing pool, also known as the primordial follicle, and the growing pool, which consists of the preantral and antral follicles. The growing pool of follicles is best reflected by anti-Müllerian hormone (AMH), a substance secreted by small antral and preantral follicles. A smaller proportion of these growing follicles are recruited each month to reach the ovulation stage. Recruitable follicles are visible on ultrasound at the luteo-follicle transition and are best detected by antral follicle count (AFC) performed with a transvaginal high-frequency ultrasound probe. While AFC can vary from cycle to cycle and is susceptible to inter-observer variability, AMH assays do not show significant inter -observer, inter-cycle, or intra-cycle variability. AMH has high sensitivity and specificity for predicting ovarian response to exogenous stimulation. Reproductive medicine professionals often use AMH to titrate the dose of gonadotropins in women undergoing IVF. Since live births in IVF have been shown to gradually increase as the number of eggs retrieved increases, reproductive medicine professionals also use AMH to predict a woman's chance of having a live birth in IVF. Sometimes low AMH levels are considered a factor in excluding women from IVF cycles. AMH less than 1.2 ng/mL falls into the poor prognosis category according to the POSEIDON criteria. The aim of this article is to highlight the results of the IVF cycle with AMH levels of ≤ 1.1 ng/mL and to study factors affecting live birth rates in this low-reserve population group. The information is intended to assist the reader in making an informed decision in case selection and treatment.

Material and methods

In this retrospective, single-center, observational study electronically stored data from women with AMH levels ≤ 1.1 ng/mL who underwent IVF between -2014 and 2019 were analyzed. Exclusion criteria were donor egg cycles, oocyte freezing cycles and incomplete cycles. Incomplete cycles were defined

as cycles that continued to stock frozen embryos without achieving a live- birth. The term 2020-2014 was chosen because complete variable information was available from 2014 and cycles carried out after 2020 were rather incomplete due to the pandemic situation. No sample size calculation was performed.

Variables Examined: *Demographic variables* included age, duration of infertility, previous live births, IVF indications (male factor, unexplained infertility, tubal factor infertility, endometriosis, and others), Body mass index, anti Müllerian hormone (ng/ml) and peri ovulatory endometrial thickness. *Stimulation variables* were the stimulation protocol, the type of gonadotrop in used, i.e. recombinant FSH/LH/hMG/both, and the time of onset of LH activity (no activity or activity from day 2 or mid stimulation). *Embryological variables* were total number of oocytes retrieved, mean embryos transferred, embryo stage at transfer, and whether transferred in a fresh or frozen embryo transfer cycle.

Outcomes: Primary outcome were live births per egg retrieval cycle. The secondary outcomes examined were cycles with no embryos available for transfer, total embryo transfer cycles, positive hCG rate defined as beta hCG greater than 25 mIU/mL on days 14/13 or 11 mIU/mL after a day 2/day 3 or day 5 embryo transfer. The results were stratified for age < 35 years and age ≥ 35 years according to POSEIDON criteria groups 3 and 4.

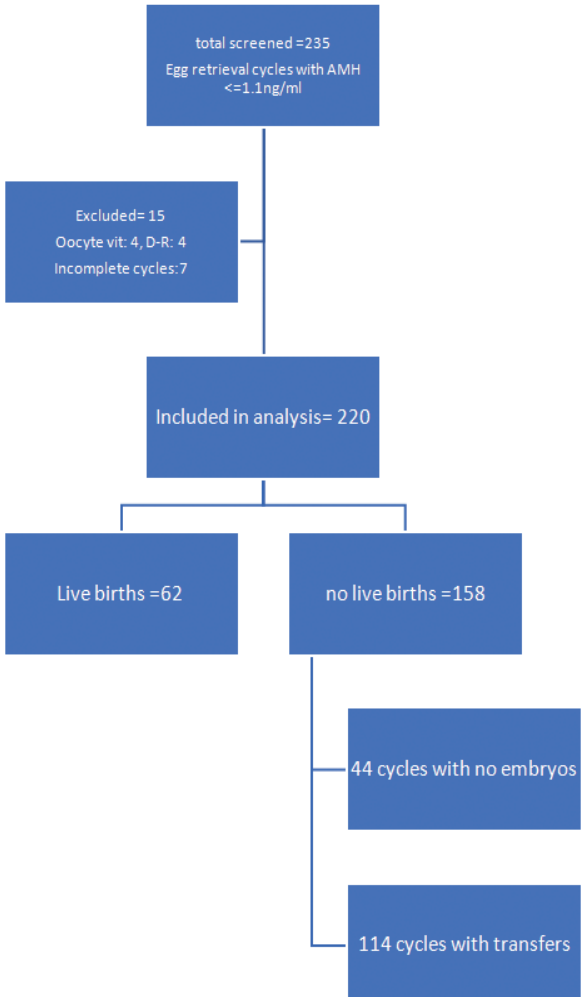
Statistical Analysis: Univariate analysis and binary logistic regression analysis was performed on SPSS version 21.0.

Results

235 women with AMH less than 1.1 ng/mL were screened for inclusion and exclusion criteria. 15 women were excluded for the following reasons: 4 oocyte freezing, 7 incomplete cycles, 4 egg donation cycles. Finally, 220 completed cycles were included in the analysis. Of all the stimulated cycles, 62 (28.2%) cycles resulted in live birth and 158 (71.2%) cycles resulted in no live births. (Figure 1) No oocytes were retrieved in 9 (4.1%) cycles.

35 women (15.9%) had no embryos available for transfer, either due to total fertilization failure or failure to cleave or failure to reach the blastocyst stage, or because they were aneuploid in pre-implantation genetic screening. A total of 196 cycles of embryo transfer (fresh + frozen) took place using embryos that developed from 176 cycles. Cycles with no available embryos, total embryo transfer cycles, positive beta hCG rate, and miscarriage rates stratified by age are shown in Table 1.

