AOGD BULLETIN

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Enlightening the Path for Next Generation of Gynaecologists

Dedicated Issue:
Assisted Reproductive Technology

AOGD SECRETARIAT
Department of Obstetrics & Gynaecology,
3076, Teaching Block, IIIrd Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029
Tel.: 011-26546603, 26593221 E-mail: secretaryaogd2019@gmail.com
Website: www.aogd.org

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Department of Obstetrics and Gynecology
3076, Teaching Block, IIIrd Floor
All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029
Tel No: 011-26546603, 26593221
Email: secretaryaogd2019@gmail.com
www.aogd.org

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Dr J B Sharma
Ph. No. 011-26546603; Email: secretaryaogd2019@gmail.com

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From the President's Pen

Dear Friends

The third issue of AOGD Bulletin is devoted to "Assisted Reproductive Technology (ART)". Since the birth of first IVF baby in 1978, we have come a long way in which ART has changed the face of human reproduction. Millions of couples who in the past could not achieve parenthood have been blessed with their own offspring. With each passing day more and more couples are resorting to this mode of reproduction. Nothing gives more smiles to parents and doctors than achieving success with this technology. More advances in the field will follow. However, we shall strive to use this science for genuinely indicated conditions. Cost remains an important issue. Let us extend this technology to all those who need it.

Dr Sunesh Kumar
President, AOGD

From the Secretary's Desk

Dear Friends

Greetings from AOGD

The June issue of AOGD bulletin on 'Infertility' was received very well. Moving further, the present issue is on 'Assisted Reproductive Technology'. The aim is to provide evidence based practice points to all our members.

A number of academic activities were conducted under the aegis of AOGD, this month.

The Annual Conference of AOGD is on 28th - 29th September, 2019. There are 9 pre-congress workshops on 26th – 27th September, 2019. The online registration is open. I request you all to participate in large numbers to make this conference a great success.

Dr Vatsla Dadhwal
Hon. Secretary

Monthly Clinical Meeting

Monthly Clinical Meet will be held at All India Institute of Medical Science (AIIMS), New Delhi on **Friday, 26th July, 2019 from 04:00pm to 05:00pm**.

From the Editor's Desk

Dr J B Sharma
Editor

Dr Reeta Mahey

Dr P Vanamail

Dr Vidushi Kulshreshtha

Co-Editors

After an issue on basic evaluation and management of infertile couple, which was appreciated by most members as conveyed through encouraging messages, emails and phone calls, we are pleased to bring the third issue of Bulletin from the AIIMS AOGD office on "Assisted Reproductive Technology"

which is dedicated to IVF and has been edited by Dr Reeta Mahey and her team.

As discussed in the previous issue, with increasing incidence of infertility, the referrals for ART are also increasing. Initially, IVF was done only for tubal factor infertility. But now after 40 years since the birth of first IVF baby, IVF has gone beyond imagination in terms of indications and advancements. In addition to tubal factor infertility, it is also done in patients with male factor, endometriosis, PCOS, unexplained infertility and those who fail to conceive in 3-4 IUI cycles. Another indications are decreased ovarian reserve and third party reproduction in couples with compromised factors.

The present issue is started with first article on "Understanding the Physiology of IVF" by Dr Sunita Arora which is the most important part when we study ART.

Dr Sonia Malik and Dr Nidhi Jha will be discussing about "Fertility options in Endometriosis" as endometriosis is a commonly encountered disease among infertile women.

In IVF, there is a big controversy about whether or not to do routine freezing or not. Dr HD Pai and Dr Manisha will discuss this debatable topic and will give us clarification about routine embryo freezing. "Luteal phase Support" is an integral part of IVF. Dr Neena Malhotra and Dr Anshu will discuss on luteal phase support.

The aim for IVF in today's era is to have OHSS free clinic. Dr Sudha Prasad and Dr Saumya Prasad will discuss about "Ovarian Hyperstimulation Syndrome" and will tell us how to achieve this.

Dr Neeta Singh and Dr Yogita Dogra will discuss about "Role of Immunotherapy in ART" which is an upcoming option to improve implantation.

As the incidence of young cancer is increasing, there is need to discuss about fertility preservation in cancer women. Dr Reeta Mahey and Dr Monica Gupta will discuss about "Oncofertility".

Dr Rupali Bassi will enlighten us on a budding topic of "Artificial Intelligence" in ART.

Dr B B Dash and Dr Sonia Chawla will present an interesting case report on Peritoneal leiomyomatosis after abdominal hysterectomy.

We have tried to select important topics of ART for this issue and we hope that this bulletin will be useful to our colleagues in their day to day practice. We welcome the comments and views of our readers which will help to improve the future editions of the bulletin. We wish you all a happy reading!

Editorial Team, AIIMS

Understand the Physiology: How Supraovulation Happens in IVF

Sunita Arora[1], Hrishikesh Pai[2], Nandita P Palshetkar[3]
[1]Senior Consultant, [2]Director, [3]Senior Consultant, Bloom IVF, Fortis La Femme Hospital, GK 2, New Delhi

Meet the HPO (Hypathalmo Pituitary Ovarian) Axis

Few facts needed to be understood are

- GnRh must be released in pulsatile manner to stimulate the secretion of FSH and LH[1]
- Constant release causes desensitization of receptors and consequent decreased release of gonadotropins

Control of HPO axis

- Long feedback loop - from target organ to hypothalamus and pituitary.
- Short feedback loop-pitutary hormones giving negative feedback to hypothalamus.
- Ultrashort feedback loop: Inhibition of GnRH by its own secretion
- Others: Dopamine and serotonin may directly suppress both GnRH activity and prolactin
- Norepinephrine has stimulatory effect on GnRH release.

Progesterone and Estrogen (Do they act differently)

Progesterone when high supresses LH release and when low enhances LH release unlike estrogen which acts in a different way. All these changes are evident once priming has been done by estrogen. Unlike progesterone, high estrogen has a positive feedback on LH (The reason behind LH surge). However Low estrogen levels have a suppressing effect on LH secretion.

FSH and LH hormones

FSH is the key gonadotropin which is responsible for

- Recruitment of follicles
- Selection of follicles
- Dominance during follicular phase
- Stimulates granulosa cells LH recetor expression
- Considered nurturing hormone for follicles.

LH responsible for

- normal follicular growth and devlopment.
- Full follicular and oocyte maturation
- Normal androgen and estrogen biosynthesis

How a natural cycle works

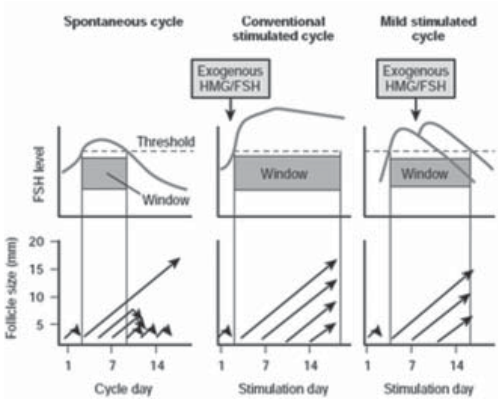
Hypothalamus releases GnRh (gonadotropin releasing hormones) which helps in follicular devlopment and hence release of estrogen which gives a positive feedback for LH surge and hence ovulation and endometrial changes.

Concept of FSH window and FSH threshold[2]

Hormonal changes for subsequent cycle start in late luteal phase of previous cycle only. The FSH starts rising and continues to rise in follicular phase till when a follicle gets recruited. This minimum level above which FSH needs to rise is called FSH threshold and the duration for which it needs to stay above threshold is called FSH window. so the word threshold signifies level and word window signifies duration.

How the window differs in stimulated cycle

In stimulated cycle in IVF as the exogenous FSH is being used which leads to increased window period, duration for which FSH stays above threshold and hence recriutment of many follicles together and hence surpraovulation. (fig 1)



The Physiology of natural cycle

Two phases into which a normal cycle is divided are follicular phase and luteal phase.

Follicular phase

Follicular phase is marked by decreasae in estrogen, progesterone and inhibin levels and hence a positive feedback for secretion of FSH. This rise in FSH which starts in luteofollicular transition of previous cycle subsequently crosses the threshold and leads to rescue of cohort of preantral follicles. Stages of devlopment

of follicle can be broadly divided as primordial, primary, secondary which are FSH independent stages and preantral and antral which are FSH resposive stages followed by preovulatory and ovulatory FSH dependent stages.

Primordial follicle: It's a non growing follicle with oocyte arrested in diplotene stage of meiotic prohase. Its important to understand that there is a continous depletion of follicles throughout lifetime. Most rapid decline occurs just before birth. The primary oocytes within these follicles remain resting until puberty.

By the age of menarche, 300,000 to 400,000 follicles remain and out of these 400 only ovulate in the lifetime.

Primary, preantral and antral follicle: As the follicle passes through different stages of development, there are simultaneous changes in the growing oocyte inside the follicle. The significant changes which occur during these different phases include proliferation of granulosa cells, enlargement of oocyte ,formation of more distinguished basal layer called zona pellucida in preantral stage, increased production of estrogen and other steroids like androgen and progestin. AS the follicle passes through these different stages there is expression of more and more FSH receptors allowing the follicle to respond to relatively low concentration of FSH. The further fate of preantral follicle depends on its capability to convert androgen dominant environment to estrogen dominant environment. In case follicle has more androgen rich environment as in case of Polycystic ovaries, the capacity to aromatize androgens to estrogen gets exceeded and hence it gets converted to more potent androgens leading to follicular atresia.

The antral follicle is characterized by accumulation of follicular fluid in the antrum . This fluid is rich in cytokines and growth factors apart from estrogen rich environment.

The two cell two gonadotropin theory[3]: The basics to understand this theory lies behind the concept that granulosa cells and theca cells need to work in unison for a final increase in estrogen levels in the blood circulation. Theca cells maily have LH receptors and granulosa cells mainly have FSH receptors but later on LH receptors are also induced under FSH effect. The P450 activity is specific for theca cells whereas aromatization is specific for graulosa cells under effect of aromatase enzymes. As granulosa cells lack P450 c enzyme, the rate of aromatization in granulosa cells is dependent on androgen made available by theca cells. So Cholestrol in presence of Cytochrome P450 is converted to testosterone and androstenedione in the theca cells which diffuses across membrane to granulose cells, which in presence of aromatase enzyme gets converted to estrogen. Hence this estrogen which finally diffuses into blood stream needs cohesive working of both granulosa and theca cells and hence two cells and two gaonadotrpin theory.

Ovulation: As the follicle matures there is a rise in estrogen levels and hence an LH surge which leads to various steps leading to ovulation. Increased follicular pressure occurs because of increased colloid osmotic pressure as a result of changes in composition of antral fluid.

LH and FSH act on granulosa cells leading to production of plasminogen activator and hence increased plasmin and increased fibrinolytic activity leading to breakdown of follicle wall. Increased level of prostaglandin E and hence increased plasminogen activator and increase PGF2 alpha leads to increased lysosomes under follicular wall.

Prostaglandin leads to ovarian muscle contraction and hence extrusion of oocyte.

Few Facts about ovulation

- Estradiol concentrations of 200 pg/mL for 50 hours or more → initiate a gonadotropin (LH) surge
- The mean duration of the LH surge is 48 hours
- A threshold of LH concentration must be maintained for at least 14 to 27 hours for full maturation of oocyte to occur.
- Ovulation will occur in the single mature Graffian follicle 10 to 12 hours after the LH peak or 34 to 36 hours after the initial rise in midcycle LH

Luteal Phase

Healthy preovulatory follicle is the key to a healthy luteal phase. The LH surge leads to luteinisation of follicles and shifts the mileu inside granulosa cells to progesterone producing cells. Progesterone secretion from corpus luteum peaks between 4 to 7 days post ovulation. High progesterone levels leads to negative feedback on GnRh and hence reducing GnRh pulse frequency and subsequently decreasing FSH and LH and finally atresia of corpus luteum around fourteen days later if pregnancy does not happen. *In stimulated cycles where Antagonist and agonist are used there is excessive suppression of intrinsic FSH and LH more so with agonist and hence a prompt luteolysis happens.*

Endometrial cycle

Histologically endometrium is divided into lower 1/3 rd of total depth called **stratum Basalis** which lies

in contact with myometrium and is uninfluenced by hormones. No cyclical changes occur here. Upper 2/3rd is **stratum functionalis** meant for blastocyst implantation. This layer is further divided into **stratum compactum** closer to lumen

Composed of glands and dense stromal cells and a deeper layer **stratum spongiosum** which contains less dense stroma and is shed during menses. Different phases according to duration can be divided into menstruation phase day 1 to day 5 to 6. Proliferative phase day 7 to day 14 and secretory phase from day 15 to 28 of cycle with normal cycle length and can vary in prolonged and short cycles.

Proliferative phase is characterized by lot of mitotic activity and pseudostratification histologically, tissue components demonstrate proliferation which peaks around 8 to 10 days of cycle corresponding to peak estradiol levels in the circulation.

Secretory phase: The first histologic sign that ovulation has occurred is appearance of subnuclear intracytoplasmic glycogen vacuoles in glandular epithelium on cycle day 17 or 18. Peak secretory level is reached 7 days after midcycle gonadotropin surge, coinciding with time of blastocyst implantation. Under the influence of progesterone, mitotic avtivity is restricted,stromal edema happens, spiral arterioles devlop, lengthen and coil. Secretory phase is typically characterized by pinopode development which can be demonstrated under electron microscope. Just before menstruation there is decidual collapse. The luteofollicular transition which starts in luteal phase of previous cycle is characterized by falling estrogen and progesterone and hence again a rise in FSH levels to begin the next cycle.

Applied Physiology

Ovarian Reserve Markers

INHIBIN: Inhibin A is secreted predominantly in the luteal phase and inhibin B in the follicular phase by granulosa cells. Inhibin B is a direct marker of ovarian reserve. Inhibin B levels decline with increasing age due to decreased number of follicles and decreased secretion by the granulosa cells. Since inhibin is decreased there is poor negative feedback and FSH level is increased.

FSH : Raised FSH indicates poor ovarian reserve

ANTI MULLERIAN HORMONE: Like inhibin, levels of anti mullerian hormone reflect the health of the granulosa cell[4].

1.8 to 2.8 ng/ml is considered normal AMH. The values less than 1.8 is considered low whereas values more than 2.8 indicate higher AMH and PCO patients.

High Basal LH Levels

A significant reduction in the rate of fertilization was observed in women with raised basal LH levels (greater than one standard deviation from the mean) undergoing treatment with IVF with ovarian stimulation using clomiphene citrate (CC), hMG or a combination of the two.

The effect of raised LH levels in the follicular phase of spontaneous menstrual cycles was also investigated and found to be detrimental[5]. A higher likelihood of pregnancy was observed when the LH level was <10 IU/L and the miscarriage rate was significantly higher in women with LH levels >10 IU/L

High LH in PCOS

Although LH receptors have not yet been identified in oocytes, excessive LH may disrupt granulosa cell communication in the cumulus-oophorus, which is critical to maintain the oocyte in the dictyate stage of meiosis until ovulation.

Thus, according to this theory, abnormal oocyte maturation could be responsible for the reduced fertility and increased miscarriage rates frequently encountered in PCOS

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Fertility Options in Endometriosis

Sonia Malik[1], Nidhi Jha[2]
[1]Programme Director, [2]Consultant, Southend Fertility & IVF, New Delhi

Introduction

Endometriosis is defined as the presence of endometrial-like tissue (glands and stroma) outside the uterus, which induces a chronic inflammatory reaction, scar tissue, and adhesions that may distort a woman's pelvic anatomy(1). Endometriosis is a disease of reproductive years, cyclical hormones stimulate growth but continuous hormones or lack of hormones suppress it. Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, dyspareunia and history of infertility(2).

