THE MUMBAI OBSTETRIC & GYNECOLOGICAL SOCIETY

MOGS MEDIA

Vol 6 | Premature Ovarian Insufficiency

Dr Rishma Dhillon Pai
President MOGS

Dr Anahita Chauhan
Secretary MOGS

Dr Rajendra Sankpal
Treasurer MOGS

Dr Pratik Tambe
Editor

Dr Sujata Dalvi
Co Editor

Dr Unnati Mamtora
Co Editor

President's Message

Dear Colleagues,
It gives me great pleasure to bring to you the sixth edition of '**MOGS MEDIA**'. This is a series of focussed newsletters where we bring to you an important subject discussed in detail with all the latest updates. This issue is on the important and common problem of **Premature Ovarian insufficiency.** This is an issue we are seeing more and more in our practise and requires everyone to upgrade their knowledge, as a lot has changed in this field**.** The editor Dr Prateik Tambe and all the contributors have made a lot of effort to bring you the latest information on the subject and we are thankful to them.

We had had a busy academic calendar with Blood health forum with many international speakers in October .Genetic testing in Obstetric practise was a practical and relevant webinar. Molecular insights in gynaecological disease in November, focussed on prevention and diagnosis of HPV and other STI's. We are all working very hard for the FEM -Fertility enhancement and management conference in collaboration with IVF Worldwide in the end of November. I am sure you have benefitted from the many focussed webinars we have been doing. I hope the 'Pearls of wisdom' videos which you are receiving regularly are adding to your knowledge. Our digital PG training programme-The NA Purandare practical training event which has hundreds of young doctors tuning in, is helping young doctors get ready for exams and clinical practise.

MOGS V Care & share programme was started by us to support our frontline workers and the women whose health we look after. PPE, N95 masks, face shields, fetal dopplers etc have been donated by us to all major and many peripheral municipal and government hospitals. We have distributed care packages to all resident doctors in government and municipal hospitals multiple time. We lent our support to hundreds of new mothers in municipal hospitals with protein supplements, masks, sanitizers etc. We need your help and support for this ongoing programme . You can donate by online payment on our website or by bank transfer.
We have many different academic and fun activities planned this year Do visit our website for updates. www.mogsonline.org and download our **upgraded app.**

Thank you once again for all your support over the years and we look forward to a wonderful year at MOGS.

Stay safe ,stay healthy.

Best Wishes

Dr Rishma Dhillon Pai
President MOGS.

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Editors' message

Dear MOGS members,

The **MOGS Media** series of newsletters have been one of the highlights of the MOGS year so far. The newsletter is themed on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists. The previous five issues on **Preterm Birth**, **Anaemia and Nutrition in Pregnancy**, **Optimising IUI Results, Endometriosis** and **PCOS** were well received and widely appreciated by readers throughout the country.

It is with great pride that we bring you the sixth issue on **"Premature Ovarian Insufficiency"**, a condition which is being encountered with greater frequency in modern practice. We examine the current evidence and guidelines from international authorities regarding best practices when treating this disorder.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative. We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

Dr Pratik Tambe
Dr Sujata Dalvi
Dr Unnati Mamtora
(Editors)

Dr Pratik Tambe
Editor

Dr Sujata Dalvi
Co Editor

Dr Unnati Mamtora
Co Editor

MOGS MEDIA

Vol 6

Mogs for Women
Our speciality is you

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Dr Unnati Mamtora DNB DGO
Diploma in Reproductive Medicine & Embryology (Germany)
Fellowship in Reproductive Medicine and Laparoscopy
Fertility Consultant, Bloom IVF, Mumbai

Dr Rohan Palshetkar
MS OBGY, FRM
MD, FCPS, FICOG, FRCOG
2nd Joint Secretary AMOGS
Joint Treasurer MAGE
Managing Committee Member MOGS, MSR

Introduction

Premature ovarian insufficiency is defined as the absence of menses or development of amenorrhoea before the age of 40. It is often associated with an unpredictable course with a minute chance of resumption of ovarian function spontaneously. As premature ovarian insufficiency can result in serious health consequences such as infertility, osteoporosis, psychological distress, ischemic heart disease, autoimmune disorders, impaired cognition and an increased risk of mortality it is important to diagnose it in a timely fashion and institute treatment as early as possible.[1]