Figure 1: Flowchart showing case selection



Women less than 35 years of age could achieve a 43% live birth rate, while those over the age of 35 could only achieve a modest 16% live birth rate. The univariate analysis is presented in Table 2. It shows that age, infertility duration and IVF indication affected live birth rate significantly, whereas body mass index, history of previous live births and AMH levels had no impact on live births in women with low ovarian reserve. Cycles with unexplained infertility were less likely to result in live births than cycles with male factor infertility. For women younger than 35, none of the parameters seemed to affect their chances of having a live birth. The transfer of blastocysts instead of day 2/3 embryos was significantly associated with a higher live birth rate. The transfer of frozen rather than fresh embryos tended to be marginal in terms

of live birth rates, especially in the younger cohort, although the effect size was small.

In binary logistic regression analysis, adjusted for pre-treatment variables as age, infertility duration, body mass index, AMH levels, endometrial thickness, previous live births, and indication, the only variables that reached significance were age (OR: 0.89 95% CI = 0.82-0.97) and unexplained infertility (OR: 0.31, 95% CI = 0.13-0.78), both of which negatively impacted the live birth rates. (Table 3)

Among the treatment strategies used, the gonadotropin type, the presence or absence of LH activity, and the time at which LH was started did not appear to affect live births. However, what significantly affected live births was whether or not the woman underwent blastocyst transfer (OR: 15,.17; 95% CI = 4.3-53.3) and her endometrial thickness (OR: 1.27; 95% CI = 1.07-1.51). The transfer of two embryos instead of one achieved only a marginal significance. The transfer strategy for fresh or frozen embryo in this cohort of low AMH women did not reach statistical significance. (Table 4)

Table 1: Table depicting various outcomes

	Overall AMH<=1.1	**>=35 years AMH<=1.1**	**<35 years AMH<=1.1**
Total egg retrieval cycles	220	125	95
Total cycles with embryos available for transfer n (percentage of total egg retrieval cycles)	176 (80)	97 (77.6)	79 (83.2)
Total Embryo transfer cycles n (fresh and frozen)	196	106	90
Positive hCG n	82	33	49
Pregnancy loss rate per positive hCG n (percentage of positive hCGs)	20 (24.4)	12 (36.4)	8 (16.3)
Live births n (percentage of egg retrieval cycles)	62 (28.18)	21 (16.8)	41 (43.15)
Twin Live births n (percentage of total live births)	6 (9.5)	1 (4.8)	5 (12.2)

Table 2: Demographic, clinical and embryological variable distribution in the live birth and no live birth cohort. Stratified by age.

	OVERALL			**>=35 yrs**			**<35 years**		
	Live Births N=62 (28.2)	No live births n= 158 (71.8)	Signifi-cance	Live Births N=21 (16.8)	No live births n= 104 (83.2)	Signifi-cance	Live Births N= 41(43.2)	No live births n= 54 (56.8)	Signifi-cance
Age (years)	33.6±3.3	36±4.2	0.01	37.1±2.3	38.4±2.8	0.32	31.82±2.02	31.42±2.4	0.25
Infertility duration (years)	5.3±3.4	6.7±5.5	<0.001	5.6±3.8	7.6±6.2	0.02	5.13±3.3	5.18±3.6	0.76
BMI (Kg/m2)	26.9±5.0	26.3±3.9	0.104	26.5±8.3	27.7±6.0	0.02	26.4±4.4	25.9±4.1	0.9
AMH (ng/ml)	0.74±0.27	0.66±0.28	0.724	0.66±0.29	0.66±0.29	0.96	0.77±0.25	0.68±0.27	0.47
Endometrial thickness (mm)	8.4±2.1	7.9±2.0	0.544	8.0±1.9	7.7±1.9	0.88	8.6±2.1	8.2±2.0	0.66
Past live births n(%)	7 (11.3)	27 (17.1)	0.196	3 (14.3)	23 (22.1)	0.32	4(9.8)	4 (7.4)	0.48
Indication									
Male	15 (40.5)	22 (59.5)		5 (23.8)	13 (12.5)		10(24.4)	9(16.7)	
Unexplained	15 (17.6)	70 (82.4)		6 (28.6)	49(46.1)		9(22.0)	21(38.9)	
Tubal	15 (27.8)	39 (72.2)	0.006	4 (19.0)	25 (24.0)	0.011	11(26.8)	14(25.9)	0.46
Endometriosis	10 (30.3)	23 (69.7)		4(19.0)	17 (16.3)		6(14.6)	6(11.1)	
Others	7 (63.6)	4 (36.4)		2 (9.5)	0 (0)		5(12.2)	4(7.4)	
Protocol									
Antagonist	57 (91.9%)	152 (96.2%)	0.3	21(100)	98 (94.2)	0.32	36(87.8)	54 (100)	0.013
Agonist	5 (8.1%)	6 (3.8%)		0 (0)	6 (5.8)		5(12.2)	0(0)	
Gonadotropin type									
hMG	25 (40.3)	61 (38.6)		9 (42.9)	40(38.5)		16(39.0)	21(38.9)	
Recombinant FSH	30 (48.4)	84 (53.2)	0.71	11 (52.4)	58 (55.8)	0.93	19(46.3)	26(48.1)	0.97
Both	7 (11.3)	13 (8.2)		1 (4.8)	6(5.8)		6(14.6)	7(13)	
LH activity									