Epidemiology

It is a very common debilitating disease that occurs in 6 to 10% of the general female population; in women with pain, infertility, or both, the frequency is 35–50%(3). About 25 to 50% of infertile women have endometriosis, and 30 to 50% of women with endometriosis are infertile. Infertile women are 6-8 times more likely to have endometriosis than fertile women. Mean age at presentation is 25 to 35 years, it is rare in premenarchal and post menopausal age group (<5 %). Surgery is the most reliable method to confirm the disease and since it is not done in asymptomatic women, the exact prevalence of Endometriosis is unknown. Prevalence in found to be high in Asians followed by whites and then black.

Signs and Symptoms

Typically, endometriosis causes pain and infertility, although 20–25% of patients are asymptomatic. Table 1 summarizes the frequency of the common symptoms of Endometriosis.

Table 1: Symptoms of Endometriosis and their incidence

Symptoms	Incidence
Dysmenorrhoea	60-80%
Chronic pelvic pain	40-50%
Deep dyspareunia	40-50%
Infertility	30-50%
Severe menstrual pain and irregular flow &/or premenstrual spotting	10-20%
Tenesmus, dyschezia, hematochezia or diarrhoea	1-2%
Dysuria, hematuria	1-2%

The symptoms of endometriosis do not always correlate with its laparoscopic appearance. The severity of endometriosis symptoms and the probability of its diagnosis increase with age, the incidence peaks in women in their 40s.

Endometriosis and Infertility

The relationship between endometriosis and infertility has been debated for many years. Endometriosis at all stages affects the fertility potential, more severe the disease, lesser is the fecundity"

In normal couples, fecundity is in the range of 0.15 to 0.20 per month and decreases with age. Women with endometriosis tend to have a lower monthly fecundity of about 0.02–0.1 per month(4). In addition, endometriosis is associated with a lower live birth rate.

How Endometriosis causes Infertility

A hallmark of endometriosis is inflammation and subsequent formation of adhesions in the pelvis. These distort the pelvic anatomy which in turn impacts the female partner's fertility in a variety of ways. The most direct consequence of adhesions can be disturbance of the anatomical relationship between the ovaries and fallopian tubes. Tubal blockage and formation of hydrosalpinges are usually seen in more advanced stages of endometriosis and these not only cause infertility but may also require excision before assisted conception. The anatomical impact of endometriosis is not the only mechanism through which endometriosis affects fertility. Indeed, minimal or mild endometriosis, where there is little anatomical impact, may still reduce the chance of spontaneous conception. It has been shown that endometriosis alters the composition of the peritoneal fluid deregulating a number of immunologic factors and increasing the level of reactive oxygen species. These changes may alter folliculogenesis and lead to poorer quality oocytes with reduced fertilization rates and poorer embryonic development and implantation (a). Peritoneal fluid from women with endometriosis may also affect tubal ciliary activity which in combination with anatomical distortion combine to reduce pickup of the ovum. Sperm motility and function is also affected, thus reducing further the chance of fertilization. Even if the oocyte is successfully picked up by the Fallopian tube and fertilized, women with endometriosis have functional alterations in eutopic endometrium which

may cause progesterone resistance and reduce implantation.

The management strategy of endometriosis in couples desiring fertility should take into account all these mechanisms to achieve optimal results.

Treatment

Treatment Options available

1. Expectant management
2. Medical management
3. Surgical management
4. Combined medical and surgical management

Treatment options for couples centre around two questions:

1. Is surgical treatment of endometriosis advisable to improve fertility?
2. Should the couple try to conceive spontaneously longer or seek assisted conception?

The most appropriate treatment for each couple will depend on a number of parameters including[5]:

- female partner's age,
- duration of infertility
- ovarian reserve
- semen analysis
- history of past surgery for endometriosis as well as
- endometriosis severity and location

Laparoscopy should be performed early in order to diagnose and stage the disease. It should be carried out by adequately trained operators. To complete their evaluation, patients should also have a complete ovarian reserve test including day 2–5 follicle-stimulating hormone (FSH) and Antimullerian hormone (AMH). Before any treatment decisions' can be undertaken, male factor investigations should also be completed. Defining the location and severity of endometriosis will help clinicians to estimate the probability of spontaneous conception and appropriately counsel couples. For this purpose, the earlier explained formal classification systems have been developed.

Role of Laproscopy in Endometriosis:

Laparoscopy is considered as a gold standard for diagnosis of Endometriosis.

ESHRE guideline 2013: A positive laparoscopy with positive histology is diagnostic of endometriosis. However, a positive laparoscopy with negative histology does not exclude endometriosis. According to NICE guidelines on Endometriosis 2017, Laparoscopy is indicated in suspected cases of endometriosis even if USG is normal and suspected deeper lesions in bowel, bladder or ureter. Steps should involve systemic inspection of pelvis and biopsy of suspicious areas to confirm endometriosis and exclude malignancy[6].

FOGSI guidelines 2017[7]: Laparoscopy is gold standard in diagnosis (Sensitivity: 97%, Specificity 95%). Tissue of biopsy may be of use and negative biopsy does not rule out endometriosis.

Management of the disease is based upon the staging done at Laparoscopy. There are two staging systems currently used:

1. American Society of Reproductive Medicine (rASRM) score
2. Endometrial Fertility Index Classification

Table. 2: Management is guided by the score obtained by these classifications

Treatment level	Monthly fecundity	Treatment recommendation
I	>3 %	Attempt non-ART conception for at least 1 year
II	2-3 %	Probable attempt non-ART conception, consider role of IVF
III	1-2 %	Probable IVF, refer to reproductive endocrinologist for fertility management
IV	<1 %	Refer to ART center for IVF

Expectant Management

Expectant management is indicated in the following conditions:

- Isolated minimal endometriosis without any other abnormal finding
- Unmarried females
- Young married, planning to conceive
- Patient approaching menopause (for pain)

Analgesics (NSAID'S) are advised for pain. Couple is encouraged to conceive, should be advised timed intercourse.

Medical Management

According to studies medical treatment is not effective, rather delays fertility restoration. Medical management mainly aims towards ovarian suppression, which can be achieved through either OCPs for 6-8 months or GnRH agonists for a period of 3-6 months. However, these are not recommended if the patient is planning for conception. According to ESHRE guidelines as well as FOGSI guidelines 2016, in patients for ART pre treatment with GnRH agonists for a period of 3 to 6 months is recommended if ovarian reserve is sufficient.

Surgical Management

Surgical treatment is indicated in following conditions

- **In minimal - mild Endometriosis**: Ablation of Endometriotic lesions plus adhesiolysis to improve fertility is effective to diagnostic Laparoscopy alone.
- **In moderate - severe endometriosis**: No studies available to answer the question whether surgical excision enhances pregnancy rates. A surgical approach, by normalising pelvic anatomic distortion and by adhesiolysis, may enhance fertility. Anyway more severe /advanced forms require a multidisciplinary approach.
- After surgical removal of endometriosis: there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate, but statistical significance was only reached in one study.
- Laparoscopic cystectomy for ovarian Endometriomas >4 cm diameter improves fertility compared to drainage and coagulation.
- Coagulation or laser vaporization of Endometriomas without excision of the pseudocapsule is associated with a significantly increased risk of cyst recurrence.

Surgical management of Endometriosis differs according to the stage of Endometriosis as diagnosed by Laparoscopy.

Recommendations (ESHRE, FOGSI)

AFS/ASRM stage I/II endometriosis-

- Perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than diagnostic laparoscopy.
- Consider CO2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporisation is associated with higher cumulative spontaneous pregnancy rates.

AFS/ASRM stage III/IV endometriosis

- Operative laparoscopy is recommended instead of expectant management to increase spontaneous pregnancy rates.
- In infertile women with Endometrioma there is **NO EVIDENCE** that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates.
- Excision of the Endometrioma capsule instead of drainage and electrocoagulation of the Endometrioma wall, to increase spontaneous pregnancy rates.
- Counselling with Endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary and recurrence, especially if the woman has had previous ovarian surgery.
- The GDG recommends clinicians to counsel women with endometrioma regarding the reduction of ovarian reserve following surgery. In the event of previous surgery, the decisions for repeat surgery should be done carefully

SURGERY should be complete and should be done by expert gynaecologist

Combined Medical and Surgical Treatment for Infertility:

In infertile women with endometriosis, the ESHRE and FOGSI recommends clinicians **not to prescribe** adjunctive hormonal treatment **before** or after surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.

Treatment options for ART

Patient should be sent to ART centre earlier than late.

I. AFS/ASRM stage I/II endometriosis:

- Intrauterine insemination with controlled ovarian stimulation instead of expectant management
- Intrauterine insemination with controlled ovarian stimulation, instead of intrauterine insemination alone.
- Intrauterine insemination with controlled ovarian stimulation within 6 months after surgical treatment.
- Not more than 4 cycles of IUI should be attempted before referring for ART.

II. AFS/ASRM stage III/IV endometriosis –

- ART is the best option

Indications of ART

IVF is appropriate treatment especially if:

- Tubal function is compromised,
- Associated Male factor infertility
- Other treatments have failed
- Age >35 years
- Long duration of infertility
- Presence of other associated factors for infertility.

Endometriosis has decreased per cycle conception rates than male factor or unexplained infertility. Recurrence rate of endometriosis does not increase after COH for IVF/ICSI. Long agonist protocol is the treatment of choice. Pre ART ovarian suppression with GnRH agonists for a period of 3 to 6 months increases clinical pregnancy rate upto 4 fold.

Role of Pre - ART surgery

ESHRE recommends complete surgical removal in cases of AFS/ASRM stage I/II endometriosis. However pre ART surgery is not recommended in cases of AFS/ASRM stage III/I Vendometriosis.

Surgery in advanced disease is done to relieve pain and only in case of anticipated difficulty in OPU. In infertile women with Endometrioma there is **NO EVIDENCE** that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates.

However cystectomy is recommended in cases of rupture, torsion, suspicious of malignancy.

Endometrioma: clinical variables to be considered when deciding whether to perform surgery or not in women selected for IVF.

Table. 5: Factors affecting decision for surgery before ART

Characteristics	Favours surgery	Favours expectant management
Previous interventions for endometriosis	None	≥1
Ovarian reserve[a]	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolateral disease	Bilateral disease
Sonographic feature of malignancy[b]	Present	Absent
Growth	Rapid growth	Stable

[a]Ovarian reserve is estimated based on serum markers or previous hyperstimulation cycles

[b]Sonographic feature of malignancy refers to solid components, locularity, echogeniety, regularity of shape, wall, septa, location and presence of peritonal fluid.

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Forthcoming Events

- Next Monthly Clinical Meeting on 26th July, 2019 (4:00-5:00 pm) at All India Institute of Medical Science (AIIMS).
- Breaking Silos Across: Adolescent to Menopause on 10th & 11th August, 2019 at Hotel Lalit, New Delhi. Org Chairperson – Prof Sudha Prasad
- "Masterclass in Gynaecologic Oncology' on 11th August, 2019, at India International Centre in collaboration with AGOI, AOGIN India, FOGSI and AOGD oncology Committee organized by Department of Obstetrics and Gynaecology, UCMS and GTB Hospital. Contact Dr Rashmi
- DGES Conference with IAGE & AOGD on 31st August & 1st September, 2019 at Hotel Jaypee Sidhartha, New Delhi.
- 41st Annual Conference of AOGD on 28th & 29th September, 2019 at Eros Hotel, Nehru Place, New Delhi.

To Freeze or not to Freeze

Hrishikesh D Pai[1], Manisha Takhtani Kundnani[2], Sunita Arora[3], Meenu Handa[4]

[1]Gynecologist & Head of IVF Unit, Lilavati Hospital, Mumbai, Consultant Gynecologist at Fortis Bloom IVF Centers at Fortis La Femme and Fortis Memorial Hospital, Gurugram, [2]Scientific Director & Chief Consultant Fertility Specialist, Fertility Square, The IVF Clinic, Mumbai
[3]Consultant Gynecologist, Bloom IVF Fortis La Femme, [4]Consultant Gynecologist, Fortis Memorial Hospital, Gurugram

Introduction

The field of cryopreservation has seen multiple advances in terms of optimization and innovation over the past few decades, with a drastic increase in the post thaw recoveryrates and success rates post thaw transfer. Cryopreservation program has now become an integral part of all IVF clinics. Though initially the technique was utilized to freeze surplus embryos left after the fresh embryo transfer, there are multiple indications now which warrant freezing of all viable embryos and transfer later in a subsequent cycle[1]. These include prevention of OHSS/OHSS free clinic, after the agonist trigger, the need of screening embryos for PGS/PGD, presence of endometrial-embryo asynchrony, etc. Besides these indications, recently there is an increasing trend towardselectively freezing all embryos with transfer in the subsequent cycle/s with the intent of achieving better success rates[2]. The rationale behind this elective cryopreservation of all embryos is that transferring embryos in a more physiologic milieu will result in higher pregnancy rates and less maternal and perinatal morbidity[3]. However, this approach of universal freezing is surrounded by lot of controversies and there is a continuing debate about the pros and cons of this strategy.

Indication for Embryo Freezing

In addition to freezing surplus embryos left after the transfer in the fresh cycle, the various indications where infreezing all embryos followed by transfer in subsequent remote cycleseems beneficial include:

- **Prevention of OHSS/ OHSS free clinic-** In PCOS and other women who hyperrespond to ovarian stimulation and are at high risk of OHSS (based on the number of follicles, serum estradiol levels), freezing all the embryos, suppressing the ovaries and deferring the transfer to a remote cycle, can prevents the dreaded complication. GnRh agonist is used as trigger these days to prevent OHSS as it causes early luteolysis. It however affects the luteal phase as well and there have been multiple reports of decreased pregnancy rates after use of agonist as trigger[4]. Freezing all embryos and transferring later thus seems a viable option with better success rates when GnRh agonist is used as a trigger.
- **Screening of embryos for PGS/PGD-** Screening of embryos for known genetic abnormalities or aneuploidies requires embryos to be biopsied on day3 or day 5. All the embryos are frozen and the embryos found normal are transferred in subsequent cycles.
- **Abnormal Progesterone levels**: It has been observed that if serum progesterone levels are more than 1.5ng/ml or less than 0.7ng/ml on the day of hCG, it negatively affects the pregnancy rates[5]. Freezing all embryos and thaw transfer later has been shown to have better success rates in patients with abnormal progesterone levels.
- **Thin endometrium:** Thin endometrium or sub-optimal endometrial growth on the day of trigger negatively affects the pregnancy rates. Embryo transfer in a subsequent FET cycle gives ample time for adequate endometrial preparation with or without adjuvants.
- **Patients with unexplained repeated implantation failure**: Many patients with repeated implantation failures have no discernible cause. It has been suggested that supraphysiologic levels of estradiol and progesterone following COS can impair endometrial receptivity and cause implantation failure. As uterine environment is more conducive in FET, freeze all and thaw ET is beneficial in these patients.
- **Social embryo or egg freezing:** This allows for fertility preservation enabling women to have their own biological child at a later date.
- **Electively freeze all- normoresponders with normal progesterone levels and good endometrium.** Currently, there is an increasing trend towards electively freezing all embryos with transfer in the subsequent cycle/s. it has been suggested that transferring embryos in a more physiologic environment will result in higher pregnancy rates with morbidity. However, the strategy is surrounded by many pros and cons. The additional cost of freezing and thawing adds financial burden on the patient and extra workload for the lab.