Diagnosis of premature ovarian insufficiency should be considered when the FSH level is in menopausal range on two occasions at least 4 to 6 weeks apart after four months of amenorrhoea or irregularity after the causes for secondary amenorrhea are ruled out. An FSH level > 40 IU is used to define the menopausal range according to the International Menopausal Society Guidelines. Recent ESHRE guidelines recommend an FSH level of >25 IU. History of oral contraceptive pills or hormone replacement therapy should be noted if any to avoid incorrect interpretation of the hormonal value. These agents should be withdrawn at least 6 weeks before hormonal evaluation. The routine use of serum Anti-Mullerian Hormone levels is not recommended due to its inaccuracy in this setting.[1,2]

Clinical characteristics

Presentation
Any woman of age less than 40 years with menstrual irregularities or amenorrhoea
Clinical evaluation
1. History Menstrual history: age of menarche, prepubertal development, bleeding pattern, last menstruation Menopausal symptoms Obstetric and gynaecological symptoms

Uterine and ovarian surgery, parity, psychological symptoms, sexual function
Autoimmune disease especially adrenal and thyroid disease
Past medical history
Past medical history
Inherited conditions like Turner syndrome
Previous cancer and treatment (radiotherapy and chemotherapy)
Viral illness like mumps
Eating disorders
Cardiovascular disease, osteoporosis
Family history of early menopause

2. Smoking, alcohol, dietary habits, exercise
Medications: COCs, HRT, tamoxifen, aromatase inhibitors
Examination:
Weight, height, BMI
Secondary sexual characteristics
Breast development
Genital and gynaecological examination
Cardio vascular system
Stigmata of specific disorders (Turner syndrome, autoimmune disease)

Recommended investigations

Following the diagnosis, the aetiology and the longterm consequences need to be evaluated. In absence of obvious iatrogenic causes of POI, the following investigations should be advised:

Karyotype (rule out Turner syndrome)

If karyotype is normal, FMR1 premutation testing – Fragile X premutation carrier status. The Fragile X abnormality can be detected by using the polymerase chain reaction (PCR) and methylation status by using the Southern blot analysis. This technique analyses the number of CGG repeats. It determines the individual's own risk and also the risk of having affected children. However, individuals with Fragile X due to missense and deletions of FMR1 will not be diagnosed by the above test, they should therefore undergo sequencing of FMR1 gene if there is clinical suspicion of Fragile X syndrome. During pregnancy, prenatal testing with amniocentesis or chorionic villi sampling for FMR1 mutation gene is possible.

Autoimmune screening

A. anti-thyroid peroxidase antibody
B. anti- adrenal antibody
C. coeliac serology

Hormonal evaluation serum AMH, serum FSH, serum E2

FSH: Basal measurement of the follicle stimulating hormone is used as a traditional test for evaluating the ovarian reserve and onset of menopause. FSH is a glycoprotein hormone secreted by the gonadotrophic cells of the anterior pituitary. The activity of FSH varies throughout the menstrual cycle and levels are usually measured on Day2/3. The levels are usually low at this phase and rise abnormally as a result of ovarian follicular depletion. High values indicate depleted ovarian reserve indicative of premature ovarian insufficiency in women less than 40 years of age. An FSH level >40 IU is used to define the menopausal range according to the International Menopausal Society Guidelines. Recent ESHRE guidelines recommend an FSH level of >25 IU.

serum E2 levels less than 50 pmol/L

serum AMH: Ovarian reserve reflects the quality and quantity of the available oocytes. This reserve has become indispensable for the better understanding of the reproductive potential. AMH is a glycoprotein hormone produced by the granulosa cells of the ovary. It belongs to the transforming growth factor beta family. The secretion of the AMH increases at puberty and peaks at the age of 24 years. Gradually with age, the AMH levels decline and reach the lowest levels at menopause. There is a strong correlation between the ovarian reserve and the serum AMH levels. Measurement of the serum AMH level gives us an assessment of the ovarian reserve in the woman.[3,4]

It has been applied in various clinical conditions. AMH is highly sensitive to the changes that accompany advancing age. It excludes uncertainty associated with inter and intra cyclic variability of menstruation. AMH levels are monitored in women presenting with infertility, in PCOD, in diagnosis of ovarian failure and granulosa cell tumours. It is also useful in the diagnosis of iatrogenic damage. Currently, it is the best investigation for assessment of the ovarian reserve. However, its predictive value for future live birth remains questionable. Also, currently available kits use different assay ranges and coefficients of variants and hence there is no international standardisation of the interpretation of the values.[5-9]