Beginning with hMG	27 (43.5)	64 (40.5)	0.89	9(42.9)	42(40.4)	0.79	18 (43.9)	22 (40.7)	0.74
Midway with hMG	4 (6.5)	12 (7.6)		0 (0)	5(4.8)		4 (9.8)	7 (13.0)	
Beginning with LH	4 (6.5)	15 (9.5)		2(9.5)	13(12.5)		2 (4.9)	2 (3.7)	
Mid way with LH	6 (9.7)	11 (7)		1(4.8)	8(7.7		5 (12.2)	3 (5.6)	
No LH activity	21 (33.9)	56 (35.4)		9(42.9)	36(34.6)		12 (29.3)	20 (37)	
Total Gn dose (IU)	2658±887	2557±1107	0.28	2715±882	2698±997	0.5	2632±912	2350±1073	0.33
Total Oocytes retrieved (n)	6.47±5.5	4.08±3.1	0.012	6.05±3.0	4.13±3.9	0.53	6.68±6.40	3.97±3.39	0.07
Cycles with No embryos for transfer	0	44 (4.7%)		0	28(26.9)		0	16(29.6)	
Mean number of embryo transferred	1.48±0.57	1.17±0.84	0.003	1.48±0.6	1.17±0.83	0.026	1.49±0.55	1.18±0.85	0.014
Embryo stage									
2/3	32 (51.6)	108 (80.6)	<0.001	12 (57.1)	72 (84.7)	0.009	20 (48.8)	36 (73.5	0.014
5/6	30 (48.6)	26 (19.4)		9 (40.9)	13 (15.3)		21 (51.2)	13 (26.5)	
Fresh vs frozen transfers									
Fresh transfers	31 (50.0)	77 (48.7)	0.058	11 (52.4)	49(47.1)	0.30	20 (48.8)	28(51.9)	0.06
Frozen Transfers	27 (43.5)	30 (19.0)		10(47.6)	23(22.1)		17(41.5)	7(13.0)	
Both fresh and frozen	4 (6.5)	7 (4.4)		0 (0.0)	4(3.8)		4 (9.8)	3(5.6)	

Qualitative variables are expressed as number and (percentage of total in that column). Significance has been calculated using chi-square test for comparison of two variables and pearson's chi square test for comparison of more than two variables. Quantitative data expressed as mean +- Standard Deviation irrespective of skewness coefficient. Significance calculated using Independent Samples t-test).

Table3: Adjusted Odds for live births using pre-treatment variables

	Adjusted odds for live births	95th centile lower bound	95th centile upper bound	significance
Age	0.89	0.81	0.97	0.01
Infertility Duration	0.97	0.89	1.04	0.37
Past live births	0.89	0.40	2.41	0.82
Body mass Index	1.04	0.97	1.12	0.30
Unexplained vs. Male	0.31	0.13	0.78	0.01
Male versus Tubal	0.67	0.26	1.74	0.41
Male versus endometriosis	0.59	0.20	1.78	0.35
Male versus others	1.75	0.40	7.7	0.46
AMH	2.7	0.77	9.58	0.12

Discussion

In the present analysis of women with low reserve (indicated by AMH less than or equal to 1.1 ng/mL) undergoing IVF for various indications, it was found that a good proportion of women under the age of 35 (43%) could achieve a live birth after completing one IVF cycle. This is comparable to live birth rates per cycle of 39% in unsorted women.[2] This suggest that despite their low AMH levels, younger women do not carry poor prognosis for achieving a live birth. Similarly, studies have found that AMH is either not predictor or only a weak predictor of live birth in women undergoing IVF.[3,4] It has been found that women with AMH in the 25th to 75th percentile range have similar rates of live birth as women with AMH in the <25th percentiles and >75th percentile range. Another study suggested that AMH might predict live births in older women but not in younger women, in whom live birth rates remains stable irrespective of the AMH values.[5]

Table4: Adjusted Odds for live births using treatment variables

	Adjusted odds for live births	95th centile lower bound	95th centile upper bound	significance
Antagonist versus agonist cycle	0.39	0.09	1.68	0.21
Recombinant FSH versus hMG	0.57	0.11	3.09	0.52
Both versus hMG	0.17	0.01	2.70	0.21

LH activity from day 2 versus no LH activity	0.36	0.02	6.41	0.49
LH activity added mid-way versus no LH activity	0.21	0.01	4.17	0.31
Frozen embryo transfer versus fresh embryo transfer	0.405	0.15	1.08	0.07
Endometrial thickness	1.27	1.07	1.51	0.007
Day5/6 (blastocyst) versus day 2/3 embryo transfer	15.17	4.3	53.3	<0.001
Numbers of embryos transferred- 2 versus 1	2.75	1.08	6.95	0.03

The present study in addition reported that age is an important predicting factor for live birth rates in women with low ovarian reserve. Women aged 35 and older were able to achieve only 1/3rd the rate of pregnancy as women under 35. The 16% live birth rate for women over 35 years of age with low AMH (Poseidon criteria group 4) in the present study is comparable to the 13% live birth rate in the same Poseidon criteria in a large study by Esteves et al.[6] Similarly, in another study examining live birth outcomes in women undergoing IVF who had AMH levels < 0.5 ng/mL, live birth rates were 31%, 21%, and 10% in women < 35 years, 35-39 years and > 40 years of age.[7] Our study has shown that a diagnosis of unexplained infertility negatively affects outcomes, as does a long period of infertility.

A secondary analysis using the ROC curve to determine infertility duration cut-offs, showed that an infertility duration of 7.5 years in women with unexplained infertility after a completed IVF cycle meant a near-zero probability of live birth. Long standing unexplained infertility (median of 4-7 years) has been shown to reduce the likelihood of live birth in women undergoing IVF compared to male factor infertility or female factor infertility secondary to endometriosis.[2,8] While short term infertility (median 2 to 4 years) could do fairly well with IVF.[9]

Strategies such as using recombinant LH instead of hMG or introducing LH activity from early versus mid-stimulation did not appear to affect live birth rates. This is consistent with large scale published data.[10,11] Also, the use of the strategy of elective frozen embryo transfer made no difference to live births in this group of women. These results are also consistent with those of the published data.[12] In the present study blastocysts had an unusually high implantation probability. The unusually high rate of implantation can be explained by the fact that day 2/3 embryos may have been transferred despite the lower assigned morphological grading classification. In addition, the center changed its policy from a majority of day 2/3 embryo transfers in the early years to predominantly blastocyst culture and transfer in the later years. The improvement in live births over the years may also reflect a time-based improvement in culture media conditions. This study does not analyze the effect of pre-stimulation maneuvers such as the use of estradiol, progesterone, or COCs for cohort synchronization or the use of different forms of triggers in influencing live birth.