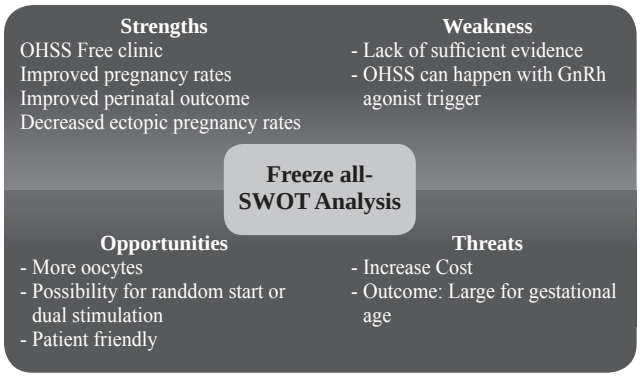
Advantages of Freeze-All

1. **OHSS free clinic** - Increased maternal safety and decreased morbidity:one of the dreaded complications of ovarian stimulation is OHSS. The newer protococls using GnRH antagonist to prevent prematutre LH surge and use of GnRhagonist as trigger and freeze all embryos, have more or less eliminated the risk of OHSS, though rare reports of OHSS after agonist have been reported.
2. **Improved Pregnancy Rates** - A higher implantation, clinical and ongoing pregnancy rates have been observed after FET than after fresh transfer[6]. Improved embryo-endometrial synchrony, and abolition of possible negative effect of ovarian stimulation on endometrial receptivity could be the possible explanation for better results after FET.
3. **Decreased incidence of ectopic pregnancy**: FET have been shown to have reduced incidence of ectopic pregnancy in many large retrospective studies[7,8]. It has been suggested that ovarian stimulation may have a negative effect on endometrial receptivity thereby increasing possibility of ectopic pregnancy. FET negates this negative impact of ovarian stimulation there by reducing the incidence of ectopic gestation.
4. **Better perinatal outcomes:** Various early researchershad observed that children born after ART are prone to preterm delivery, and have low birth weight, small for gestational age babies with increased perinatal mortality, when compared to those conceived naturally[9,10]. Recent studies have however shown that the children born after frozen embryos thaw transfer cycles have better perinatal outcome compared to those born after transfer in fresh cycles[11]. The incidence of preterm birth or low birth weight babies was found to be similar in FET cycles and natural conceptions[12]. Based on these findings it has been extrapolated that conventional ovarian stimulation can lead to abnormal hormonal milieu and suboptimal endometrial development which can lead to such adverse perinatal outcomes. Better intrauterine environment during FET not only improves the implantation and pregnancy rates but may also have a positive effect on fetal development[13].
5. **Possibility for random start protocols or dual stimulation:** Freeze all strategy allows for the possibility of starting stimulation on any day of the cycle or for dual stimulation in the same cycle in patients with low ovarian reserve. Studies have shown no difference in the perinatal outcomes of children born after luteal phase or follicular phase stimulation making this a viable option which can be more convenient for patient as well as physician[14].
6. **More oocytes**: As the freeze-all strategy eliminates the concerns about implantation window, a delay in trigger can be attempted with hope of retrieving more mature oocytes.
7. **Patient friendly**, elimination of cumbersome estrogen, progesterone hormonal monitoring.

Disadvantages of Electively Freezing all Embryos

1. **Increased cost-** The freeze all strategy adds additional financial burdens of cost of freezing and thawing as compared to fresh transfers.
2. **Not enough evidence to support the efficacy:** The available evidence showing advantage of freeze all strategy over fresh transfers is mostly in hyper responders / PCOS[15,16]. Extrapolation of these results to IVF cycles in general warrants caution. More randomized controlled trial analyzing its efficacy in normo-responders are needed before such strategy can be universally applied to all IVF cycles.
3. **Increased duration of treatment and more time to conception:** Freeze all and transfer in remote cycle increases the duration of treatment and time to conception which can add to patient frustration.
4. **OHSS following GnRH agonist trigger:** There have been occasional reports of severe OHSS following GnRH agonist trigger without luteal phase supplementation[17,18], implying that use of GnRh agonist trigger doesn't completely eliminates the risk of the dreaded complication.
5. **Large for gestational age babies:** There have been few reports showing that babies born after FET cycles are large for gestational age compared to those born after fresh transfers[19,20]. LGA babies raise a significant concern as these can be associated with adverse perinatal outcomes like still birth, birth asphyxia, shoulder dystocia, hypoglycemia etc. Whether LGA in FET cycles is related to freezing/ thawing procedure per se needs further evaluation.

SWOT analysis-Freeze all strategy



Summary

Embryo freezing is an intricate part of all IVF programs these days. The technique is definitely beneficial in certain situations like prevention of OHSS, thin endometrium, embryo-endometrial asynchrony, need of PGS/PGD, etc. However, whether electively freezing all embryos in all patients followed by subsequent thaw ETs is beneficial over fresh transfers is still debatable and warrants further studies and randomized controlled trials especially in normo-responder group.

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Luteal Phase Support-in ART cycles

Neena Malhotra[1], Anshu Yadav[2]

[1]Professor, [2]DM Resident (Reproductive Medicine), ART Division, Deptt. of Obstetrics & Gynaecology, All India Institute of Medical Sciences, New Delhi

Introduction

The need for hormonal support of the luteal phase in assisted reproductive technologies (ART) has historically been an important and debated topic among reproductive specialists. Luteal phase is the time period between ovulation and either the establishment of a pregnancy or the onset of menses two weeks later**.** Luteal phase support(LPS) in ART is the method of supporting the process of implantation with the administration of medications.

Luteal Phase in Normal Menstrual Cycles

After ovulation, the follicle collapses and the remaining granulose cells, which have acquired LH receptors under the influence of LH, rapidly undergo luteinisation and the formed corpus luteum produces progesterone and estrogen. If implantation occurs, progesterone production is restored by human chorionic gonadotrophin (hCG) release from the trophoblastic tissue.

Pathophysiology of Luteal Phase in ART Cycles

In ART cycles it is well established that luteal function is compromised[1].

There are various reasons suggested for luteal phase abnormalities in ART cycles

1. Supraphysiological concentrations of steroids due to multifollicular development during ovarian stimulation directly inhibit LH release via negative feedback actions at the HPO level and leading to defective functioning of corpus luteum.
2. With the use of GnRh agonists it takes 2-3 weeks for the pituitary function to resume completely and so the absence of LH due to pituitary suppression deprives the corpus luteum from this LH.
3. Process of follicular aspiration for oocyte retrieval disrupt the functioning of corpus luteum due to the aspiration and mechanical disruption of granulose cells. The severity of the disruption depends on the vigorousness and the number of aspirations.

Earlier it was thought that luteal phase defect occurs only in long GnRh-agonist protocol[2] due to immediate recovery of pituitary gonadotrophin release just after discontinuation of the GnRH antagonists, hypothesized that the luteal phase would be less disturbed in antagonist cycles[3]. But in further studies serum LH levels were low in luteal phase of GnRH antagonist–treated cycles, regardless of the regimen used to induce oocyte maturation. So, luteal phase support should be considered in IVF cycles with either of two.

Options for luteal phase support

The role of estradiol for luteal phase support is currently debated. But progesterone and hCG can be administered. Recently the use of GnRH agonists has also been seen in various studies.

1) Progesterone- most commonly used modality for luteal phase support. Natural progesterone has no adverse effects[4]. Synthetic derivatives i.e. 19-nortestosterone derivatives- resist enzymatic degradation and can be given orally, but secondary effects like mood changes, depression, virilization, decreases in high-density lipoproteins(HDL), and possibly teratogenic effect that limits their use during fertile cycles.

It is usually given in doses of oral dydrogesterone(30 mg/day), i.m progesterone (50-100 mg/day), aqueous progesterone s/c (25mg/day), vaginal tablet (600mg/day), vaginal progesterone 8% gel-(90mg/day). But there are no standard guidelines for the dosage and routes which one is to be preferred it varies from centre to centre.

Comparison Between Routes of Progesterone Administration

There are characteristic endometrial histological changes for every route like orally, vaginally, or i.m. injection through which progesterone can be administered[5]. Oral method have erratic absorption and requires a higher dose due to " first-pass" liver metabolism, lower bioavailability and have sedative and anxiolytic effects[6]. Micronization increase the efficiency of delivery due to decrease in particle size and shortening of its dissolution time[7]. Intramuscular injections are painful and difficulty to self administer. Vaginally delivered progesterone due to preferential trafficking to the uterus leads to a higher progesterone

concentration in the endometrial tissue compared to the blood serum. Vaginal anatomy with its rugae and rich vascular plexus provides an ideal environment for absorbing drugs and also bypasses the first pass hepatic effect and avoid undesired side effects with more consistent serum levels, which can remain elevated for up to 48 hours[8].

So the use of oral progesterone is clearly inferior to intramuscular or vaginal administration and is associated with an increased rate of side effects due to its metabolites. While intramuscular delivery of progesterone continues to remain an option, an increasing number of fertility specialists prefer the vaginal route of delivery. At present, there are insufficient data for a direct comparison between intramuscular and vaginal progesterone therapy; therefore, physicians should be guided by their own clinical experience.

2) GnRh –agonist luteal support

GnRHa is also recently being used as a modality for luteal phase support. Studies have shown that single injection of GnRH-agonist (triptorelin, 0.1 mg), given on luteal day 6, significantly improved the pregnancy, implantation, and delivery rate, compared with a placebo, in both GnRH-agonist and antagonist protocols. This effect was more pronounced in patients on the GnRH- antagonist protocol[9] There is no increase risk of birth defects seen with inadvertent administration of GnRHa during a conception cycle.

3) Human chorionic gonadotropins (hCG)

Luteal phase support with hCG is not superior to progesterone. In a recent Cochrane review and meta-analysis[10], including 15 studies,investigated progesterone versus hCG regimens even with subgroup analysis of progesterone versus hCG and progesterone versus progesterone + hCG. No significant difference was seen between the interventions, except for OHSS.

Timing of Start and Duration LutEal Support

Most IVF practitioners arbitrarily start progesterone supplementation after oocyte retrieval and elect to continue it, if the patient is pregnant, until 8 to 12 weeks of gestation. This practice is based mostly on relying on ‘‘experience of others’’ and a ‘‘comfort level’’ on the part of clinicians to do what is ‘‘necessary’’ to maximize the success rates.

Conclusion

Luteal phase supplementation in IVF stimulated cycles is a well-established practice that will continue in the future. Success rates seem similar with IM and vaginal administration with patient preference for the vaginal route.

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Ovarian Hyperstimulation Syndrome

Sudha Prasad[1], Saumya Prasad[2]
[1]Director Professor and IVF Coordinator, [2]Senior Resident IVF & Reproductive Biology Centre, Maulana Azad Medical College, New Delhi

The ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation or in early pregnancy. The syndrome was first reported in 1943 (Rydberg et al.[1], 1943; Davis et al.[2], 1944). It is typically associated with exogenous Gonadotropin stimulation & is rarely observed with other agents (e.g. Clomiphene citrate, Gonadotropin releasing hormone analogues). The first fatal cases were described in 1951 by Gotzsche (EstebanAltirriba, 1961).[3]

The incidence of OHSS varies between different types of fertility treatment. In conventional cycle of in vitro fertilisation (IVF), mild OHSS has been estimated to affect around one-third of cycles, while the combined incidence of moderate or severe OHSS varies from 3.1% to 8%.[4] OHSS is rare following ovulation induction with clomiphene, or monofollicular ovulation induction with gonadotropins, but it has been reported. Very rarely, OHSS may occur spontaneously, in association with pregnancy[5]

Certain patients and cycle characteristics increase the risk of OHSS[6] (**ASRM 2016**):

- Young patients < 35 years with good ovarian reserve.
- Lean women
- Polycystic Ovarian syndrome
- Women with Previous history of OHSS
- Increased antral follicular count (> 24)
- Increased anti mullerian hormone levels (>3.4ng/ml)
- High or rapidly rising E2 levels (> E2 3,500 pg/ml)
- Development of ≥25 follicles
- ≥24 oocytes retrieved

Etiopathogenesis of OHSS

The primary physiological change underlying OHSS is increased capillary permeability with the resulting loss of fluid into the third space. In the susceptible patient, human chorionic gonadotropin (hCG) administration for final follicular maturation and triggering of ovulation is the pivotal stimulus for OHSS, leading to overexpression of vascular endothelial growth factor (VEGF) in the ovary, release of vasoactive-angiogenic substances such as interleukins, tumor necrosis factor-α, endothelin-1 which causes increased vascular permeability, loss of fluid to the third space, and full-blown OHSS.[7]

Diagnosis

The diagnosis of OHSS is made on clinical grounds. Typically patient presents with abdominal distension and discomfort following the hCG injection which is used to promote final follicular maturation prior to oocyte retrieval. There may be a preceding history of an excessive ovarian response to stimulation, but the absence of such a history does not rule out a diagnosis of OHSS.

OHSS is clinically divided into two groups: **early and late OHSS**.

'**Early**' OHSS usually presents within 7 days of the hCG injection and is usually associated with an excessive stimulation response.

'Late' OHSS typically presents 10 or more days after the hCG injection and is usually the result of endogenous hCG derived from an early pregnancy. Late OHSS tends to be more prolonged and severe than the early form.[8]

Main Symptoms of OHSS are:

- Abdominal bloating
- Abdominal discomfort/pain, need for analgesia
- Nausea and vomiting
- Breathlessness, inability to lie flat or talk in full sentences
- Reduced urine output
- Leg swelling
- Vulval swelling

Differential diagnosis of OHSS

Important differential diagnoses include pelvic infection, pelvic abscess, appendicitis, ovarian torsion or cyst rupture, bowel perforation and ectopic pregnancy. OHSS should not, therefore, be the 'default diagnosis' for women presenting with abdominal pain during fertility treatment.

Characteristics in History

- Time of onset of symptoms relative to trigger
- Medication used for trigger (hCG or GnRH agonist)
- Number of follicles on final monitoring scan
- Number of eggs collected
- Were embryos replaced and how many?
- Polycystic ovary syndrome diagnosis?

Examinations:

- **General:** assess for dehydration, oedema (pedal, vulval and sacral); record heart rate, respiratory rate, blood pressure, body weight.
- **Abdominal:** assess for ascites, palpable mass, peritonism; measure girth.
- **Respiratory:** assess for pleural effusion, pneumonia, pulmonary oedema.

Investigations:

- Complete blood count
- Haematocrit (haemoconcentration is seen in OHSS)
- C-reactive protein (severity)
- Urea and electrolytes (hyponatraemia and hyperkalaemia are observed in OHSS)
- Serum osmolality (OHSS is characterised by hypo-osmolality)
- Liver function tests (elevated enzymes and reduced albumin are noted)
- Coagulation profile (elevated fibrinogen and reduced antithrombin)
- hCG (to determine outcome of treatment cycle) if appropriate
- Ultrasound scan: to measure ovarian size, pelvic and abdominal free fluid. Ovarian Doppler should be considered if torsion suspected.

Other tests that may be done according to severity

- Arterial blood gases
- D-dimers
- Electrocardiogram (ECG)/echocardiogram
- Chest X-ray
- Computerised tomography pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan

Several schemes have been developed for classifying the severity of OHSS[9-12], with no clear agreement between investigators.

Proposed RCOG classification of severity of OHSS published in greentop guideline no.5 in February 2016.

Mild OHSS:

1. Abdominal bloating
2. Mild abdominal pain
3. Ovarian size usually < 8 cm

Moderate OHSS

1. Moderate abdominal pain
2. Nausea ± vomiting
3. Ultrasound evidence of ascites
4. Ovarian size usually 8–12 cm

Severe OHSS

1. Clinical ascites (± hydrothorax)
2. Oliguria (< 300 ml/day or < 30 ml/hour)
3. Haematocrit > 0.45
4. Hyponatraemia (sodium < 135 mmol/l)
5. Hypo-osmolality (osmolality < 282 mOsm/kg)
6. Hyperkalaemia (potassium > 5 mmol/l)
7. Hypoproteinaemia (serum albumin < 35 g/l)
8. Ovarian size usually > 12 cm

Critical OHSS

1. Tense ascites/large hydrothorax
2. Haematocrit > 0.55
3. White cell count > 25 000/ml
4. Oliguria/anuria
5. Thromboembolism
6. Acute respiratory distress syndrome

Rarely, OHSS may be associated with life-threatening complications, including renal failure, acute respiratory distress syndrome (ARDS), haemorrhage from ovarian rupture, and thrombo-embolism.