The serum FSH level is used as a conventional marker of ovarian reserve and it increases in the perimenopausal period. The serum AMH levels become undetectable in the within 5 years of onset of menopause. Several studies have shown that the serum AMH levels are low in the women who present with symptomatic POI. Also, in the era of cryopreservation, the screening of women can help in prediction of the women with chances of developing POI and subsequent fertility preservation options may be discussed. Promising results have also been reported for incipient POI and autoimmune ovarian failure.[10-12]

There is a large amount of inter- and intra- cyclical variability associated with the serum FSH levels which make it an unreliable and inaccurate marker for determining the ovarian reserve.

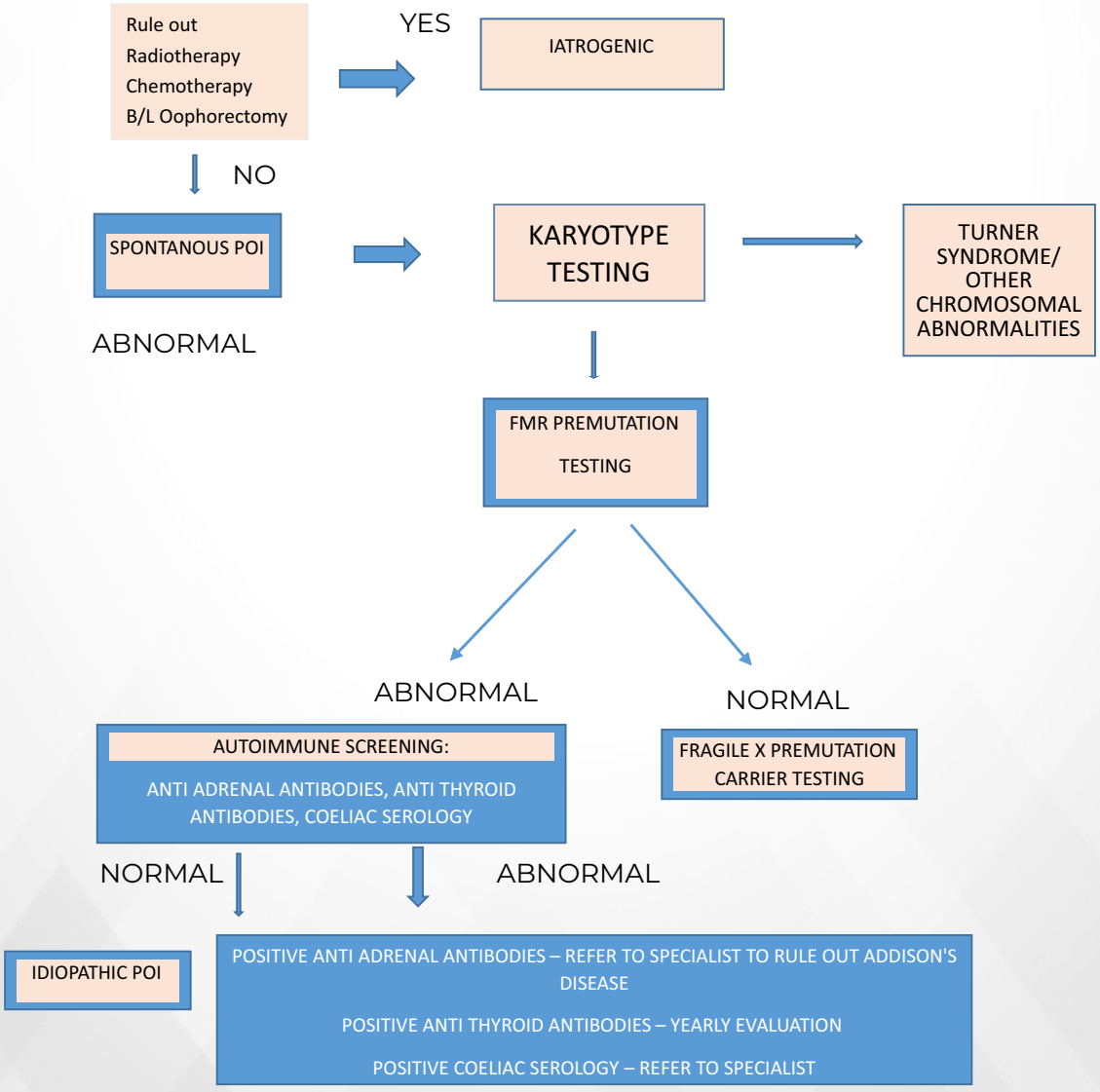
The more consistent levels of AMH throughout the menstrual cycle make it more reliable for the same. Serum AMH levels are used as a marker for fertility decline as the concentration of the hormone decreases with the decline in the pool of the primordial follicles, thus making it a useful tool for determining POI. The deficiencies in the apoptotic mechanisms of oocytes is associated with the decline in the follicular pool. AMH is a marker of non-cyclical ovarian activity. It is a stable hormone and its level doesn't fluctuate with the menstrual cycle. Since the levels of serum FSH fluctuate during the menstrual cycle, they are in accurate in determining the ovarian reserve as far as the fertility point of view is considered. The specificity and sensitivity of FSH was 28.57% and 78.65% respectively and for AMH it was significantly better was 80% and 78.95% respectively.[13]