In conclusion, it is possible to identify women with low ovarian reserve with good prognosis for IVF live birth. These are women under 35 with any cause of infertility and women over 35 with a short period of infertility and a known cause of infertility such as male factor, endometriosis, or tubal factor. The antagonistic protocol, using hMG instead of recombinant FSH and performing fresh embryo transfer instead of elective frozen embryo transfer, works as well as the alternative and is likely to be patient -friendly and cost effective.

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Calendar of Virtual Monthly Clinical Meetings 2021-22

28th May, 2021	B L Kapoor Hospital
25th June, 2021	All India Institute of Medical Sciences
30th July, 2021	Sitaram Bhartia Hospital
3rd September, 2021	Army Hospital (Research & Referral)
24th September, 2021	Deen Dayal Upadhyay Hospital
29th October, 2021	PGIMSR & ESI Hospital
19th - 21st November, 2021	43rd Annual Conference
26th November, 2021	MAMC & Lok Nayak Jai Prakash Narayan Hospital
7th January 2022	Sir Ganga Ram Hospital
28th January, 2022	ABVIMS & Dr Ram Manohar Lohia Hospital
25th February, 2022	UCMS & Guru Tek Bahadur Hospital
1st March, 2022	VMMC & Safdarjung Hospital
29th April, 2022	LHMC & Smt. Sucheta Kriplani Hospital
27th May, 2022	Apollo Hospital

Events Held in February 2022

S N.	Date	Event
1	03.02.2022	**"Optimizing Nutrition and Mental Health of Adolescents"** by Adolescent Committee
2	05.02.2022	CME **"Multidisciplinary Approach to Breast Lump and Fertility Preservation in Breast Cancer"** by Multidisciplinary Committee
3	08.02.2022	Salvaging Tube Medically and Surgically by DGFSW and AOGD
4	12.02.2022	Webinar on **"Infertility"** with IMA- South Delhi under aegis of Infertility Committee
5	13.02.2022	Online Adolescent Health Problems Counseling with Pratishandi
6	18.02.2022	CME on **"Hypertensive Disorders of Pregnancy"**
7	18.02.2022	PPH Workshop at SGT Medical College and Hospital, Gurugram under aegis of Multidisciplinary Committee
8	19.02.2022	"Delving into Clinical Concerns of Intrahepatic Cholestasis of Pregnancy" by Safe Motherhood Committee
9	19.02.2022	FOGSI- WHO Training on "Respectful Abortion Care" by AOGD
10	19.02.2022	Physical CME by Infertility Committee with IMA- South Delhi
11	21.02.2022	PG Forum on **"Recurrent Pregnancy Loss"**
12	22.02.2022	CME on **"Pregnancy in Thalassemic Women"** by QI committee in association with DGF
13	24.02.2022	**"A journey from Reconstruction to Rejuvenation- by Minimal Invasive Approach"** by Endoscopy Committee
14	25.02.2022	AOGD Monthly Clinical Meeting at UCMS & GTB Hospital
15	26.02.2022	**"Breast & Ovarian Cancer"** by Oncology Committee

Events to be Held in March 2022

S. N.	Date	Events
1	01.03.2022	CME on "I care for Contraception" with FOGSI Family Welfare Committee Association
2	01.03.2022	Public Forum on "Polycystic Ovary"
3	05.03.2022	Webinar on "Anorectal Physiology for the Gynecologist" by Urogynaecology Committee
4	08.03.2022	Women's day Celebration by AOGD & DGF
5	9.03.2022	"Adolescent Health Medical Concerns" by SGRH under aegis of AOGD
6	10.03.2022	Case Based Discussions in Fetal Medicine by Fetal Medicine and Genetics Committee
7	12.03.2022	Physical Workshop by AOGD at Safdarjung Hospital
8	12.03.2022	CME by MAMC with Fet & Gen Committee, SFM
9	19.03.2022	CME on"Towards Elimination of Cervical Cancer-Translating Guidelines to Practice" by Oncology Committee
10	21.03.2022	PG Forum Class on " Endometriosis"
11	22.03.2022	CME on "Rh Negative Pregnancy" by Multidisciplinary Committee
12	23.03.2022	CME on "PCOS" by FOGSI Endocrinology Committee in association with AOGD
13	24.03.2022	"Robotics in Gynaecology: A Masterclass by Endoscopy Committee
14	29.03.2022	Physical CME by Infertility Committee AOGD
15	31.03.2022	"Fetomaternal Infections : Prevention and Care" by AOGD & SFM Delhi Chapter

Journal Scan

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The effect of ovarian follicle size on oocyte and embryology outcomes

Shapiro BS, Rasouli M, Verma K, Raman A, Garner FC, Aguirre M, Kaye L, Bedient C. *The effect of ovarian follicle size on oocyte and embryology outcomes. Fertil Steril. 2022 Mar 30:S0015-0282(22)00136-4.*