Management of OHSS?

Women with OHSS can be managed as outpatient or inpatient according to symptoms and severity

1. **OUTPATIENT:**

   Women with mild and many moderate OHSS can be managed on an OPD basis. Baseline history, examination and investigation should be done for these patients.

   A. Women should be encouraged to drink to thirst rather than to excess.[13] Fluid intake of atleast 1 litre is advised. Outpatient management may be aided if patients are able to maintain fluid input–output charts. Urine output of less than 1000 ml per 24 hours or a positive fluid balance of greater than 1000 ml over 24 hours should prompt medical review to assess severity.

   B. For pain relief analgesia using paracetamol or codeine is appropriate. **NSAIDS should not** be used as they may compromise renal function in patients with OHSS.[14]

   C. Women should be advised to avoid strenuous activity and sexual intercourse for fear of injury or torsion of ovaries.

   D. Women should continue progesterone luteal support but hCG support is not to be given.

   E. Paracentesis of ascitic fluid may be carried out on an outpatient basis by the abdominal or

transvaginal route under ultrasound guidance.

F. Review every 2-3 days is likely to be adequate.

G. Baseline laboratory investigations should be repeated if the severity of OHSS is thought to be worsening. Haematocrit is a useful guide to the degree of intravascular volume depletion**.**

Urgent clinical review is necessary if women develops any of these signs[15]:

1. Increasing abdominal distension and pain
2. Shortness of breath
3. Tachycardia or hypotension
4. Reduced urine output (less than 1000 ml/24 hours) or positive fluid balance (more than 1000 ml/24 hours)
5. Weight gain and increased abdominal girth
6. Increasing haematocrit (greater than 0.45).

2. **INPATIENT**

A. Hospital admission should be considered for women who:

1. Are unable to achieve satisfactory pain control
2. Are unable to maintain adequate fluid intake due to nausea
3. Show signs of worsening OHSS despite outpatient intervention
4. Are unable to attend for regular outpatient follow-up
5. Have severe/ critical OHSS.

B. Multidisciplinary assistance should be sought for all women with critical or severe OHSS who have persistent haemoconcentration and dehydration.

C. Features of critical OHSS should prompt consideration of the need for intensive care.

D. A clinician experienced in the management of OHSS should remain in overall charge of the woman's care.

E. **Monitoring:** Women admitted with OHSS should be assessed at least once daily. Blood pressure, pulse, respiratory rate should be monitored 4 hourly. Body weight, abdominal girth, and fluid intake and output should be measured on a daily basis, along with complete blood count, haematocrit, serum electrolytes, osmolality, coagulation profile and liver function tests and ultrasound to assess ovarian size and ascitis.

F. **Management of symptoms:** Relief of abdominal pain and nausea forms an important part of the supportive care of women with OHSS. Analgesia with paracetamol and opiates, if required, is appropriate, while NSAIDs should be avoided as they may compromise renal function.[14] Antiemetics drugs should be used in possibility of early pregnancy such as prochlorperazine, metoclopramide and cyclizine.

G. **Management of fluid balance:**

1. Allowing women to drink to thirst represents the most physiological approach to replacing volume.
2. Women with severe OHSS with persistent oliguria and haemoconcentration despite initial colloid volume expansion may need invasive monitoring and should be discussed with the anesthetist.
3. I/V crystalloids such as normal saline should be used. Most women will need a fluid intake of 2 to3 litres in 24 hrs guided by a strict fluid balance chart.
4. Diuretics should be avoided as they further deplete intravascular volume, but they may have a role in a multidisciplinary setting if oliguria persists despite adequate fluid replacement and drainage of ascites.
5. Women with persistent haemoconcentration and/or urine output less than 0.5 ml/kg may benefit from colloids. Human albumin, 6% hydroxyethylstarch (HES),dextran, mannitol and haemaccel have been used for this purpose. These hyperosmotic agent act by increasing intravascular oncotic pressure which draw third-space fluid back into the intravascular space.

H. **Management of ascitis and effusion:**

Indications for paracentesis include the following:

1. Severe abdominal distension and abdominal pain secondary to ascites
2. Shortness of breath and respiratory compromise secondary to ascites and increased intra-abdominal pressure
3. Oliguria despite adequate volume replacement, secondary to increased abdominal pressure causing reduced renal perfusion.

Paracentesis should be carried out under ultrasound guidance and can be performed abdominally or vaginally.

I. **Management of risk of thrombosis:**

Severe OHSS is a prothrombotic state due to

haemoconcentration and vascular endothelial dysfunction. The incidence of thrombosis inwomen with severe OHSS is between 0.7% and 10%.[16] Women with severe or critical OHSS and those admitted with OHSS should receive LMWH Prophylaxis. The duration of LMWH prophylaxis should be individualised according to patient risk factors and outcome of treatment.

J. **Role of GnRH antagonist and cabergolin:** one obervational study[17] has suggested that GnRH antagonist (cetrorelix, ganirelix) 0.25 mg daily from days 5 to 8 post oocyte retrieval administration in women with established severe early OHSS may result in quicker regression of the syndrome. Another observational studies[18]also suggest that dopamine agonists (cabergolin) 0.5 mg daily for 8 days may have a beneficial role in the treatment of established OHSS.

K. **Role of surgery:**

Surgery is only indicated in patients with OHSS if there is a coincident problem such as adnexal torsion, ovarian rupture or ectopic pregnancy.

Risks associated with pregnancy and OHSS?

The incidence of multiple pregnancies, GDM, placental abruption, preeclampsia, prematurity and low birthweight is higher in cases of pregnancy complicated by severe OHSS. Therefore, such a pregnancy should be considered as a high risk pregnancy, and followed/treated as such.[19]

Prevention of OHSS?

Risk of OHSS should be assessed in all patients undergoing ovarian stimulation. Methods that can be used in order to prevent OHSS in these patients are[6]**: (ASRM 2016)**

A. **Primary**

1. **Insulin- Sensitizing agents:** Metformin suppresses insulin levels & decreases ovarian androgen production with improved ovulatory rates. By improving intraovarian hyperandrogenism, it is theorized that metformin can affect the ovarian response by reducing the number of nonperiovulatory follicles and thereby reduce estradiol secretion. Dose: 500mg three times daily or 850 mg twice daily during IVF stimulation in PCOS patients reduces incidence of OHSS.
2. **Reducing dose of Gonadotropins** (Mild/ Minimal protocol): using low dose of gonadotropins for stimulation in high risk patients reduces the risk of OHSS.
3. **GnRH antagonists protocols:** The use of antagonist compared with long GnRH agonist protocols was associated with a large reduction in OHSS and there was no evidence of a difference in live-birth rates.
4. **Low dose of HCG:** The trigger of oocyte maturation with low dose of HCG in high-risk patients reduces the risk of OHSS
5. **Alternative agents to HCG for trigger**: Use of GnRH agonists (0.2–0.3 mg triptorelin, 0.5 mg buserelin, 0.5-4 mg leuprolide acetate) instead of HCG for trigger results in a lower incidence of OHSS.
6. **Avoiding HCG for Luteal phase support**
7. **In vitro oocyte maturation (IVM):** It involves retrieval of immature oocytes at the germinal-vesicle stage followed by IVM & ICSI.
8. **Aspirin:** Aspirin decreases the level of histamine, serotonin, platelet-derived growth factor, or lysophosphatidic acid, that can further potentiate the physiologic cascade of OHSS. Dose: 100 mg aspirin given from the first day of the menstrual cycle when IVF was performed, and continued until menstruation, a negative pregnancy test, or the ultrasonographic detection of embryonic cardiac activity.

B. **Secondary**

1. Cycle cancellation
2. **Coasting**: Coasting involves withholding further gonadotropin stimulation & delaying hCG administration until E2 levels plateau or decrease significantly. Coasting should not be more than 3 days as it is detrimental for oocyte quality.
3. **Cryopreservation/ Segmented cycle:** Cryopreservation involves freezing of all embryos to be thawed & transferred at a later date. Early OHSS may occur but it almost eliminates the risk of late OHSS.
4. **Intravenous albumin and HES:** This is high molecular fluid.
5. **Dopamine agonists**: Treatment with a dopamine-receptor agonist such as cabergoline may result in a reduction of VEGF production and a subsequent reduction in OHSS. Dose :0.5 mg daily for 8 days from the day of hCG trigger.
6. **Calcium gluconate infusion**: Calcium infusion (10 ml of 10% IV Ca gluconate in 200 ml saline on the day of oocyte retrieval and days 1, 2, and

3 after oocyte retrieval) can effectively prevent severe OHSS and decreases OHSS occurrence rates.

7. **Luteal phase GnRH antagonist** :0.25 mg daily from day 5 -8 post OPU with or without embryo transfer causes rapid resolution of early onset severe OHSS by decreasing the serum estradiol level.

OHSS free clinics

The concept of OHSS free clinic is need of hour in ART today. This approach includes pituitary down-regulation using a GnRH antagonist, ovulation triggering with a GnRH agonist, vitrification of oocytes or embryos and transfer of embryos later in unstimulated cycle (Frozen embryo transfer).[20]

Key Points

1. Ovarian hyperstimulation syndrome is a mostly iatrogenic and self-limiting disorder which is seen in ART cycles.
2. Women at risk for this disorder should be identified prior to stimulation, and various prevention methods should be selected that minimize the risk of OHSS.
3. When signs of OHSS occur, the patient must be adequately informed and hospitalization should be proposed at the slightest deterioration.
4. The mainstay of OHSS treatment includes fluid resuscitation and prophylactic anticoagulation. Paracentesis or culdocentesis may be recommended for management of OHSS when a large amount of ascites is present.
5. Few cases of severe/critical OHSS can be life threatening therefore multidisciplinary team should be involved in management of such cases.
6. Each ART centre must try for OHSS free clinic with all precautions.

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Role of Immunotherapy in Recurrent Miscarriage/ Recurrent Implantation Failure

Neeta Singh[1], Yogita Dogra[2]

[1]Professor, [2]DM Fellow, Division of Reproductive Medicine, Department of Obstetrics & Gynaecology, All India Institute of Medical Sciences, New Delhi

Background

Adjuvant immunotherapy treatments in IVF are intended to improve the outcome of assisted reproductive technique (ART) in both the general ART population as well as subgroups such as patients with recurrent miscarriage (RM) or recurrent implantation failure (RIF). The reasoning behind the use of these therapies is that they may correct an immunological imbalance resulting in better and unrelenting implantation of the developing embryo, eventually leading to an enhanced live-birth outcome.[1]

Natural Killer Cells in Reproduction:

Natural killer (NK) cells found both in uterine mucosa and peripheral blood lymphocytes are an indispensable part of our innate immune system.They are large granular lymphocytes and are derived from haematopoietic progenitor cells in the bone marrow and express surface antigen CD 56. Mainstream (90%) of peripheral NK (pNK) cells are CD 56 dim and CD 16+ whereas most of uterine NK (uNK) cells are CD 56 bright and CD 16-. NK cells by liberating granular components (perforins, granzymes) within their cytoplasm or by secretion of cytokines such as interleukin-10, tumour necrosis factor alpha, transforming growth factor – beta and interferon-gamma cause cytotoxicity by inducing apoptosis or lysis of target cells.[2] The number of CD56+ cells fluctuates during various phases of the menstrual cycle with an exponential increase in mid-secretory phase starting 6-7 days after LH surge, the beginning of an assumed time of implantation.

NK cells in RIF/RM:

The increased uNK cells in the endometrium of women with reproductive failure (such as infertility, RM and pre-eclampsia) has evoked their role in the pathogenesis. However, the outcomes from several studies are diverse, and despite the advent of the measurement of the number of cells in clinical practice, there is presently no resounding evidence they are the cause of reproductive failure.[3]

A number of studies have shown raised peripheral blood natural killer (PB NK) cells (both the total CD56+ and CD56dim populations) in women with RIF[4] Raised uNK cells in prepregnancy endometrium from women with RIF after IVF has also been observed.[5]

The pro and anti-inflammatory cytokines form a tricky signalling network, and the physiological balance between them is desperate for embryo implantation and pregnancy maintenance. The proinflammatory cytokines include Th1-type cytokines (such as IFN-γ and TNF-α) and other cytokines (such as IL-1, IL-6), whereas the anti-inflammatory cytokines are Th2 type cytokines (such as IL-4 and IL-10) and other cytokines (such as TGF-β1).

Kwak-Kim et al. reported that infertile women with multiple implantation failures have significantly elevated Th1/Th2 cytokine-producing cell ratios in the peripheral blood when compared to normal controls.[6]

Immunotherapy in RIF/RM:

1. Corticosteroids: For the likelihood of successful implantation, the administration of corticosteroids around the time of implantation has been wished-for as an approach to normalize NK cell activity and cytokine expression, and subdue the inflammatory mediators to improve the endometrial receptivity. However, several RCTs have failed to demonstrate any effect of peri-implantation corticosteroids on embryo transfer (ET) outcome.[7] In contrary, improved ET outcome with corticosteroids has been observed in patients with serum autoantibodies like antithyroid antibodies, ANA positive, men with anti-sperm antibodies etc.[8]

   Dosage protocols used by various investigators:

   - 0.5 mg dexamethasone for five days from time of ovulation to ET;
   - 5 mg prednisolone daily from the day of oocyte retrieval to pregnancy test;
   - 20 mg of prednisolone daily for two weeks before IVF in men with antisperm antibodies.

2. G-CSF: It is a hematopoietic-specific cytokine produced by bone marrow cells, stromal cells, fibroblasts, and macrophages, which mend macrophage phagocytosis, as well as oxidation, which is decisive for embryo implantation. G-CSF also stimulates neutrophil proliferation, recruits dendritic cells, and regulates the T-cell response.

Besides, G-CSF affects embryo implantation by fostering vascular remodelling of the endometrium, local immunomodulation, and the expression of genes involved in cell adhesion. The subcutaneous injection of G-CSF can improve the outcome of patients with recurrent miscarriage[9] and the intrauterine infusion of G-CSF in women with a thin endometrium increases the thickness of the endometrium and pregnancy rate.

Dosage protocols used in various studies:

- Available as 0.5 ml single-use prefilled syringe containing 300 µg of Filgrastim (sterile, clear, and colourless preparation)
- Fresh cycle protocols:
  a) 300 microgram (0.5ml) intrauterine instillation on day of hCG trigger; if ET less than 6mm on day of ovum pick up (OPU)- second dose 2 to 3 days after OPU and ET done same day;
  b) On the day of trigger – 6 to12 hrs before hCG;
  c) On the day of administration of progesterone;
  d) On the day of OPU or 5 days before ET;
  e) 2-3 days before ET.
- In the FET (Frozen embryo transfer) cycle:
  a) G-CSF instilled when dominant follicle reaches 12 x 12mm;
  b) On day 14 of FET.

3. Intravenous fat emulsions:It contains glycerine, soybean oil and egg phospholipids. While the precise mechanism by which intralipid intervenes immune modulation rests unspecified, its active ingredient, soybean oil is adept of inhibiting pro-inflammatory mediators, mainly type 1 helper T cells. It accumulates in macrophages and alters the functions of macrophages as well as reticuloendothelial system.The fatty acids within the emulsion act as ligands to stimulate peroxisome proliferator-activated receptors expressed by NK cells which decline their cytotoxicity. It also reduces Th1/Th2 ratio and suppresses abnormal NK cytotoxicity, thus enhancing the likelihood of implantation and clinical pregnancy.