Ultrasonography of the pelvis

Baseline sonography of pelvis to access the uterus and the ovaries including the size, ovarian volume and the antral follicle count (AFC). AFC less than 5, thin endometrium <4 mm, reduced ovarian volume are the commonly observed findings.

Dual Energy Xray Absorptiometry (DXA) scan to assess bone density

Fig 1 Investigations



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Fertility Management

Dr Pratik Tambe MD FICOG
Chairperson, AMOGS Endocrinology Committee (2020-22)
Governing Council member, ICOG (2021-22)
Chairperson, FOGSI Endocrinology Committee (2017-19)
Managing Council member, MOGS and ISAR

Background and aetiopathogenetic mechanisms

Ovarian ovulatory and endocrinological inefficiency, including diminished ovarian reserve and premature ovarian insufficiency (POI), represents one of the main causes of female infertility. Premature ovarian insufficiency often has a genetic basis; the most common genetic cause of POI is Turner syndrome, caused by a missing or partially missing X chromosome.

Pre-mutations of Fragile X syndrome are also highly associated with POI. Premutation carriers of Fragile X syndrome have CGG trinucleotide expansions of about 50 to 200 repeats. Various defects in transcription factors, steroidogenic enzymes, or gonadotrophic receptors may also play a role. NR5A1 is a key gene required for gonadal function, and variants are associated with a wide phenotypic spectrum of disorders of sexual development, and are found in 0.26-8% of patients with premature ovarian insufficiency.[1]

A systematic review of 97 studies which were eligible for review trying to identify the associations and mechanisms of the impact of environmental pollution on premature ovarian insufficiency were studied in a landmark publication in 2017. Phthalates, bisphenol A, pesticides and tobacco were the most reported substances having a negative impact on ovarian function with an increased follicular depletion leading to an earlier age of menopause onset. These effects were found when exposure occurred at different times throughout the lifetime from the prenatal to the adult period, possibly due to different mechanisms and the primary mechanism seemed to be an increase in atresia of pre-antral follicles.[2]

By definition, premature ovarian insufficiency is the loss of normal hormonal and reproductive function of ovaries in women before age 40 as the result of premature depletion of oocytes. The incidence of POI increases with age in reproductive-aged women, and it is highest in women by the age of 40 years. Reproductive function and the ability to have children is a defining factor in quality of life and social acceptance for many women. We review the available fertility management strategies and current guidelines on this topic including fertility preservation which is now widely available to women and fertility treatment for women with or at risk for POI.[3]

The ESHRE Guideline on Premature Ovarian Insufficiency was published in 2016 and the ESHRE Guideline Development Group recommends the following diagnostic criteria:
1. oligo/amenorrhea for at least 4 months and
2. an elevated FSH level >25 IU/L on two occasions 4 weeks apart.[4]

Physiology and ovarian reserve

The ovarian reserve refers to the population of primordial follicles as a measure of the the procreative capacity. The number of oocytes peaks at 6 to 7 million around 20 weeks of gestational age in utero and falls precipitously until birth when there are 400,000 oocytes remaining. The average reproductive lifespan is about 450 monthly ovulatory cycles, with approximately 1000 follicles remaining by menopause. Anti-Mullerian hormone (AMH) correlates with the number of primordial follicles, indirectly measures the ovarian reserve and is widely used today as a determinant of fertility potential.[5]