Objective: To identify relationships between the size of punctured ovarian follicles and subsequent embryology outcomes. **Design:** Prospective observational cohort study. **Setting:** Private fertility center. **Patients:** One hundred fifty-seven oocyte retrievals performed during the study period. **Interventions:** The diameter of punctured follicles was ultrasonically measured during routine oocyte collection. The resulting embryos were group-cultured to the blastocyst stage and classified into 8 groups according to follicle size (≤9.5, 10-12.5, 13-15.5, 16-18.5, 19-21.5, 22-24.5, 25-27.5, and ≥28 mm). **Main outcome measure:** Rate of good-quality blastocysts per follicle puncture. **Results:** This study included 4,539 follicle punctures, 2,348 oocytes, 1,772 mature oocytes, 1,258 bipronuclear (2pn) oocytes, and 571 good-quality blastocysts derived from 157 oocyte retrievals. The per-puncture yields of oocytes, mature oocytes, 2pn oocytes, and good-quality blastocysts were associated with the size of the punctured follicle. The rates of good-quality blastocysts per punctured follicle were 2.2% (≤9.5 mm), 6.2% (10-12.5 mm), 11.9% (13-15.5 mm), 14.5% (16-18.5 mm), 18.9% (19-21.5 mm), 17.5% (22-24.5 mm), 15.9% (25-27.5 mm), and 16.0% (≥28 mm). When compared with the overall average, punctures of follicles in groups ≤12.5 mm in diameter had significantly inferior yields of good-quality blastocysts, whereas punctures of follicles in groups 19-24.5 mm in diameter were associated with significantly greater than average yields of good-quality blastocysts. Other groups did not differ significantly from average. No correlation was observed between follicle diameter and ploidy of biopsied blastocysts. **Conclusions:** Punctures of follicles ≤12.5 mm in diameter rarely result in good-quality blastocysts. The yield of good-quality blastocysts progressively increases with follicle size up to approximately 19 mm in diameter, with no substantial decline above that size. The ploidy of the blastocysts that form appears to be unaffected by follicle size.

Follicular activation in women previously diagnosed with poor ovarian response: a randomized, controlled trial

Díaz-García C, Herraiz S, Pamplona L, Subirá J, Soriano MJ, Simon C, Seli E, Pellicer A. *Follicular activation in women previously diagnosed with poor ovarian response: a randomized, controlled trial. Fertil Steril. 2022 Apr;117(4):747-755.*

Objective: To investigate whether ovarian fragmentation for follicular activation (OFFA) improves ovarian reserve markers and in vitro fertilization (IVF) outcomes in women with poor ovarian response (POR). **Design:** Randomized, controlled trial, with parallel assignment. **Setting:** University hospital. **Patient(s):** Thirty-four women with POR according to the European Society of Human Reproduction and Embryology criteria. **Intervention(s):** Women with POR were randomly allocated to receive ovarian fragmentation in 1 ovary or to no intervention (control group). Ovarian reserve markers were followed at 2-week intervals for 6 months. In vitro fertilization cycles were initiated when the antral follicle count (AFC) doubled or at the end of follow-up. **Main outcome measure(s):** The primary outcome was the number of metaphase II (MII) oocytes obtained. Antral follicle count, antimüllerian hormone level, and reproductive outcomes were recorded as secondary outcomes. Exploratory outcomes included surgical results and analysis of protein and gene expression. **Result(s):** Ovarian fragmentation for follicular activation resulted in an increase in AFC in the intervention ovary compared with the control ovary and an increase in total AFC in the OFFA group compared with controls. Serum antimüllerian hormone and follicle-stimulating-hormone levels did not improve in the OFFA group throughout the follow-up period. Fifteen patients from each arm underwent IVF. In the control group, 33 MII oocytes

were retrieved and 18 embryo transfers were performed, with a 20% pregnancy rate and an 18.7% live birth rate per cycle. In the OFFA group, 23 MII oocytes were retrieved and 11 embryo transfers were performed, with a 13.3% pregnancy rate and a 6.7% live birth rate per cycle. Reproductive outcomes did not significantly differ between the groups. Hippo pathway inhibition was confirmed by an 18.8% reduction in the phospho-YAP/YAP (Yes-associated protein 1) ratio and BIRC and CCN overexpression after fragmentation. **Conclusion(s):** Ovarian fragmentation for follicular activation in women with POR resulted in an increase in AFC but did not modify IVF outcomes when compared with controls.

Infertility, Miscarriage, Stillbirth, and the Risk of Stroke Among Women: A Systematic Review and Meta-Analysis

Liang C, Chung HF, Dobson AJ, Mishra GD. Infertility, Miscarriage, Stillbirth, *and the Risk of Stroke Among Women: A Systematic Review and Meta-Analysis. Stroke. 2022 Feb;53(2):328-337.*

Background and purpose: Stroke is one of the leading causes of mortality, and women are impacted more from stroke than men in terms of their absolute number and in having worse outcomes. A growing number of studies have explored the association between pregnancy complications, pregnancy outcomes, and stroke. Limited studies, however, have investigated links involving infertility, miscarriage, and stillbirth, which could plausibly be associated via a background of endocrine conditions, endothelial dysfunction, and chronic systematic inflammation. This review aims to summarize current evidence and provide up-to-date information on the associations of infertility, miscarriage, and stillbirth, with stroke incidence. **Methods:** A comprehensive literature search was conducted for cohort and case-control studies on associations between infertility, miscarriage, stillbirth, and stroke up to September 26, 2020. Seven databases were searched: PubMed, Embase, Cochrane, CINIHL, PsycINFO, Wanfang, and CNKI. Random-effects models were used to estimate the pooled hazard ratios (HRs) and 95% CIs. **Results:** Sixteen cohort studies and 2 case-control studies enrolling 7 808 521 women were included in this meta-analysis. Women who had experienced miscarriage or stillbirth were at higher risk of stroke (miscarriage: HR, 1.07 [95% CI, 1.00-1.14]; stillbirth: HR, 1.38 [95% CI, 1.11-1.71]) than other women. The HRs of stroke for each additional miscarriage and stillbirth were 1.13 (95% CI, 0.96-1.33) and 1.25 (95% CI, 1.06-1.49), respectively. In subgroup analysis, increased risk of stroke was associated with repeated miscarriages and stillbirths (miscarriage ≥3: HR, 1.42 [95% CI, 1.05-1.90]; stillbirth ≥2: HR, 1.14 [95% CI, 1.04-1.26]). Associations between infertility and stroke were inconsistent and inconclusive (HR, 1.07 [95% CI, 0.87-1.32]). **Conclusions:** Miscarriage and stillbirth are associated with increased risk of stroke among women, which could be used as a contributing risk factor to help identify women at higher risk of stroke.