   Even though the data regarding the effect of intralipid on the live birth rate is minimal, the potential for intralipid therapy as a cheap treatment strategy in improving reproductive outcome cannot be negated. Singh et al showed a statistically significant increase in implantation rate and live birth rate in women who received intravenous intralipid with prior implantation failure after IVF/ICSI.[10]

   Dosage:

   - 4 ml in 250 ml normal saline over 30-60 min intravenous infusion. Fresh cycle- on day of OPU (after retrieval). The infusion is repeated within one week of positive pregnancy test and then every two weeks until the end of the first trimester.

4. Intravenous immunoglobulin (IVIG): It contains an immunoglobulin G antibody that endorses differential cell receptor expression, reduces natural killer (NK) cell activity, and regulates the Th1/Th2 response by increasing Th2 cell production, which is valuable for clinical pregnancy.[11]

   Dosage protocols used in various studies:

   - During the IVF cycle, IVIG to be administered at 400 mg/kg body weight or 500 mg/kg body weight or dosage of 20/25 g at least once. At different stages of the treatment cycle (e.g., before gonadotropin stimulation, on day of egg retrieval, on days before embryo transfer, date of known pregnancy), IVIG to be initiated and continued for variable length of time (e.g., during pregnancy up to 7, 13, 20, or 28 weeks or until delivery).
   - 25g- At least once during the IVF cycle, additional dose in the first trimester, then four weekly if CD56+ values still elevated.
   - 400mg/kg- 24 hours before embryo transfer, Day 15 (if biochemical pregnancy confirmed), three weekly in the first trimester. 200mg/kg dose administered monthly from 13^{th} – 35^{th} week of gestation.

     Keeping in view of the expense, unclearstratification criteria, and risk associated with use; the use of IVIGshould be considered only in the context of well-designedprospective trials.[1]

5. Intrauterine peripheral blood mononuclear cell (PBMC): Keeping in view of the rationale thatmaternal immune cells are necessary to achieve immunetolerance to embryonic implantation and placentation, intrauterine infusion of PBMChas been explored as a potential therapy for patients withrecurrent implantation failure.[1] Recently, it has been validated that intrauterine administration of autologous PBMC activated by human chorionic gonadotropin (hCG) commendably improves embryo implantation and IVF outcomes not only in patients with three or more IVF failures[12] but also in patients with thin endometrial thickness.

   Dosage protocols used by various investigators:

   - The blood sample is taken on the day of trigger in order to isolate PBMCs using a separation protocol based on Ficoll. PBMC are cultured for 72 hours, 1×10^6 cells in 0.4 ml were transferred

into the endometrial cavity two days before embryo transfer or day 1 of ovum pick up.

- PBMCs were collected two days before ET, cultured with hCG (10IU/ml) for 24 hours and instilled one day before ET.

6. Tacrolimus: Th1 and Th2 mediate immune rejection and tolerance, with RIF being associated with high peripheral blood Th1/Th2 ratio. A Th1 immune response is associated with allograft, as well as embryo rejection.[6] Tacrolimus inhibits antigen-induced lymphocytic proliferation, cytotoxic T-cell formation, IL-2 receptor expression and production of IL-2 and interferon-gamma.[13]

   Dosage:

   - Tacrolimus to be started two days before ET and continued until the day of a pregnancy test, for a total of 16 days. The daily dosage of tacrolimus is 1–3 mg depending on the degree of Th1/Th2 elevation; mildly increased Th1/Th2 ratio (≥10.3 and <13.0) to be treated with 1 mg of tacrolimus daily; moderately increased Th1/Th2 cell ratio (≥13.0 and <15.8) with 2 mg of tacrolimus daily. Patients with highly increased Th1/Th2 cell ratio (≥ 15.8) have to be administered 3 mg of tacrolimus daily.

7. Adalimumab: Adalimumab, a tumour necrosis factor alpha [TNFa] blocking antibody, nurtures the hope that patients with abnormally high TNF secretion may benefit from treatment.[1]

   Dosage:

   - Two injections 40 mg each at a 2-week interval. Approximately 2 to 3 weeks following the second injection, other TNF-a/IL-10 ratio measured. If initial elevation persisted, an additional two injections to be administered approximately 3 to 4 weeks following the second injection. ET to be done 66 days after last adalimumab injection.

     Considering the risk associated with treatment, it should only be used in the context of exploratory, Institutional Review Board (IRB)-approved studies.[1]

Conclusions

Immunotherapies intended at improving the prospect of livebirth in IVF treatment have widely proven to be ineffectiveor have been insufficiently investigated to make final recommendations for their use. In the context of indeterminate benefits and significant risks of immunotherapy, further studies need to be contemplated on distinct subgroups like RIF/RM where the potential for benefits might exist.

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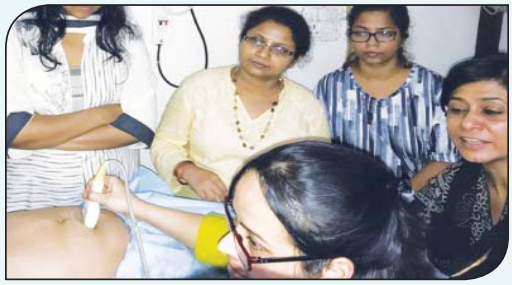

- CME on "Babies born too small, too soon" on 6th June, 2019 at SJH under Safe Motherhood Committee, Fetal Medicine and Genetics Committee & Multidisciplinary Committee AOGD & Narchi.

- CME on 'Women's Health Dialogue – Healthy Pregnancy' on 7th June, 2019 by DGF North under the aegis of AOGD



- CME on 'Managing Midlife-Ageing Gracefully' on 8th June, 2019 Org by FOGSI Midlife Committee, IMS-Delhi chapter, FOGSI Medical Education Committee under the aegis of AOGD



- CME on 'Prevention of PTL and Sonoendocrinology' on 15th June, 2019 Dr Nagori and Sonal Panchal.


- Cancer Screening and Health Camp was organised under the aegis of Oncology & Rural Health Committees AOGD 16th June, 2019 at SK wedding bells, Dilshad Garden, Delhi

- CME on 26th June, 2019 by DGF (N), Narchi, Breast & Cervical Cancer Awareness Screening and Prevention Subcommittee AOGD & Breast Committee FOGSI.

- Monthly Clinical Meeting on 28th June, 2019 at VMMC & Safdarjung Hospital

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2. Cutting Edge technology in Obstetrics and Gynaecology ( )
3. Preventive Oncology ( )
4. Miscellaneous ( )

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Preconference workshops (Tick any one)

26th September 2019

1. Ist Trimester USG - Quality Control ( )
2. Urogynaecology ( )
3. Ovulation induction and IUI ( )
4. Preventive Oncology ( )

27th September 2019

5. Endometriosis (video workshop) ( )
6. Obstetric skills ( )
7. Endoscopy ( )
8. Saving mothers ( )
9. Medico-legal aspects in Obs & Gynae ( )

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IVF in Medically Complicated Patient - A review

Kaberi Banerjee
Medical Director, Advance Fetility and Gynaecology Centre, New Delhi

Introduction

The new reproductive technologies, such as in-vitro fertilization (IVF), are becoming increasingly common, enabling infertile couples to become parents and create families. IVF is a complex series of procedures mostly involving the healthy looking infertile couples. It involves many important steps including ovarian stimulation, oocyte retrieval and laboratory techniques to achieve maximal rates of fertilization and embryo development and embryo transfer (ET).

But it can be more complicated in infertile females with medical disorders. Now a days the average women's age at marriage and child bearing is ever increasing which further increases the chances of medical illnesses in these females. These medical problems may affect the fertility of the female by affecting the egg reserve, may be it aggravated or may cause life-threatening risk during pregnancy or teratogenic effects on fetus or obstetric complications. In this review article, the precautions and the changes in the treatment course of IVF steps are explained in various medical disorders.

Hypertension

Now a day's pregnancy by assisted reproductive technology (ART) is increasingly common in our societies, especially in advanced maternal age. Hypertension is more frequent in ART-treated women as it increases the risk of placental complications, which appear to be compounded in ART versus unassisted pregnancies[1]. It will not affect the fertility of the female but the ovarian stimulation markedly increases plasma renin and urinary aldosterone excretion in coordination with increase in plasma estradiol and progesterone[2]. The renin-angiotensin system is affected which leads to high blood pressure by exogenous hormones and aggravates the condition during IVF stimulation. So, the patient should be shifted to pregnancy safe antihypertensive medications in the stimulation phase as some antihypertensive have teratogenic effects on embryo/fetus. Methyldopa (0.5–3gm/day in 2 divided doses) and labetalol (200–1200 mg/day orally in 2–3 divided doses) are appropriate first-line agents and beta-blockers and angiotensin-converting enzyme inhibitors are not recommended in pregnancy as it may cause adverse fetal effects, fetal growth restriction and low placental weight[3,4]. Methyldopa is a centrally acting α2-adrenergic receptor agonist which inhibits vasoconstriction via a central mechanism by reducing catecholamine release. It decreases central sympathetic outflow, decreasing systemic vascular resistance without decreasing cardiac output. The side effects of methyldopa include fatigue, depression, poor sleep and decreased salivation. Labetalol a non-selective β-blocking agent with vascular α-1-receptor blocking capabilities is widely used in pregnancy with side effects of fatigue, lethargy, exercise intolerance, sleep disturbance and bronchoconstriction. Oral nifedipine and verapamil are used as second line agents. Calcium channel blockers (CCBs) inhibit the influx of calcium ions to vascular smooth muscle, resulting in arterial vasodilation; nifedipine act predominantly on the vasculature and verapamil acts primarily on the heart. Side effects of CCB use in the mother include tachycardia, palpitations, peripheral edema, headaches and facial flushing. Hydralazine is predominantly used intravenously for the treatment of severe hypertension in pregnancy. It selectively relaxes arteriolar smooth muscle.

Adverse effects include headache, nausea, flushing, and palpitations. Proper surveillance of these cases can prevent the complications related to the hypertension though the standard protocol is used during the IVF procedure.

Diabetes Mellitus

Diabetes mellitus (DM) is a major public health problem worldwide[5]. It lowers the fertility of the female. In Type 1 DM, there is general dysfunction of the hypothalamic–pituitary–ovarian (HPO) axis that leads to disruption in hypothalamic pulsatile secretion of gonadotropic releasing hormone (GnRH) and lower basal level of luteinizing hormone (LH)[6]. There is higher incidence of premature menopause, antiovarian antibodies and Hashimoto's thyroiditis in Type 1 DM leading to menstrual disturbances[7]. There is higher prevalence of impaired sexual arousal and inadequate lubrication in these females. The polycystic ovarian syndrome (PCOS) is highly prevalent in women with Type 2 DM that lead to hyperandrogenism causing anovulation[7]. The strict metabolic control may prevent subfertility and also reduces the risk of congenital malformations in fetus like ventricular septal defect (VSD) and patent ductus arteriosus (PDA)[8]. Though

the mechanism of malformations is not clear, animal studies have revealed that pregestational DM induces oxidative stress, which activates cellular stress signaling leading to dysregulation of gene expression and excess apoptosis in the target organs, including the neural tube and embryonic heart[9].

As HbA1c is the measure of average glycemic control over a 3 months period, therefore, it does not necessarily reflect a level of glycemic control during organogenesis and embryogenesis. So embryo transfer can be planned if blood sugar levels are controlled inspite of high HBA1C as per many studies and also with our experience. Ideally periconceptional HbA1C should be less than 7% for planning the fertility treatment[8]. As per American Diabetes Association 2016 guidelines, the normal glucose values should be fasting <100 mg/dl, postprandial <140 mg/dl and during the night 60–90 mg/dl. If the targeted values of glucose couldn't be reached with the diet, insulin and metformin treatment should be initiated[10].

The goal of treatment in Type 1 & 2 DM is tight control of blood glucose levels and to adjust diet, exercise, metformin and insulin to achieve tight control of carbohydrate metabolism

Cardiovascular Disease

Cardiovascular disease (CVD) is one of the most common causes of mortality worldwide. Females with PCOS have increased serum concentrations of CVD risk markers like C-reactive protein (CRP), homocysteine (Hcy) etc.[11]. There is a meta analysis that suggests PCOS is significantly associated with increased risk of structural and coronary heart disease (CHD)[12]. The typical symptoms of an underlying cardiovascular issue include – chest pain, pain or discomfort in the arms, the left shoulder, elbows, jaw, or back, dyspnea, nausea and fatigue, fainting attack, sweating. It is linked to obesity, dyslipidemia, glucose intolerance and hypertension in these patients. So in cases of PCOS, controlled ovarian stimulation should be done and in cases of ovarian hyperstimulaton syndrome (OHSS), embryo transfer should be deferred with proper counseling of the couple. In OHSS, due to leakage of fluid through the impaired blood vessels both within and outside the ovary, there is massive fluid-shift from the intravesicular bed to the third compartment results in intravascular hypovolemia with concomitant development of edema, ascites, hydrothorax and/or hydropericardium further can lead to pulmonary embolism.

As we know physiological alterations occur during pregnancy like - increases in blood volume, cardiac output and heart rate, decrease in blood pressure and systemic vascular resistance with hypercoagulable state that increases the risk of thrombo-embolic events, further enhanced by venous stasis, so, prepregnancy risk assessment and counselling is indicated in females with history of heart disease who are planning for pregnancy. In mild left ventricular impairment, hypertrophic cardiomyopathy, native or tissue valvular heart disease, unoperatedatrio-septal defect (ASD) or ventricular septal defect (VSD), repaired Tetralogy of Fallot, most arrhythmias, pregnancy can be planned after taking fitness from cardiologist. In some heart diseases, pregnancy is contraindicated – Marfan syndrome with dilated aortic root, severe left heart obstructive lesions, pulmonary hypertension, and severe left ventricular dysfunction (EF < 40%)[13]. So, it is always required to take fitness from cardiologist for giving anesthesia and also for carrying pregnancy. If it is not advisable, then surrogacy is the best option[14].

Epilepsy

Epilepsy is a common neurological disorder in females. Epileptic seizures affects the fertility of the female by altering alter the hypothalamo-pituitary-ovarian axis and can lead to derangement of reproductive hormone levels which includes high LH levels, deranged LH/FSH ratio >2, high androgen (DHEA) levels and low progesterone levels. There is high incidence of PCOS in epileptic women[15]. In epileptic females hyposexuality and orgasmic dysfunction leads to decrease in libido. Antiepileptic drugs used as treatment of epilepsy may also produce reproductive and endocrinal disturbances leading to infertility[16]. In this situation, neurologist consultation is must for fitness for general anesthesia and also carrying the pregnancy. Patient should not have fit one year prior to the conception[17,18]. The pregnancy should be planned if associated with good seizure control and less fetal exposure to antiepileptic drugs. It is also important to shift the patient to pregnancy safe medications - lamotrigine and levetiracetam that are not associated with significant increased risks of congenital malformations[19]. Lamotrigine blocks voltage-gated sodium channels and stabilizes their inactive state and levetiracetam inhibits the release of the excitatory neurotransmitter by binding to synaptic vesicle protein SV2A and these may cause behavioral changes (e.g. irritability, agitation, hyperactivity, cognitive slowing) and somnolence.

Standard protocol for ovarian stimulation should be used but OHSS should be avoided. If patient is not fit

(i.e seizure episode less than 1 year) for the pregnancy, then surrogacy should be the option.