The degree of residual ovarian function in women with POI is variable and despite a reduced ovarian reserve and an unflattering s AMH value, approximately 5-10% of women with POI may experience spontaneous ovulation, conception and live birth. However, ovulation may be infrequent and may lead to a significant increase in time to pregnancy (TTP) when compared to women with normal ovarian reserve. The majority of women with POI have infertility and will require fertility treatment. Women at risk for POI due to genetic predisposition, medical conditions and gonadotoxic treatment will benefit from fertility preservation, which needs to be offered by clinicians at the appropriate juncture.[6]

In vitro fertilisation with autologous oocytes

Timed intercourse and intrauterine insemination are inappropriate methodologies and which should not be adopted in the clinical setting of POI.

In vitro fertilisation (IVF) with autologous oocytes is an effective treatment for women with POI when the residual ovarian reserve is sufficient for ovarian stimulation. However, even women who exhibit a reasonable number of antral follicles on a baseline ultrasound scan and borderline s AMH values may turn out to be poor responders when stimulated with gonadotropins and therefore, appropriate counselling prior to starting the treatment cycle is of paramount importance.

Women with POI require significantly higher doses of exogenous gonadotropins to initiate folliculogenesis. Furthermore, they commonly exhibit a poor response to stimulation with only four or fewer follicles available for oocyte retrieval. Limited oocyte recovery results in fewer or no embryos available for transfer or cryopreservation. The quality of the oocytes also may be poor as compared to normal responders, resulting in poor embryo progression over time and blastocyst formation may be lower than expected.

As a result, patients with POI may require multiple IVF cycles to achieve conception and the success rate per started cycle is lower than a comparable control cohort. The factors contributing to IVF failure include reduced ovarian reserve, poor oocyte quality, advanced maternal age, suboptimal endometrial milieu and insufficient number of embryos for transfer. After running multiple stimulations, enough embryos may be cryopreserved and pooled over time for a single embryo transfer.[7]

In vitro fertilisation with donor oocytes

Women with undetectable or extremely low s AMH values benefit from IVF with donor oocytes. Women who have exhausted their options with autologous oocytes may also be counselled for donor oocytes, provided it is socioculturally acceptable to the couple. For women with POI due to a genetic cause who wish to avoid genetic disease transmission, IVF with donor oocytes may be a promising option.

Oocytes from genetically related or unrelated young reproductive age women can be utilised. There is a substantial body of evidence which reports high success rates using oocyte donation to the tune of approximately 50-60% per embryo transfer leading to ongoing pregnancies and live births. The ideal oocyte donor is young (age < 30 years), has had at least one child of her own and is free from infectious and medical disease.

In the past decade, oocyte vitrification techniques have been developed for oocyte cryopreservation, which yield comparable results to fresh oocytes. Frozen donor oocytes are now commercially available via private oocyte banks in western countries, while in India it is more common to perform IVF with fresh donor oocytes.

In women with iatrogenic POI due to cancer radiotherapy, pregnancy rates may also depend on whether the patient sustained endometrial injury secondary to pelvic radiation. Oocyte cryopreservation prior to cancer treatment should be offered to such women and they should be counselled regarding the availability of such fertility preservation services.

Cryopreservation and vitrification

In women who require gonadotoxic chemotherapy or pelvic radiation that results in iatrogenic acute POI, oocyte and/or embryo cryopreservation are the best fertility preservation options. According to the American Society for Reproductive Medicine (ASRM), these are no longer considered experimental therapies. Chemotherapy regimens including highly gonadotoxic alkylating agents like cyclophosphamide are highly toxic to the ovary in a dose-dependent manner.

Live birth rates for embryo cryopreservation are approximately 30–40%; rates for oocyte cryopreservation are only slightly lower. Cryopreservation via vitrification reduces the risk of ice crystal formation during freezing and improves oocyte survival after thawing leading to nearly 95-100% retrieval and increases live birth rates. Meta-analyses have

suggested that pregnancy rates after IVF or intracytoplasmic sperm injection (ICSI) with vitrified oocytes are similar to that for fresh oocytes; and evidence suggests there is no increase in chromosomal abnormalities, congenital anomalies or development delay in offspring from pregnancies resulting from cryopreserved oocytes when compared to the general population.[7,8]

In vitro maturation (IVM)