AOGD Monthly Clinical Meeting Held at UCMS & GTB Hospital on 25th February 2022

Cervical cancer: complex presentation with definite solutions

Suman Chaudhary, Bindiya Gupta, Amita Suneja, Sruthi Bhaskaran, Abha Sharma

Cervical cancer is one of the most common malignancy that affects women worldwide. The present case highlights the fact that in cases where initial management is not appropriate, it may lead to disastrous consequences. We present a case of 51 years old P3L3, who had undergone total abdominal hysterectomy for post coital bleeding and discharge PV and was referred to us for postoperative VVF repair with histopathology report of squamous cell carcinoma (tumour tissue of 6x6 cm). PET-CT revealed metastasis to ovary and anterior abdominal wall near incision line. She had also received complete course of adjuvant chemo radiation and additional chemotherapy for cutaneous metastasis. In addition, she had an associated papillary thyroid malignancy. After detailed investigations, all the complexities were discussed in multidisciplinary tumor board meeting where decision of salvage surgery was taken with thyroid surgery in the second sitting. After extensive counselling the patient underwent a salvage surgery consisting of bilateral salpingo-ophorectomy and vault biopsy with transvesical fistula repair and excision of subcutaneous nodule. She received 6 cycles of adjuvant chemotherapy post surgery. On post-operative follow-up after six months the fistula repair is successful, there has been no recurrence and the patient is now planned for thyroid surgery.

A Tale of Miraculous Survival of Two lives: Snakebite in Pregnancy

N Tyagi, PS Modi, A Singh, K Guleria, A G Radhika

Although snake envenomation is not uncommon in the developing countries, it is a rare event in pregnancy as women are generally indoor workers. We present a case (only second case in last 30 years in our department) of snake bite in pregnancy with miraculous survival of both the mother and the fetus. Mrs X, G2P1L1 at 30 wk 2 d presented to casualty 2 hrs after a snake bite. She had ptosis, blood in vomiting and ghabrahat, was given ASV immediately and intubated for impending respiratory arrest. After extubation on day 3, she was reintubated for respiratory complications and received a second dose of ASV for development of additional haematological derangement. Gradual improvement was seen in her neurological, respiratory and haematological parameters and she was discharged on day 8 after confirmation of normal maternal and fetal status. Later, she delivered at term uneventfully and has healthy, normal female baby. This case highlights why clinicians should be well versed with the management of snakebite and its complications when faced with such an emergency. Generally associated with poor outcomes in terms of considerable maternal and fetal mortality, our case had an excellent outcome because of timely institution of emergency care and treatment.

Pregnancy with breast agony: A double whammy

A Singla, V Mohan, R Agarwal, S Jain, S Prakash, B Priya, N Kaur

Gestational gigantomastia or gravid macromastia is a rare idiopathic condition presenting as exacerbated incapacitating breast enlargement during pregnancy is a physically and psychological debilitating condition. It was first reported in 1648 by Palmuth. Case Report: Gravida4, Para1, 27 years old presented during 3rd month of pregnancy with excessive increase in size of bilateral breasts with swellings in both the axillae as well. Routine antenatal, hormone and autoimmune investigations were within normal limits including serum prolactin levels. Patient was apprised of pros and cons of treatment options in terms of either medical management with bromocriptine, surgical treatment, or conservative approach. Our case opted for conservative approach in conjunction with the surgical consultation. Active assistance was given by our team in form of customized shoulder sling, use of innovative ways to support her breast to prevent complications due to huge breast weight and helped her to prolong pregnancy upto 34 weeks period of gestation uneventfully. Patient

developed discomfort, breast pain, backache and breathing difficulty and underwent cesarean section at 34 weeks for obstetric indication. Postpartum breast feeding could not be done due to excessive breast size. On postpartum follow up till 5 months, spontaneous regression was noted with decrease in breast size from brassiere size of 52 D to current of 40 D.

The incidence of Gestational gigantomastia is 1 in 28,000 to 1 in 1,00,000 pregnancies. It can present with a myriad of symptoms though the etiology is still debatable. A diverse range of treatment options are available from conservative to medical to finally surgical correction but counselling of the woman and the family is what is of utmost importance because not only it has physical symptoms but a lot of social and mental stigma too. Conservative treatment can be very forgiving especially in select women along with psychological and family support as proven by our case. A sound knowledge about this rare condition is necessary for, especially for all the obstetricians as most women affected belong to the reproductive age group.