Thromboembolic Conditions

Thromboembolism is a rare but life threatening condition in IVF. Though it is not affecting the fertility of the female but the prophylaxis should be important in some cases of IVF. The risk of thrombosis is more in women with a previous DVT, who develop OHSS and over 40 years age with a thrombophilia, so, the thromboprophylaxis should be considered. It should be started at the start of GnRH agonist administration in long protocol or at the start of gonadotropin administration in antagonist protocol in the form of low molecular weight heparin (LMWH) at the dosage 0.6–1 mg per kg per day subcutaneously and compression stockings. In very high-risk cases, aspirin and warfarin can also be added. LMWH should be stopped 14 to 16 hours before oocyte pick up (OPU) to reduce hemorrhagic complications and resumed 12 to 24 hours after procedure depending on the condition[20]. Aspirin or warfarin should be stopped 5 to 7 days before OPU & start LMWH 0.6–1 mg per kg twice daily. The aspirin can be started after 24 hours of OPU and same for warfarin also in case of surrogacy. It cam be extended throughout first trimester or in severe cases throughout pregnancy[20,21].

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with characteristic exacerbations and remissions that affects multiple organ systems. In SLE, fertility is affected may be due to advanced age at the time of presentation leading to poor ovarian reserve or cyclophosphamide induced premature ovarian failure or may be due to Implantation failure because of presence of antinuclear antibody (ANA)[22]. Prepregnancy counseling is important in view of maternal morbidity (pregnancy induced hypertension, prematurity, stillbirth, SLE flare, and nephritis flare) and fetal morbidity (preterm birth, intrauterine growth restriction, neonatal death because of congenital heart block).

In SLE, IVF treatment should be indicated only in patients with normal creatinine, after complete remission of the autoimmune disease for at least 1–2 years and fitness should be taken from the rheumatologist. Controlled ovarian stimulation, use of donor eggs in case patient is not fit for IVF hormonal injections, single embryo transfer, avoidance of OHSS, administration of co-adjuvant therapy and use of estrogen and progesterone through a non-oral route may constitute the safest approach[22]. Lupus flares (renal and hematologic with the musculoskeletal flares) and thrombosis should be avoided in these cases. In very high-risk active cases (disease with significant organ impairment), surrogacy will be the best option[14].

Obesity

Obesity is a chronic (long-term) disease results from the accumulation of excess fat on the body. According to the World Health Organization (WHO), if the body mass index (BMI) equals to or is greater than 25 kg/m^2, it is considered overweight, whereas if the BMI equals to or is greater than 30 kg/m^2, it is considered obesity[23]. It affects the fertility by disturbing the hypothalamic-pituitary ovarian (HPO) axis. The sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) levels are decreased and leptin levels are increased leading to inhibition of ovarian steroidogenesis and hyperandrogenism. It is associated with an increased risk of type 2 diabetes mellitus, gall- bladder disease, essential hypertension, hypercholesterolemia, coronary heart disease, asthma and osteoarthritis. It is also associated with to PCOS. IVF treatment is difficult to plan due to menstrual irregularity. They might require a significantly higher dose of gonadotropins and longer stimulation durations, without greatly affecting the pregnancy outcomes[24]. There may be difficulty during intubation while giving general anaesthesia, sometimes difficult to perform OPU due to difficult ultrasound identification of follicles and may be difficult to do embryo transfer. Obesity impairs the response of women to assisted conception treatments leading to lower reproductive outcomes[25,26].

Thyroid Disorders

Thyroid hormones directly affect reproductive hormones. Hypothyroidism and hyperthyroidism are common, important and often reversible or preventable cause on infertility. Euthyroid reference values for TSH assay is 0.4–4.0 mIU/L, the free T_4 assay has a range of 0.3–6.0 ng/dL and total T_4 assay range is 1.00–24 µg/mL.

Hypothyroidism

Hypothyroidism is associated with decreased plasma concentrations of estrogens and androgens with deficient LH secretion. There may be reduced libido and anovulation. With IVF stimulation, the condition might become better. So, tight control of thyroid

function is must for better reproductive outcomes. As per ASRM guidelines, in hypothyroidism, TSH should be less than 2.5 µIU/ml and the treatment of choice is levothyroxine[27,28]. The thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility. Levothyroxine treatment may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L.

Hyperthyroidism

In hyperthyroidism, there may inadequate mid-cycle LH surges leading to anovulation. With IVF stimulation, the condition might exacerbrate. In hyperthyroidism, FT4 should be at the upper end reference range & low TSH level (0.1-0.4 mU/L) and propyl thiouracil (PTU) is recommended before pregnancy & in 1st trimester and in 2nd trimester it is preferable to shift to methimazole (MMI)/ carbimazole (CMZ)[29]. In recurrent IVF failure, thyroid antibodies screening should be done in euthyroid women and intravenous immunoglobulins can be given in positive cases[30]. During IVF, HCG for ovulation should be very helpful to compensate low LH levels. After embryo transfer, good luteal support should be given.

Hyperprolactinemia

Hyperprolactinemia is a common endocrine cause of infertility. It may cause galactorrhoea, headache and may be vision loss. Prolactin secreting tumours are classified as microprolactinoma (< 1 cm) and macroprolactinomas (>1cm) depending on tumour size[31]. It lowers the fertility by inhibiting 5α-reductase activity and increases adrenal androgen secretion leading to the anovulation and also induces hyperinsulinemia. Excessive prolactin secretion decreases the pulsatile release of GnRH impairing the pituitary production of FSH and LH[32]. In IVF during ovarian stimulation, prolactin and estradiol levels are increased and progesterone also induces acute release of prolactin through an increase in GnRH. There might be transitory hyperprolactinemia which further increase number of larger (> 12 mm) follicles and with more mature oocytes and better IVF success rates. If serum prolactin levels are more than 30 µg/L or in cases of galactorrhoea with normal levels, it should be controlled dung the IVF cycle with cabergoline or bromocriptine that are safe in pregnancy also and in cases of macroadenomas, trans – sphenoidal surgery will be the option if tumour is not shrinking in size. Medications should be stopped immediately after positive pregnancy test in case the size of tumour was less than 1 cm before pregnancy otherwise it is continued.

In conclusion, the prior identification and preparation of the patient at increased risk of complications will enable the clinician to avoid problems in advance, anticipate the necessary management, and optimize outcomes.

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Oncofertility - Current Trends and Recommendation

Reeta Mahey[1], Monica Gupta[2]
[1]Associate Professor, [2]DM Resident Reproductive Medicine, Department of Obstetrics and Gynaecology, AIIMS, New Delhi

Introduction

Infertility is a major concern among female cancer survivors in reproductive age group. Approximately 80% of cancer survivors suffer from reduced fertility as the treatment of most cancers involve chemotherapy and radiotherapy which may be gonadotoxic or in case of gynaecological malignancies treatment involves surgical removal of reproductive organs(1). The burden of infertility in these patients is increasing due to increase in cancer incidence and recent advances in medical and surgical treatment which has improved 5 year survival of cancer patients(2).

Oncofertility is a sub-speciality which bridges oncology and reproductive research to expand and explore options for preserving future reproduction ability in young cancer survivors(3). American Society of Reproductive Medicine (ASRM) advocates a multidisciplinary team (MDT) approach to fertility preservation (FP) which includes a medical oncologist/ haematologist, gynaecologist, psychologist, social worker and psychosocial counsellor(4). This approach will minimise the time frame for fertility preservation.

Cytotoxic agents especially alkylating agents accelerate the age related decline in follicular reserve in females and combination chemotherapies advance reproductive age by approximately 10 years resulting in premature ovarian insufficiency (POI)(5).

Methods of Fertility Preservation

The American Society of Clinical Oncologist (ASCO) have updated their recommendation in 2018 regarding FP. The following options for FP in adult females are recommended(6):

- **Embryo cryopreservation** – It is an established technique for fertility preservation
- **Oocyte cryopreservation** – This technique is no longer considered experimental as of 2012 by American Society of Reproductive Medicine (ASRM). It is an option for patients without a male partner, are unwilling to use donor semen or have religious or ethical objections to embryo freezing.
- **Ovarian transposition/Oophoropexy** can be performed in patients who need pelvic irradiation. But patients should be counselled regarding risk of radiation scatter and failure of procedure. The procedure should be performed close to radiation since there is risk of remigration of ovaries.
- **Conservative gynaecological surgery** – For early stage cervical cancer stage 1A2 to 1B with diameter less than 2 cm and invasion less than 10 mm, uterine sparing surgery, radical trachelectomy can be performed. Also in other gynaecological cancers less radical surgery like ovarian cystectomy in early stage ovarian cancers can be performed.
- **Ovarian suppression** – The evidence for ovarian suppression agents like GnRH agonist is conflicting and recommended only as a second option in cases where the established fertility preserving options (oocyte, embryo or ovarian tissue cryopreservation) are not feasible especially in young breast cancer patients with the hope of reducing the chances of chemotherapy induced ovarian insufficiency.
- **Ovarian tissue cryopreservation and future transplantation** – This method is still considered experimental in some countries but the advantages are that it can be performed immediately and there is no need of ovarian stimulation, there is full restoration of ovarian function when transplanted back and this is the only technique feasible in pre-pubertal girls. However its safety in patients with leukemias needs further investigation. This procedure is of limited benefit in patients with reduced ovarian reserve and contraindicated in patients with ovarian carcinoma or cancers that metastasize to the ovaries. Encouraging live birth rates have been reported with this technique with approximately 130 live births till date(7).
- **Sperm cryopreservation** - It is an effective technique for FP in young post-pubertal men receiving cancer treatment. Other methods such as testicular tissue cryopreservation and reimplantation are still considered experimental. Chemotherapy causes damage to quality of sperms and DNA integrity even after one cycle. Even if there is less time before initiation of chemotherapy, patients should be encouraged for sperm cryopreservation because of the possibility of future fertility with ICSI with very limited amount of sperms as well.

Treatment Protocols

Oocyte and embryo cryopreservation are the most established FP options and hence is described in detail for clinician benefit. These are the gold standard

options but require at least two weeks for ovarian stimulation and oocyte retrieval prior to start of cancer treatment. These procedures can be started any time of the cycle – follicular or luteal phase. Financial implications also need discussion as this procedure is not government funded in many countries. Only limited number of oocytes or embryos can be preserved with this procedure in contrast to ovarian tissue cryopreservation where large number of primordial follicles can be preserved and endocrine function is also restored after reimplantation.

For oocyte or embryo cryopreservation GnRH antagonist based protocol is employed for COS as it takes lesser time than conventional long agonist protocol (2 weeks versus 4-6 weeks) with equivalent oocyte yield. For women with hormone sensitive cancers aromatase inhibitor based protocols are employed. In conventional start GnRH antagonist protocol the patient has to wait for menses to start COS which may delay the cancer treatment. Hence various random start stimulation protocols are now employed for COS in these patients.

In random start COS ovarian stimulation can be started on any day of the cycle irrespective of menses. The hypothesis behind random start protocols being that there are multiple waves of follicular recruitment during inter-ovulatory interval which can be targeted for stimulation and moreover the endometrial receptivity is not of concern when stimulation is performed for cryopreservation. Various types of random start protocols can be employed[8]:

A. Early follicular start can be done if patient presents after menses and the lead follicle is less than 12 mm in diameter (Fig. 1A).

B. Late follicular start – if patient presents beyond day 7 of menses and lead follicle is > 12 mm but serum progesterone is less than 2 ng/ml. Gonadotropins are started and after spontaneous LH surge antagonist is started when the lead follicle of second cohort crosses 12 mm with rest of the procedure remaining the same (Fig. 1B).

C. Luteal phase – Once the follicle reaches 18 mm exogenous hCG or GnRH agonist trigger is given and after 2-3 days gonadotropin stimulation begun (Fig. 1C).

D. Luteal halt – In this method menses are preponed by administering injection cetrorelix 250 microgram for 2-3 days or 3 mg single dose so that there is breakdown of corpus luteum and progesterone is withheld (Fig. 1D). Only recombinant FSH should be used for stimulation as LH may prevent luteolysis.

Random start protocols have been found to significantly reduce time between FP and start of cancer treatment without compromising oocyte number, maturity or competence[9].

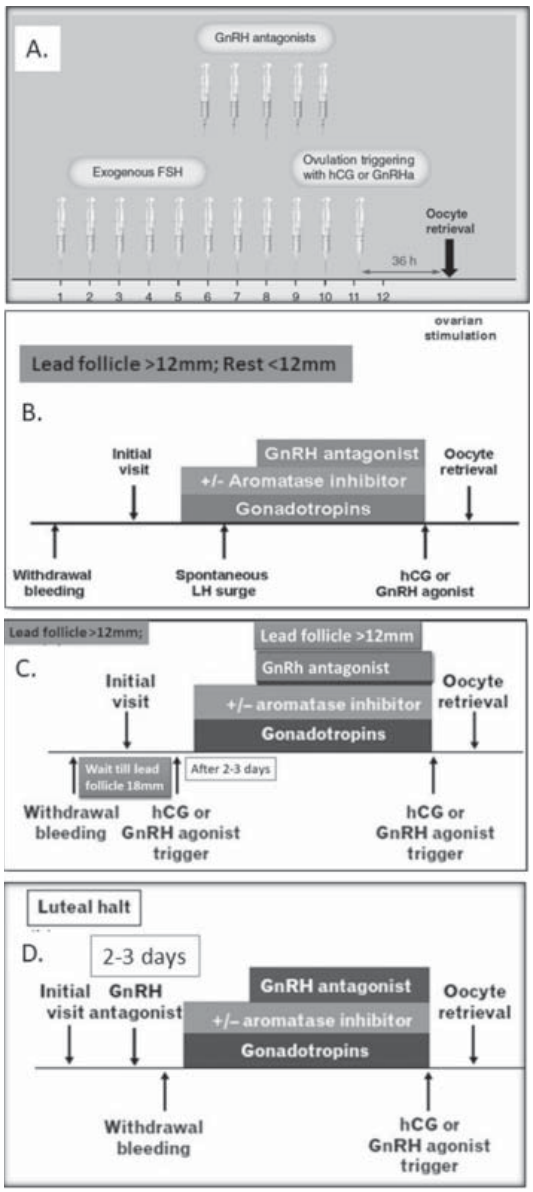

Figure 1. A. Early follicular phase B. Late follicular phase C. Luteal phase D. Luteal halt

In hormone sensitive cancers like endometrial cancer and estrogen receptor positive breast cancer supraphysiologic rise in estrogen during COS (10 fold) can be detrimental to cancer prognosis. Hence aromatase inhibitors most commonly letrozole in a dose of 2.5 to 5 mg is used during COS as shown in Figure 2. Letrozole causes significant suppression of estrogen levels (<500 pg/ml), releases negative feedback of HPO axis and hence increases follicular growth by increasing FSH. The oocyte and embryo quality is not affected when Letrozole is added either in conventional or random start protocol[10].

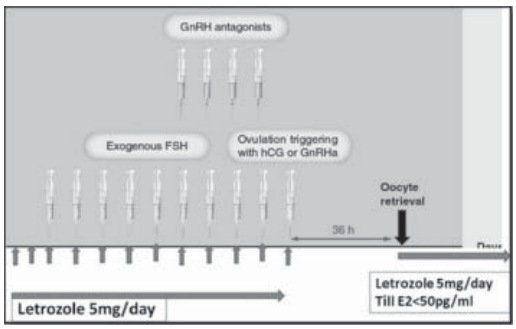

Figure 2. Stimulation protocol for hormone sensitive cancers.

Post Cancer Treatment Fertility Issues

According to ESMO, no particular time interval following cancer diagnosis is considered optimal for planning pregnancy. This will depend on multiple factors like time required for completion of cancer treatment, risk of relapse, age and ovarian reserve as well as patient wishes[11]. In patients desiring pregnancy post treatment ovarian reserve assessment should be made at least 12 months post-chemotherapy. Also a minimum of 6-12 month time interval is desired between last cancer treatment and start of controlled ovarian stimulation (COS). The safety of COS in patients with hormone sensitive tumours who are not on anticancer systemic therapy is yet to be established, however since pregnancy is generally safe in these patients, ART procedures may be considered[12].