Immature oocytes not yet exposed to luteinising hormone or human chorionic gonadotropin are retrieved from unstimulated ovaries and matured in a medium in vitro from prophase I to metaphase II stage. This is an experimental technique and there are no established criteria regarding the ideal timing of oocyte retrieval, aspiration technique or selection of culture media. Oocytes are fertilised via ICSI. Live births have been reported but the implantation and pregnancy rates are lower than with traditional IVF.[9]

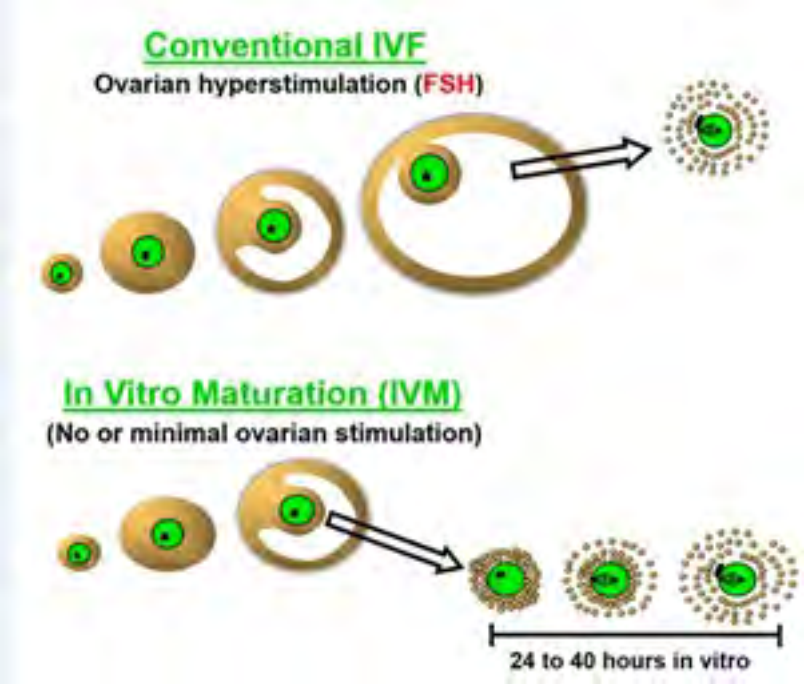

Fig 1 IVF vs IVM

Ovarian tissue cryopreservation

Cryopreservation of ovarian tissue prior to gonadotoxic therapy is a promising method of fertility preservation. Prior to cancer therapy, the cortex of the ovary that contains ovarian follicles is dissected off and cryopreserved.

After successful cancer treatment or during complete remission, the cortical ovarian tissue can be thawed and transplanted to the pelvis (orthotopic transplantation onto the ovarian medulla or nearby peritoneal window) or extrapelvic subcutaneous tissues such as the forearm or abdomen (heterotopic transplantation). Orthotopic transplantation has the unique advantage of the possibility of natural fertilisation.

Ovarian function usually lasts up to five years after transplantation. Successful pregnancies and live births after orthotopic transplantation have been reported, at rates of approximately 30% and 23-25%, respectively. Heterotopic transplantation requires IVF after oocyte retrieval and two successful live births of twins have been reported.[10,11]

In vitro activation

Women with POI have diminished and variable ovarian function. In vitro activation is a method of "activating" or recruiting residual follicles into the pool of primordial follicles, which can develop into mature oocytes. Studies have reported live births after activating residual follicles in vitro with Akt stimulators or PTEN inhibitor with subsequent ovarian tissue auto-transplantation or egg retrieval for IVF. A recent study showed that after ovarian fragmentation and Akt stimulation, 45% of the subjects demonstrated multiple antral follicles.[12,13]

Stem cell therapy

Recent research on oogonial stem cells (OSC) or germline stem cells has challenged the belief that the mammalian ovary contains a fixed and finite number of oocytes. Several studies have reported the isolation of OSCs from adult rodent, mice and human ovaries. Successful isolation of OSCs from fresh or cryopreserved human ovarian tissue has been reported. In a microenvironment where OSCs interact with somatic ovarian cells, OSCs have been shown to generate follicles capable of forming oocytes. In rodents, healthy offspring have resulted.