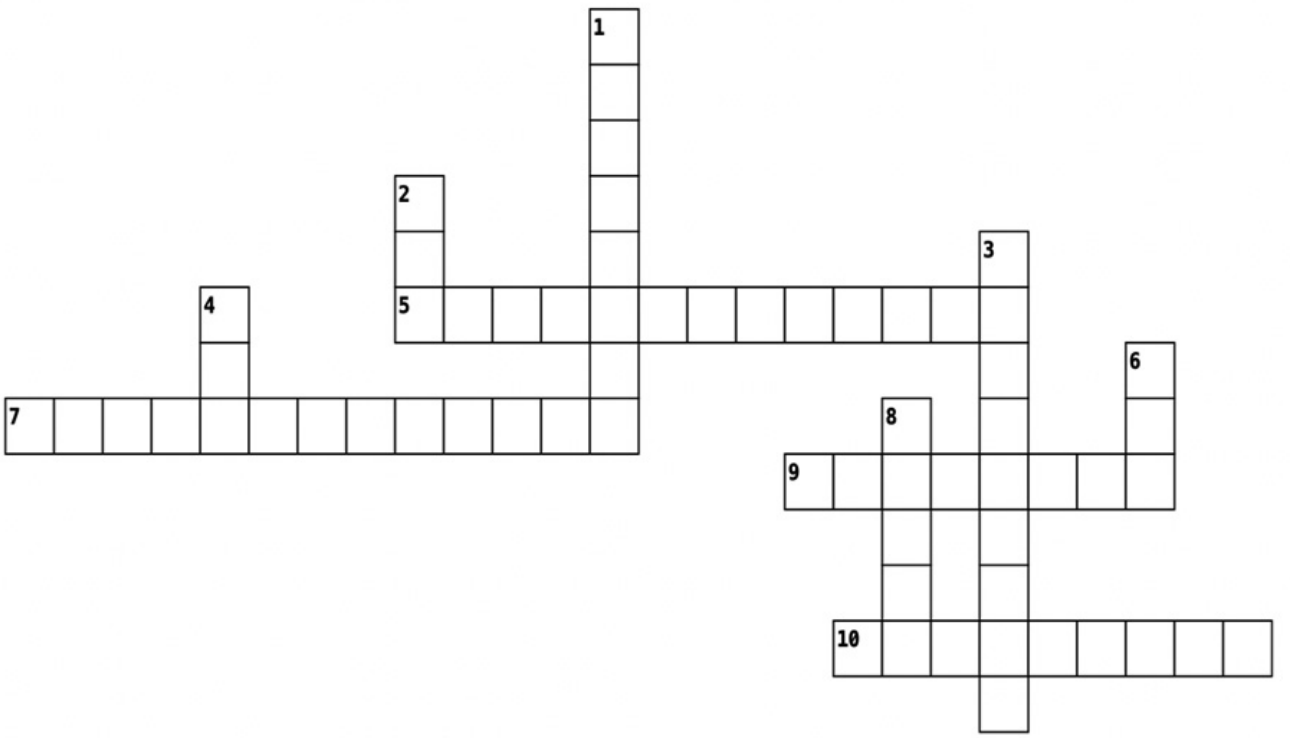
Chhaya Remains in Shadows

A G Radhika, Amita Suneja

Background: The nonsteroidal contraceptive Centchroman was approved and licensed in 1991 and launched as Saheli & Choice-7 in 1992. It was included in the National Family Planning Programme under the trade name "Chhaya" in April 2016. Both national and hospital statistics document very low utilization of Centchroman. The objective of the study was to determine the reasons for the low utilization of Centchroman (Chhaya). Methods: We conducted a prospective observational (analytical) study in the Department of Obstetrics and Gynecology at UCMS & GTB Hospital, Delhi from September 2019 to January 2022. Women were recruited from outpatient clinic and post-partum wards after counselling for contraception after necessary ethics clearance. Results: Only 65 women were recruited for the study in the initial 22 months. Route cause analysis identified the lack of easy availability of the pills with the women especially in postpartum period as an easily correctable factor. The strategy of providing at 3 months dosage to the postpartum women at the time of discharge from hospital was adopted. This resulted in a five fold increase in users. In all, 470 women were enrolled for the study. The mean age of recruitment was 26 years +/- 5 years. The Centchroman acceptors were majorly primipara (47%) and postpartum women (83%). The discontinuation rate was 4.87%. Delayed menstrual cycle was observed in 4-10%. There was one failure, the lady underwent MTP. **Conclusions:** Ready availability of the contraceptive pill empowers women to use the same at free will any time. However, it is important to maintain a continuous supply through the network of ASHA workers and at the primary healthcare facilities. There is also the felt need to increase awareness amongst stakeholders and medical personnel for the use of Centchroman.

Cross Word Puzzle

Niharika Guleria[1], Rekha Bharti[2]
[1]Senior Resident, [2]Professor, Obstetrics & Gynaecology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi



Across

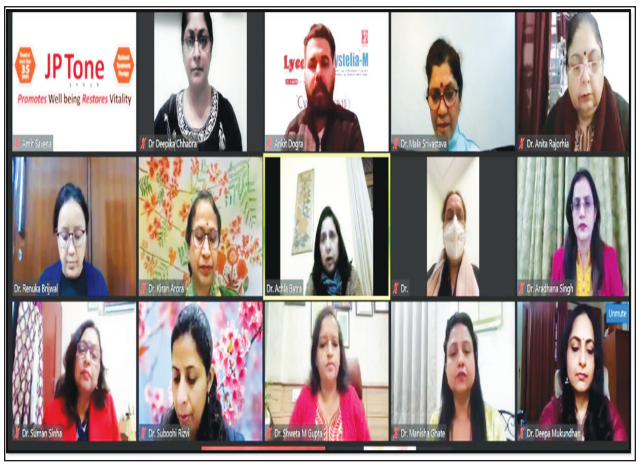
5. Gold standard management of hydrosalpinx prior to IVF
7. Preferred method of cryoprerservation of oocytes
9. Syndrome associated with thin endometrium
10. Ovarian stimulation drug used to lower estradiol levels in breast cancer patients

Down

1. Preferred method of endometrioma capsule removal
2. The test used for sperm vitality
3. Name of strict criteria used for sperm morphology
4. The preferred modality for diagnosis of adenomyosis
6. Donor gametes can be stored for a maximum period of how many years
8. Poseiden group of a 30-year old female with poor ovarian reserve

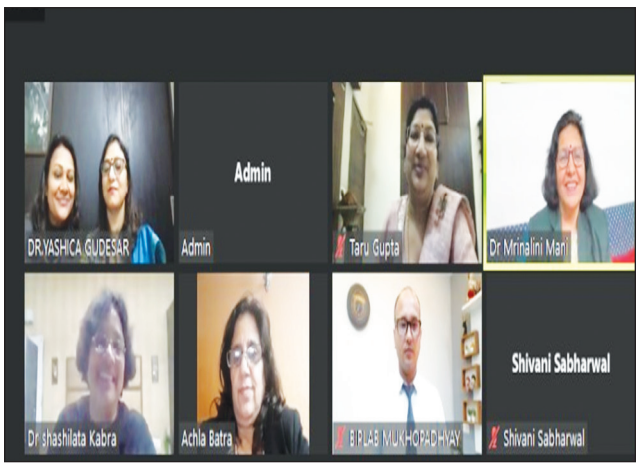
Mail the answers to editorsaogd2021@gmail.com. The correct answers and names of the three winners will be announced in the next issue.