Role of Health Care Providers

ASCO recommends that health care providers dealing with young cancer patients should include discussion on a number of oncofertility issues early during consultation and before treatment starts, including[6]:

- Risk of infertility and premature menopause with cancer treatment.
- Impact of type of cancer, disease prognosis, urgency of initiating treatment on the FP procedure.
- Undergoing any above mentioned FP treatment does not guarantee pregnancy in future.
- Offer referral for FP to reproductive specialists in patients who desire FP or are uncertain.
- FP procedures do not affect the cancer treatment outcome or prognosis.
- Post- chemotherapy return of menstruation does not always indicate a return of fertility. Approximately 40% of women less than 35 years who resumed menses post treatment were found to be sub-fertile due to diminished ovarian reserve.

The consultation should be documented in treatment notes and written information should be provided to all patients.

Conclusion

With increased survival of young cancer patients due to advanced cancer treatment and improved FP techniques, it is now possible for these patients to have their own genetic offspring. But to achieve favourable outcome for these patients there is a need to develop multidisciplinary oncofertility teams that can coordinate various aspects of oncofertility care.

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Artificial Intelligence in IVF

Rupali Bassi
Consultant, Dept. of IVF & Reproductive Biology, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi

Artificial Intelligence is now a widely accepted phenomenon coming up in the field of medicine. Currently, there is no proper definition, although it can be broadly described as machine's ability to learn and exert intelligent behavior[1].

Apart from assisted reproductive technology this novel system is currently being utilized in a wide range of clinical scenarios, as in gynecological oncology for timely and early detection of disease to the future prediction of survival. In the field of obstetrics, it has been used in assessment and analysis of fetal heart rate. This approach is also used in uro-gynaecology for successfully predicting the outcome of surgical procedures[2,3].

In spite of tremendous research in the field of in Vitro Fertilization, still only one third of the patients go home with a healthy baby. Newer technologies based on applied mathematics, bioinformatics and computational medicine are being utilized to devise and implement novel strategies for improvement in the field of assisted reproduction.

Historical Aspects

The initial few reports of use of artificial Intelligence in the field of medicine were recorded as early as the 1960s.The initial approaches included the use of Bayesian classifier which was followed by the neural networks, symbolic learning (using decision trees), and machine learning[3].The recent models have been utilizing a mode called the deep learning Artificial Intelligence. Deep learning is a modality that allows the computer to discover a structure in a large dataset using a back-propagation algorithm and conduct small changes in its parameters in order to achieve an algorithm with the optimal representation of the database.

It has been almost 20 years since the concept of artificial intelligence started when, Kaufmann et al proposed IVF using Cortex Pro neural network software. This network comprised of just four inputs primarily freezing, age, number of eggs recovered, number of embryos transferred, one hidden layer of four nodes and one output. The total predictive power of this methodology was limited to 59%.[4]

Sixteen artificial intelligence (AI) and machine learning (ML) approaches were reported last year at the 2018 Annual Congresses of American Society for Reproductive Biology (9) and European Society for Human Reproduction and Embryology (7)[5]

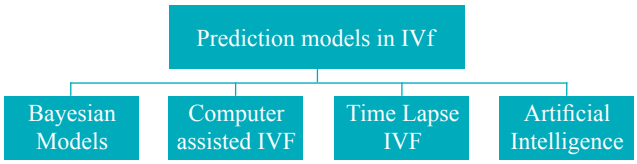

Fig 1: Outline of sophisticated models and software employed in the IVF laboratory and analysed in this review[6]

Artificial Intelligence and Infertility Management

Almost every aspect of patient care has been investigated using artificial intelligence. In dealing with male partner aspects of sperm morphology, sperm identification and their relation to IVF outcome has been analysed.

Furthermore, AI has been increasing used in identification of empty or oocyte containing follicles, assessment of oocyte and embryo quality, predicting embryo cell stages, predicting blastocyst formation from oocytes, assessing human blastocyst quality, predicting live birth from blastocysts, improving embryo selection, and also for developing optimal IVF stimulation protocols.

One of the most important characteristic feature of this system that is, "learning through training" modality. The term intelligent is used as it resembles the capacity of the brain to learn, assimilate and recall this knowledge in anticipation of a future event. The interesting feature of this modality is that the network self-adapts and changes its structural characteristics according to the information that flows through the network neurons[7].

Artificial Intelligence Technique

This method utilizes an Artificial Neural Network (ANN) approach for predicting IVF outcome. Clinically, an ANN represents a technological combination of a "learning", self-adapting and predicting system. It is an application based system that includes a number of functions e.g. it is an ability to associate symptoms to a specific disease this creates a "learning" path by cumulatively integrating specific data.

An artificial neural network comprises of simple processing elements connected together to form a network of nodes. These nodes utilize a mathematical model for processing the information.

Various neural network classifiers can be obtained by altering the network architecture and the choice of the algorithm designed. This shall infer the strength (weights) of the connections in the network to produce a desired signal flow. During the process of classification a random subspace ensemble of classifiers are used. This helps in training the classifiers by drawing a subset of all available features. As a result it is possible to partially solve the problem of low number of samples in the training set.

The artificial intelligence techniques commonly used for a classification system of biomedical images. Once the specific area of interest is delineated, it is processed and classified further categories which helps the machine to take out a simplified and desired outcomes. A multilayer Perceptron Network with using the backpropagation algorithm is commonly used in IVF scenarios. They are based on the followings steps: (i) segmentation –(ii) feature extraction; and (iii) classification.

Artificial Intelligence Techniques for Embryo and Oocyte Classification

Currently multiple morphological embryo scoring systems have been proposed and reviewed for selecting embryos to transfer. With the advancements in the precision of imaging and diagnostics this is being explored ad infinitum. Hence, the experience and expertise of the embryologist does determine the overall success of evaluation.

Morphological oocyte assessment is still controversial, although oocyte scoring systems have been proposed to help choose the best oocytes to be fertilized[11].

In order to decrease the subjectivity of these observations, specific Embryo selection algorithms using the time-lapse(TL) monitoring systems of embryo development, had been introduced into the market. Despite its excellent reviews, it has not been able to demonstrate efficacy over the conventional incubation systems.

In 2013 Manna etal compared the various AI methodologies for classifying the oocytes and embryos. He concluded that the methodology using image classification based on a textural descriptor (local binary pattern) and on a random subspace ensemble of Levenberg–Marquardt neural networks had an effective classification performance. Although the numbers used in the paper were too less and the results were preliminary, requiring further research[8].

Artificial Intelligence Techniques for Sperm Selection

Girela et al in 2013, studied the co-relation of Life style and environment on semen parameters using Artificial Intelligence. Based on simple questionnaire, they developed an artificial neural network which could predict the results of the semen analysis. They further stated that the semen parameter that is best predicted using this methodology is the sperm concentration. Although the accuracy for motility is slightly lower than that for concentration, it is possible to predict it with a significant degree of accuracy. This tool could be useful in early diagnosis of patients with seminal disorders or in the selection of candidates to become semen donors[12].

Other aspects of semen analysis and sperm selection have also been studied. Wald M with his colleagues designed an AI program for predicting the outcome of IVF/ICSI employing surgically removed spermatozoa. Amongst the multitude of factors studied only maternal age and sperm type were found to be of statistical significance using reverse regression analysis. This program was only able to success- fully predict failed attempts with an accuracy of 82%[13].

Artificial Intelligence Techniques for Predicting the outcome of IVF Cycles

As early as the turn of century there have been a lot of effort into the formulation of ANN models for prediction of IVF outcome. They are being increasingly used for enhancing and promoting personalized IVF, where it helps in providing individualized numerical estimates in predicting the IVF outcome[14]. The number of variables used are huge, thereby improving the accuracy of prediction.

A study in Australia by Tan et al studied a total of 10,208 embryos from 1,603 patients were extracted. AI was used to predict the IVF outcome in terms of the fetal heart outcome. The neural network took a raw TL video as the input and produced a continuous probabilistic score (range 0-100%) as the output. This score was calibrated to the probability that the 93% of the time, given embryo would develop into a fetal heart[15].

Artificial Intelligence Techniques for PGS

Currently, AI for embryo selection is being positioned on the market as a tool to pre screen for and identify

Table 1. Summary of features used for the prediction of IVF result.

Treatment Characteristics	Embrya Characteristics		
Type of controlled ovarian hyperstimulation (i.e., long and short agonist, antagonist protocol) FSH dosage Days of stimulation Basal E_2 (pg/mL) Peak E_2 level (pg/mL) Basal LH (mlU/mL) Basal FSH (mlU/mL) Basal AFC Inhibin B Activin AMH CA-125 Serum Vascular endothelial growth factor (VEGF) Challenge tests with clomiphene citrate Ultrasonographic markers such as the AFC, total ovarian volume and blood flow 3D ultrasonographic endometrial volume assessment on the day of hCG administration Endometrial thickness 3D ultrasonography and power Doppler angiography Follicular fluid volume at egg recovery Follicle size at egg recovery Number of eggs inseminated Selection of euploid eggs Number of normal eggs fertilized	Mean grade of embryos replaced Morphological scoring of human pronuclear zygotes Morphology score of the two best embryos available for transfer Cumulative embryo score Number of embryos cleaved (number of embryos that have been divided) Early cleavage morphology Early cleavage time Equality of blastomeres Number of embryos Fragmentation rate Regularity of cells 4-cell embryos at day 2 Appearance of cytoplasm (darkness) Freezing Prewash total motile sperm count Postwash total motile sperm count Nucleus characteristics Visibility of nuclei in the cells Prewash total motile sperm count at egg recovery Postwash total motile sperm count at egg recovery Totla number of embryos cultured Number of embryos cultured on day 3 The ratio between the number of top embryos on day 3 and the total number of cultured embryos on day 3 (quality ratio)	Female age Infertility factor Body Mass Index Mean ovarian volume (cm^3) Trauma Previous live births Previous abortions Duration of infertility Diagnosis of infertility Previous IVF cycles Smoking Transfer Data Type of catheter Transfer day Physician performing embryo transfer Embryo transfer Embryo transfer technique Transfer with or without ultrasound guidance Difficulty of transfer Type of fertilization (ICSI or IVF) Luteal support regimen	Male age Family history Personal history Sperm characteristics Sperm motility Sperm function tests Strict criteria for sperm morphology Chromatin packaging assessment Sperm DNA integrity assessment Hypoosmotic swelling test Hemizona assay Zona pellucida - induced acrosome reaction

Fig multitude of variables used to predict IVF outcome[10]

viable embryos with a low likelihood of genetic defects before subjecting them to prenatal genetic testing. This can help us in significant cost savings for couples who are planned for prenatal genetic screening[5]

Conclusion

AI is an upcoming field and this technology may become routine in clinical IVF settings within the next 5 years. It is a fully automated system, requiring no human input and hence is not subjected to any inter-grader or intra-grader variability.

Although, a very careful interpretation of the dynamics and potential of such system is required. A harmonic balance should be maintained using the clinical judgment and decision making tools. It is imperative to note that the integral parts of clinical management cannot be substituted by any form of artificial intelligence in its present form. This tool, furthermore, requires a complete and extensive training and a robust statistical evaluation of the degree of its predictive power in order to be adopted in an optimal way and establish its dynamics.

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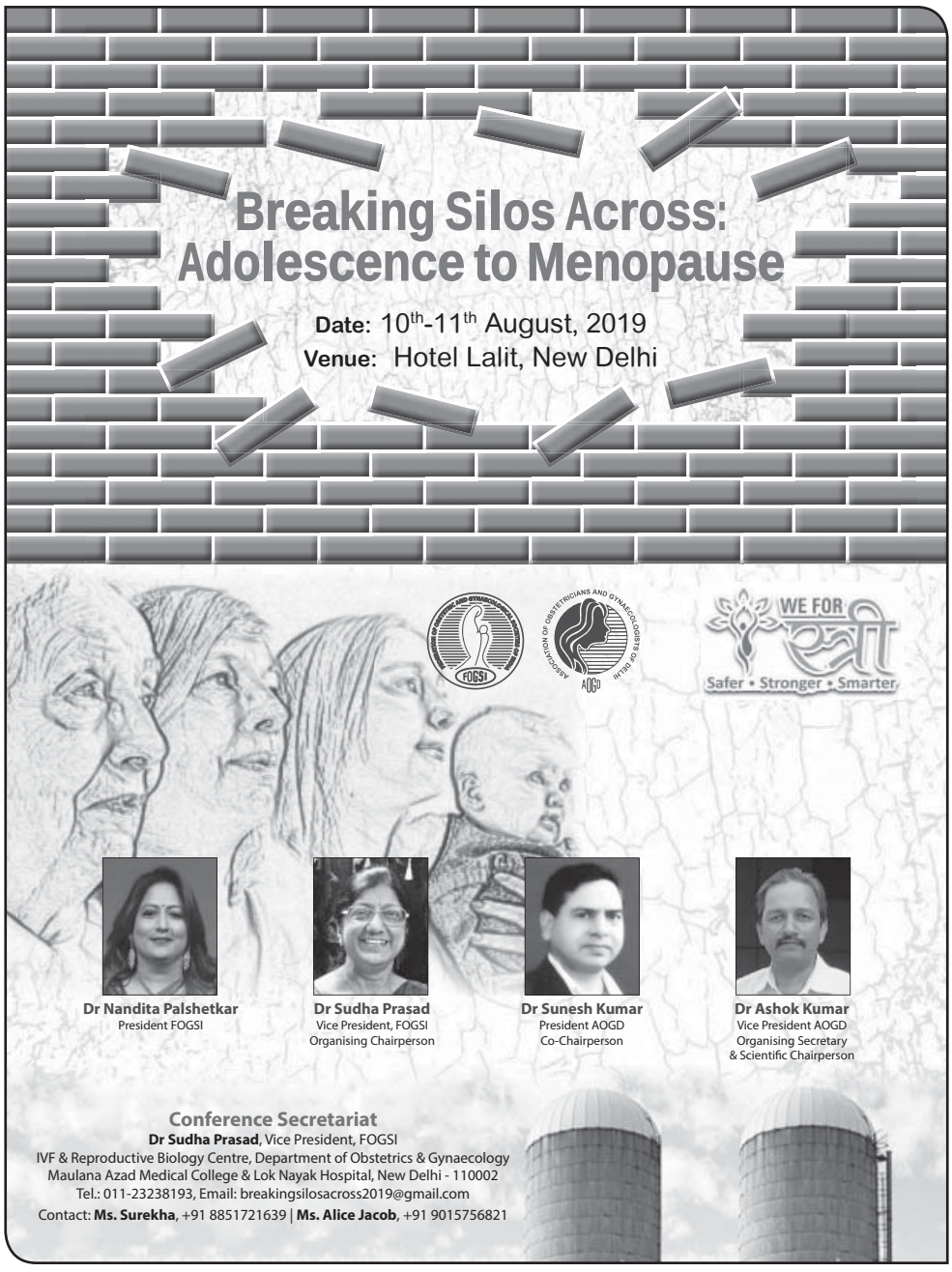

Peritoneal Leiomyomatosis: Is morcellator the real culprit?

Bhumika Shukla[1], Sonia Chawla[2], B B Dash[3]

[1]Clinical Fellow, [2]Consultant, [3]Director & Head, Rejoice Gynae Endoscopy Training Center, New Delhi

Background

Leiomyoma represents the most common gynecologic and uterine neoplasm. Laparoscopic myomectomy is now the gold standard treatment for fibroid uterus[1]. First laparoscopic morcellator was introduced by Steiner et al. for laparoscopic tissue removal[2]. Since then many instruments have been introduced to help the surgeon and widen the scope of laparoscopic surgery.

With advancement in the use of power morcellation, there has been an increase in rare but important entities like parasitic myomas and Leiomyomatosis peritonealis disseminate[3,4].