Embryonic stem cells and pluripotent stem cells have been induced into primordial germ cell-like cells (PGCLCs) in vitro; primordial germ cells also give rise to oocytes. These findings have the potential to revolutionise the field of reproductive endocrinology for women with infertility secondary to POI. However, the role OSCs or PGCLCs play in the female ovary has not yet been fully elucidated. It still remains unclear how stem cells can be utilised to improve reproductive function and there is currently no therapy involving OSCs proven to contribute to the development of functional human gametes and further research is required.[14,15]

Challenges with ART

As noted above, the success of ART in patients with POI is variable and is governed by a host of factors, many of which may not be modifiable. By definition, women with POI are poor responders and they satisfy the ESHRE criteria for poor responders.

Bologna criteria for poor responders

The European Society of Human Reproduction and Embryology (ESHRE) has standardised the criteria for poor ovarian response via the Bologna criteria. At least two out of three following criteria are required to define poor ovarian response during IVF:

1. Maternal age > 40 or any other risk factor for poor ovarian response
2. prior poor ovarian response (≤ 3 oocytes with a conventional stimulation protocol)
3. abnormal ovarian reserve test (antral follicle count (AFC) less than 5-7 follicles or anti-Müllerian hormone (AMH) less than 0.5-1.1ng/mL). ESHRE also indicated that history of two episodes of poor ovarian response after a maximum stimulation protocol is enough to define poor ovarian response.[16]

A variety of methods have been applied to improve ovarian response including increased gonadotropin dosage, modulation with gonadotropin-releasing hormone (GnRH), flare-up regimes, adjunctive human growth hormone therapy, minimal ovarian stimulation with clomiphene citrate and unstimulated or natural cycle IVF. However, the outcomes of these treatments have been less than satisfactory.

POSEIDON stratification

The POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) group reported a new approach for the definition and management of patients suffering from POR. Their aim was to determine the ideal stimulation for obtaining a euploid embryo for a successful transfer. This new approach classified the low responder women into four groups according to age, ovarian reserve and stimulation response with the aim of determining the prognosis.[17]

Group 1 Patients younger than 35 with sufficient ovarian reserve parameters (AFC ≥5, AMH ≥1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response

Subgroup 1a <4 oocytes retrieved

Subgroup 1b 4–9 oocytes retrieved

Group 2 Patients older than 35 with sufficient ovarian reserve parameters (AFC >5, AMH >1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response

Subgroup 2a 4 oocytes retrieved.

Subgroup 2b 4–9 oocytes retrieved.

Group 3 Patients younger than 35 with poor ovarian reserve parameters (AFC <5, AMH <1.2 ng/mL)

Group 4 Patients older than 35 with poor ovarian reserve parameters (AFC <5, AMH <1.2 ng/mL)