Events Held in February 2022



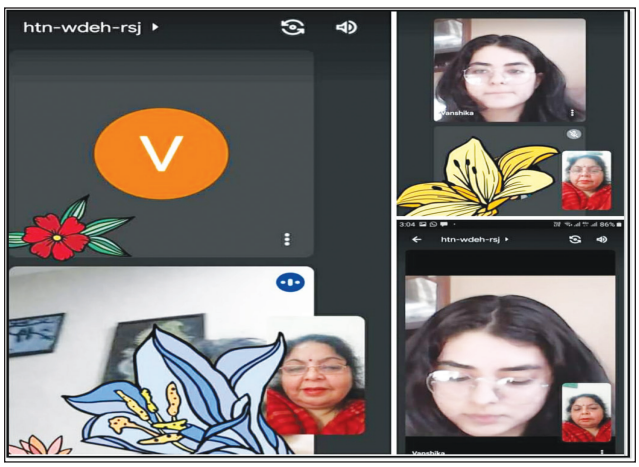
Optimizing Nutrition and Mental Health of Adolescents

Multidisciplinary Approach to Breast Lump



Salvaging Tubes Medically and Surgically

Webinar on "Infertility"



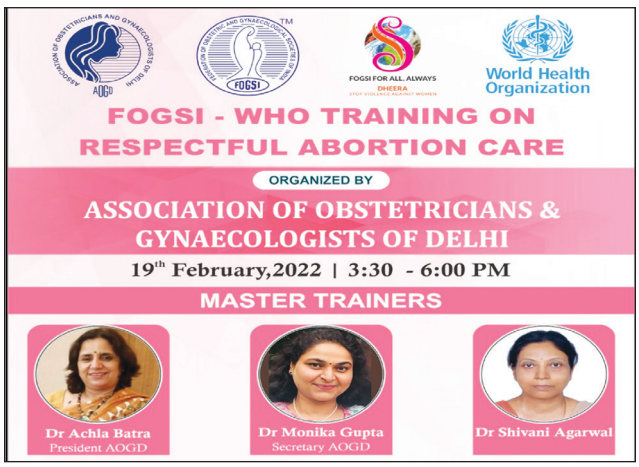
Adolescent Health Problems Counseling with Pratishandi

CME on "Hypertensive Disorders of Pregnancy"

PPH Workshop at SGT Medical College and Hospital

CME on Intrahepatic Cholestasis of Pregnancy

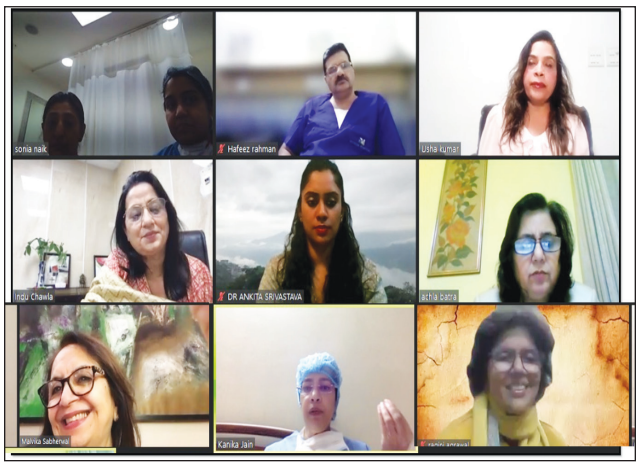
Dydrogesterone in RPL & Carbetocin in PPH Prevention



FOGSI - WHO Training on "Respectful Abortion Care" by AOGD , 19th Feb

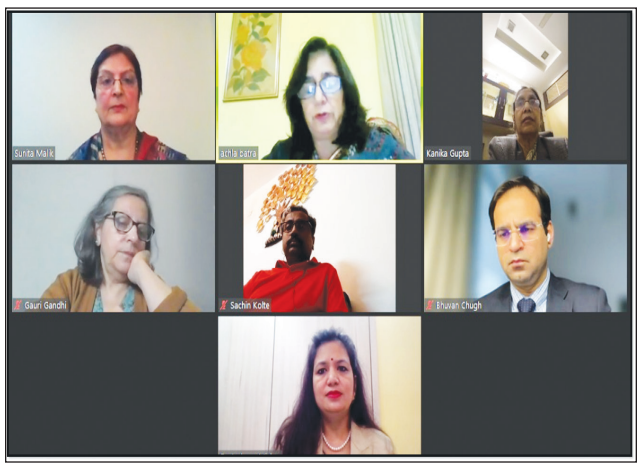
PG Forum on " Recurrent Pregnancy Loss"

"Pregnancy Outcomes in Thalassemic women



"Master class on " Vaginoplasty to Reconstruction to Rejuvenation "

Monthly Clinical Meeting at UCMS



"Breast & Ovarian Cancer"

Elected AOGD President & Vice President 2022-23

Post	Elected
AOGD President	Dr Asmita Rathore (MAMC & LNJP Hospital)
AOGD Vice President	Dr Y M Mala (MAMC & LNJP Hospital)

Elected AOGD Subcommittee's Chairpersons 2022-24

Subcommittees	Elected
Breast and Cervical Cancer Awareness, Screening & prevention Sub-committee	Dr Mrinalini Mani (Guru Gobind Singh Hospital)
Infertility Sub-committee	Dr Manju Khemani (Max Smart Super Specialty)
Rural Health Sub-committee	Dr Shivani Aggarwal (Kasturba Hospital)
Multidisciplinary Sub-committee	Dr Kiran Guleria (UCMS & GTB Hospital)

Association of Obstetricians & Gynaecologists of Delhi

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Mobile No:.....Email: .....

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Date of Birth: Date..... Month ..... Year .....

Member of Any Society:.....

Proposed by: .....

Cheque/DD / No: .....

Cheque/Demand Draft should be drawn in favour of: **Association of Obstetricians & Gynaecologists of Delhi**

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Send Complete Membership Form Along With Cheque / DD and Photocopy of required documents.

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Association of Obstetricians and Gynaecologists of Delhi

Office Bearers 2021-22

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