Disseminated peritoneal leiomyomatosis (DPL) has been strongly linked with power morcellation[5] and usually reported after laparoscopic myomectomy. Here, we report a very rare case of iatrogenic diffuse peritoneal leiomyomatosis (DPL) in a woman after abdominal hysterectomy.

Case Report

A 38-year-old woman P2L2 presented to outpatient clinic for vague abdominal discomfort for the past 1 month. She had undergone abdominal myomectomy in 2014 and total abdominal hysterectomy with bilateral salpingo-oophorectomy for fibroid uterus in 2016.

On examination, her vitals were stable. Abdomino-pelvic examination was normal. A transvaginal ultrasound detected a 6.3x3.4cm ill-defined heterogeneous hypoechoic solid lesion with significant vascularity seen in uterine fossa and another 4.4 x 3.2 cm well defined heterogeneous hypoechoic solid lesion seen in right iliac fossa adjacent to undersurface of anterior abdominal wall muscle plane with significant peripheral vascularity probably of muscle origin. MRI demonstrated multiple well defined enhancing solid masses in right lower abdomen and right pelvic cavity suggestive of recurrence/ metastasis/ sarcomatous deposit of uterine fibroid (Fig. 1A). Given the patient's history of leiomyomas with hysterectomy, she was suspected to have diffuse peritoneal seeding and implants of fibroids. The patient was planned for laparoscopic exploration. Intraoperative, multiple leiomyomas were identified and resected. The two largest were of size approximately 6x6cms, one in anterior abdominal wall attached to rectus sheath & omentum and another in left ovarian fossa adherent to lateral pelvic wall and sigmoid colon (Fig.1B). Total 5 different implants of leiomyomas were removed. Histopathologic examination confirmed postoperative diagnosis of diffuse leiomyomatosis. The patient had an unremarkable postoperative course and reported asymptomatic till date.

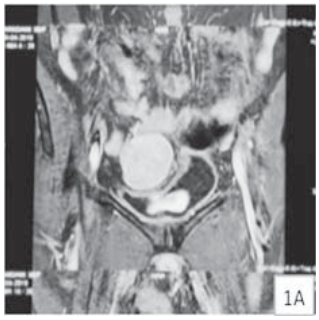

Fig 1A: MRI film showing parasitic myoma anterior to bladder.

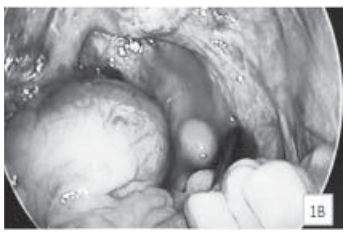

Fig 1B: Per operative view showing parasitic myomas in uterine and ovarian fossa

Discussion

Disseminated peritoneal leiomyomatosis (DPL) is an exceedingly rare benign disorder characterized by multiple vascular leiomyomas growing along the submesothelial tissues of the abdominopelvic peritoneum. The exact incidence is not known with fewer than 200 cases reported in literature so far[6]. First defined by Taubert et al, it is usually discovered incidentally in women of reproductive age[7]. It can mimic ovarian or peritoneal cancer. Although the pathogenesis of this disorder is still unclear, the hormonal factors are seen to play an important role, inferred from documented associations with pregnancy, long-term use of oral contraceptives, and, occasionally, granulosa cell tumors of the ovary[8].

The recent increase in incidence of parasitic myomas & DPL after minimally invasive endoscopic procedures has started a new debate about the potential role of morcellator as an etiological factor[9].

Considering the risk of spread of benign and malignant tissue, in 2014, the US Food and Drug Administration (FDA) published a safety communication regarding "the use of laparoscopic power morcellation during hysterectomy and myomectomy"[9]. The warning by US FDA and multiple cases of parasitic myomas and DPL discouraged electromechanical morcellation worldwide.

Various studies have independently identified morcellation of myomas during myomectomy and morcellation of the uterus during hysterectomy as risk factors for iatrogenic parasitic myomas.

However, we here want to emphasize that DPL and parasitic myomas can occur even after open abdominal surgery without using morcellator. As in our case, patient underwent total abdominal hysterectomy and had recurrence of multiple parasitic fibroids all over the abdomen. The present case reiterates that even an abdominal surgery can trigger the development of parasitic myomas. Multiple myomectomy is likely associated with myoma particle implantation in the abdominal cavity. Small particles invisible to the naked eye could have been disseminated and implanted in the abdominal cavity. Similar few cases have also been reported by other authors[10,11]

A major decrease in number of laparoscopic surgeries was observed worldwide post US FDA Statement. Various other societies (AAGL & ACOG) also reviewed the issue. The American Association of Gynecologic Laparoscopists (AAGL)[38] and the American College of Obstetricians and Gynecologists (ACOG)[39] have concluded that all existing methods of tissue extraction carry risks and that all modalities of tissue extraction should remain available.

Conclusion

This case highlights the importance of surgical vigor in removing all the pieces of morcellated specimens at the time of surgery. Although postulated as a strong risk factor, morcellator might not be the real culprit. Even manual morcellation in open surgery may result in DPL. So discouraging morcellation may preclude many women from the benefits of minimal access surgery.

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Clinical Proceedings of AOGD Clinical Meeting held at VMMC & Safdarjung Hospital, New Delhi on 28th June, 2019

Role of Ultrasound in Labour Management

Pratima Mittal, Rekha Bharti, Divya Pandey, Suchhandana Dasgupta, Anubhuti Mohan, Supriya Gupta

Background: Extensive evidence in the past has demonstrated the value of ultrasound in the prenatal fetal assessment. Over the last 10 years, studies suggest that ultrasound may play an important role in labour management.

Three studies carried out at Vardhman Mahavir Medical College and Safdarjung hospital, using ultrasound for prediction of vaginal delivery before IOL, assessment of progress of labour and prediction of 3rd stage complications were presented.

300 nulliparous women with singleton baby in cephalic presentation undergoing IOL at term underwent digital vaginal examination (DVE) and transperineal ultrasound (TPU) for assessment of foetal head perineal distance. On comparing HPD at DVE and TPU it was observed that in most of the cases at higher station of head the difference between digital examination and USG was 6-7 cm compared to 3-4 cm at lower station. We plotted ROC for prediction of vaginal delivery by HPD measured on DVE and TPU. At HPD cutoff of ≤7 cm by DVE and ≤4.39 cm by TPU, HPD measured at TPU had higher sensitivity and NPV. Also with each cm increase in fetal HPD above the cut off, risk of cesarean delivery increased by 47%. On logistic regression analysis HPD measured on TPU was found to be a significant predictor of caesarean delivery, hence failure of IOL. This association was not seen with HPD measured by DVE.

In another study, 215 term nulliparous women with singleton pregnancy and cephalic presentation in active labour were assessed by digital vaginal examination and ultrasound done at admission, and every 4 hourly till delivery, making a total of 458 observations. Cervical dilatation, fetal head station were measured by transperineal ultrasound and head position by transabdominal ultrasound. Cervical dilatation measured by DVE showed excellent correlation with USG, Kappa = 0.837, p <0.0001.The head station and head position had fair correlation: kappa=0.353 and 0.554 respectively, p <0.0001 for both.

In the third study, 100 primigravida women delivered vaginally had transabdominal ultrasound started just after delivery of fetus, repeated every 2 mins till delivery of placenta or maximum for 30 mins. Change in myometrial thickness of upper & lower segment was assessed and evaluated serially till the placenta was delivered. All women received active management of third stage of labour. 84 women expelled placenta within 6 minutes and had no 3rd stage complication. 10 women expelled placenta between 6 to 30 minutes, all had atonic PPH, 5 responded to medical management, 3 had balloon tamponade and 2 had surgical intervention. 6 women had retained placenta and underwent MRP. At ROC cut off of ≥ 1.98 for ratio of upper and lower uterine segment, PPV and NPV for 3rd stage complications were 96.5% and 84.2%, respectively.

Conclusion

As the head perineal distance increases the difference in the observations on digital vaginal examination and TPU also increases. Fetal head perineum distance of ≤4.39 cm on transperineal ultrasound can successfully predict the vaginal delivery. Each cm increase in fetal HPD above 4.39 cm increases the risk of cesarean delivery by 47%.

Ultrasound can be used for monitoring of active stage of labour; cervical dilatation on USG has excellent correlation whereas head position and station of head have fair correlation with vaginal examination measurement. Repeated PV examinations can be avoided by intrapartum use of USG.

Ultrasound can predict abnormal 3rd stage events like PPH or retained placenta and is helpful in preparedness for management of complications.

Pregnancy with SLE

Anita Kumar, Anjali Dabral, Archana Kumari, Deepti Pachuri, H P Anand

Case Summary

32 years old, G3P1L0A1, known case of SLE since 14 years of age, but not on any treatment presented

to ANC OPD at nine weeks of gestation. She had spontaneous abortion at 3months gestational age 2 years back and and a preterm LSCS in 2017 at 28wks i/v/o absent end diastolic flow and anhydramnios. She delivered a 900gm baby with congenital complete heart block which expired within few hours of birth. Both of her pregnancies were unsupervised without any medication for SLE. In her present pregnancy, CBC, LFT, KFT, urinalysis, 24hr urine protein and other routine antenatal investigations were normal. ENA profile revealed: - ANA +ve - anti ds DNA ab +ve - anti Ro/La ab +ve - APLA -ve Complement level were normal. She was started on Folic acid, Ecospirin and Hydroxychloroquine 200mg twice a day in consultation with rheumatologist. Fetal echo with doppler was done at 18 -26weeks every 2 weeks along with routine ANC investigations and received Tab dexamethasone 4mg OD (20-26 wks in view of previous CCHB). Repeat anti dsDNA ab levels and complement levels were WNL. Patient was admitted at 35 weeks of gestation for pain in lower abdomen and had LSCS at 36 weeks in view of persistent pain abdomen with previous preterm LSCS. The male baby of 2.2 kg was admitted in nursery for 24 hours for evaluation of neonatal lupus. It had no cutaneous manifestations or abnormal CVS findings. CBC and ECG were normal. Neonatal jaundice developed on day 2 (serum bil 11mg/dl) which resolved gradually. She was discharged after 1 week on hydroxychloroquine with advice to follow up after 6 weeks in PNC clinic and continue rheumatology consultation.

Discussion

SLE is characterised by periods of remission and relapse. Its incidence is 1 in 1000 in Asians women. Diagnosis is done by the new 2012, the systemic lupus international collaborating clinics (SLICC) classification criteria. Maternal risks are lupus flares (10 to 60 %), lupus nephritis and preeclampsia while fetal risks are early pregnancy loss, preterm labour, FGR and NLS (neonatal lupus syndrome). NLS is characterised by cutaneous, hematologic and hepatic abnormalities which resolve with the clearance of the antibodies by six to eight months of life. The most common and serious issue is congenital heart block (CHB), the incidence of which is 2% in anti Ro/La ab + ve pts and 18% with prior affected child. Diagnosis of lupus flare during pregnancy is difficult due to pregnancy induced thrombocytopenia, palmar/facial erythema and preeclampsia. Pregnancy outcome is best if women conceive after remission of 6 months and have no lupus nephritis or anti phospholipid Ab.

Prevention of CCHB: Hydroxychloroquine(HCQS) should be initiated between 6-10 wks of gestation if pt is not already on medication. Maternal corticosteroid administration for t/t of CHB controversial. **Prevention of adrenal crisis**: Stress dose glucocorticoid treatment during labour is given to the patients who were on chronic corticosteroids. **Postpartum care**: Monitor for SLE exacerbation. Pre-pregnancy maintenance therapy should continue. Ligation/IUD/POP/MPA are safer option for contraception. Combined OCP should be avoided.

Conclusion

Pregnant woman with SLE poses high risk for materno-fetal morbidity. For best outcomes lupus activity should be quiescent for 6 months before conception. Multidisciplinary care with close monitoring is essential for good pregnancy outcomes.

Answer: June Issue

Crossword

Across:

1. Aspermia
2. Klinefelters
3. Leydig

Down:

4. Asherman
5. Turner
6. Interceed
7. Inhibin B
8. Aromatase

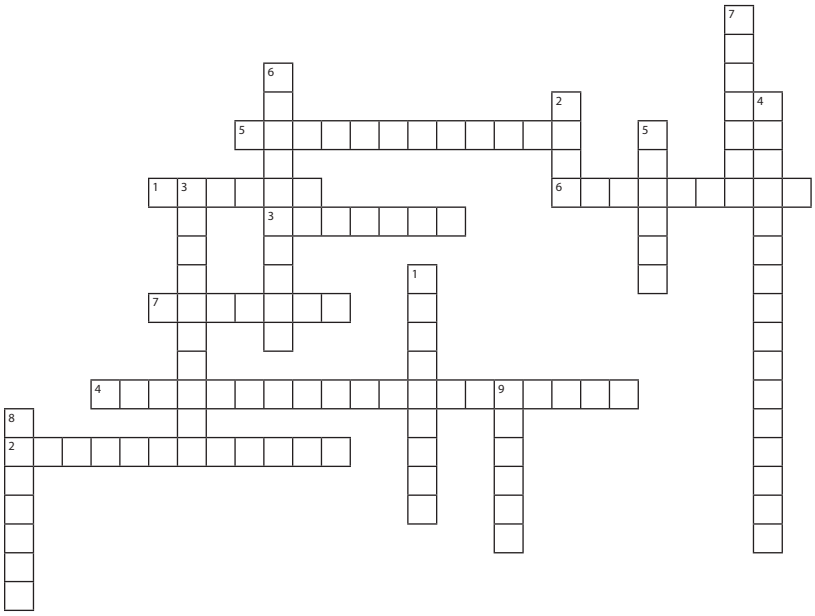
Pictorial Quiz

1. Sharma's hanging gall bladder sign, TB
2. Bicornuate Uterus, Laparoscopy
3. Intrauterine adhesion

The Maze of Knowledge

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

CROSSWORD



Top to down

1. Which drug needs to be given through out ovarian stimulation in patients with breast cancer for oocyte cryopreservation
2. The commonest immunological marker said to be responsible for developing OHSS by increasing vascular permeability
3. Most commonly used protocol in patients with diminished ovarian reserve
4. Which drug is said to be most gonadotoxic
5. Which is the most common cancer going for fertility preservation
6. Name for the combination of recombinant FSH + recombinant LH
7. In Which grading of OHSS is a patient with ARDS fall
8. Intralipid used as a adjuvant therapy in patients with RIF works on which immune cells
9. Which immune cells are thought to have pathological role in recurrent implantation failure if seen to be increased in endometrium

Right to left

1. Most preferred protocol for oocyte cryopreservation in cancer patients- _____ START
2. Which is the most common electrolyte abnormality in severe OHSS in-patients
3. Vasopressin receptor antagonists which have proven to have role in OHSS treatment
4. Long acting FSH agonist
5. Most commonly used modality for luteal phase support
6. Strategy adopted to fully eliminate the risk of late onset OHSS
7. Most commonly used strategy for prevention of early onset OHSS- _____ TRIGGER

PICTORIAL QUIZ

Q1. Which ART procedure is depicted in the picture ?

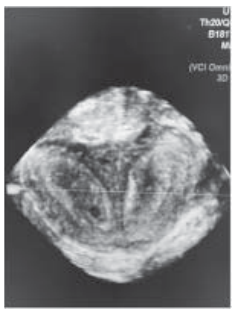
_____

Q2. What is the needle shown in the picture ?

_____

Q3. Identify the uterine pathology and what is shown in the picture ?

_____



Watsapp your answers to **9211656757.** Names of first three correct entries will be mentioned in the next issue

Refer page 52 for previous answer key.

SUNRISE GROUP OF HOSPITALS PRESENT IN ASSOCIATION WITH AOGD & DGES

26 SURGERIES PLANNED FROM 8.00 A.M. TO 8.00 P.M. ON 20TH JULY 2019 AND CME ON 21ST JULY WITH WORLD RENOWNED FACULTIES.

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