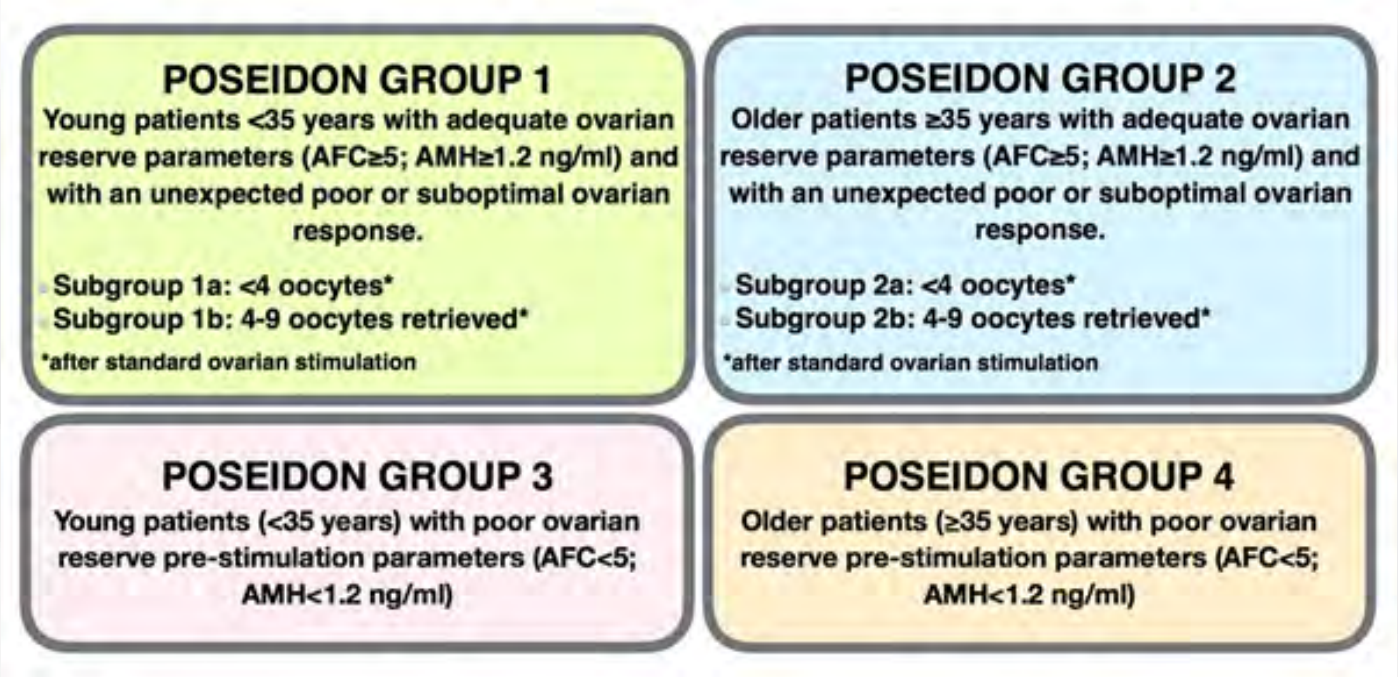

Fig 2 POSEIDON Group classification

DHEA pretreatment

Dehydroepiandrosterone (DHEA) is an endogenous steroid produced in the zona reticularis of the adrenal cortex and by ovarian theca cells. In the ovary, it promotes follicular development and granulosa cell proliferation by increasing intraovarian androgen concentrations. DHEA also enhances the level of follicular insulin-like growth factor-1 (IGF-1), which promotes folliculogenesis by enhancing the effect of gonadotropins and reducing follicular regression. Supplementation with DHEA is controversial, with views among clinicians varying considerably.[18]

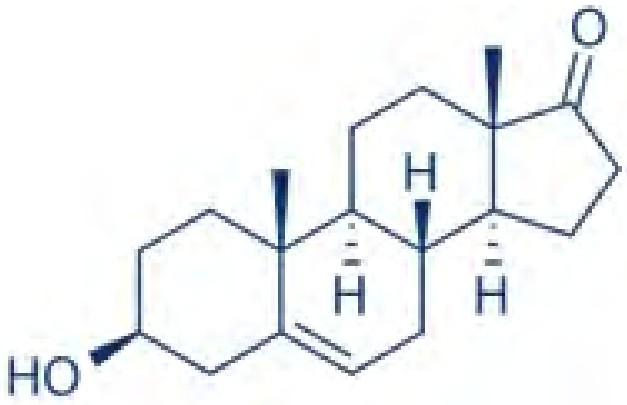

Fig 3 DHEA chemical structure

A meta-analysis from 2016 included eight RCTs, ten cohort studies and three case-control studies and found statistically significant increases in the pregnancy rates of patients treated with DHEA (RR 1.53, 95% CI 1.25-1.86, p<0.0001).[19]

Another subsequent meta-analysis in 2017 included four RCTs, three retrospective studies and one prospective study. Clinical pregnancy rates were significantly higher in the DHEA group (OR 1.47, 95% CI: 1.09-1.99). However, subgroup analysis based on RCTs revealed that there was no significant difference between the groups (OR 1.08, 95% CI: 0.67-1.73).[20]

A recent trial of 151 POR patients undergoing DHEA supplementation showed positive association with clinical pregnancy rate (OR=4.93, 95% CI 1.68-14.43, p=0.004). Additionally, in the study group, the multivariate analysis showed that serum dehydroepiandrosterone-sulfate (DHEA-S) levels < 180 µg/dL were significantly associated with a rate of retrieved oocytes > 3 (OR = 5.92, 95% CI 1.48-23.26, p = 0.012). They concluded that DHEA supplementation improves IVF outcomes of PORs. In PORs with DHEA pretreatment, women with lower DHEA-S level may have greater possibility of attaining more than 3 oocytes.[21]

The most recent meta-analysis from 2019 with 9 prospective RCTs and 833 patients showed that compared to the controls, patients treated with DHEA exhibited increases in the number of retrieved oocytes (MD 0.91; 95% CI 0.23-1.59; p = 0.009), clinical pregnancy rate (RR=1.27; 95% CI, 1.01-1.61; p = 0.04) and live birth rate (RR, 1.76; 95% CI, 1.17 - 2.63; p = 0.006).[22]

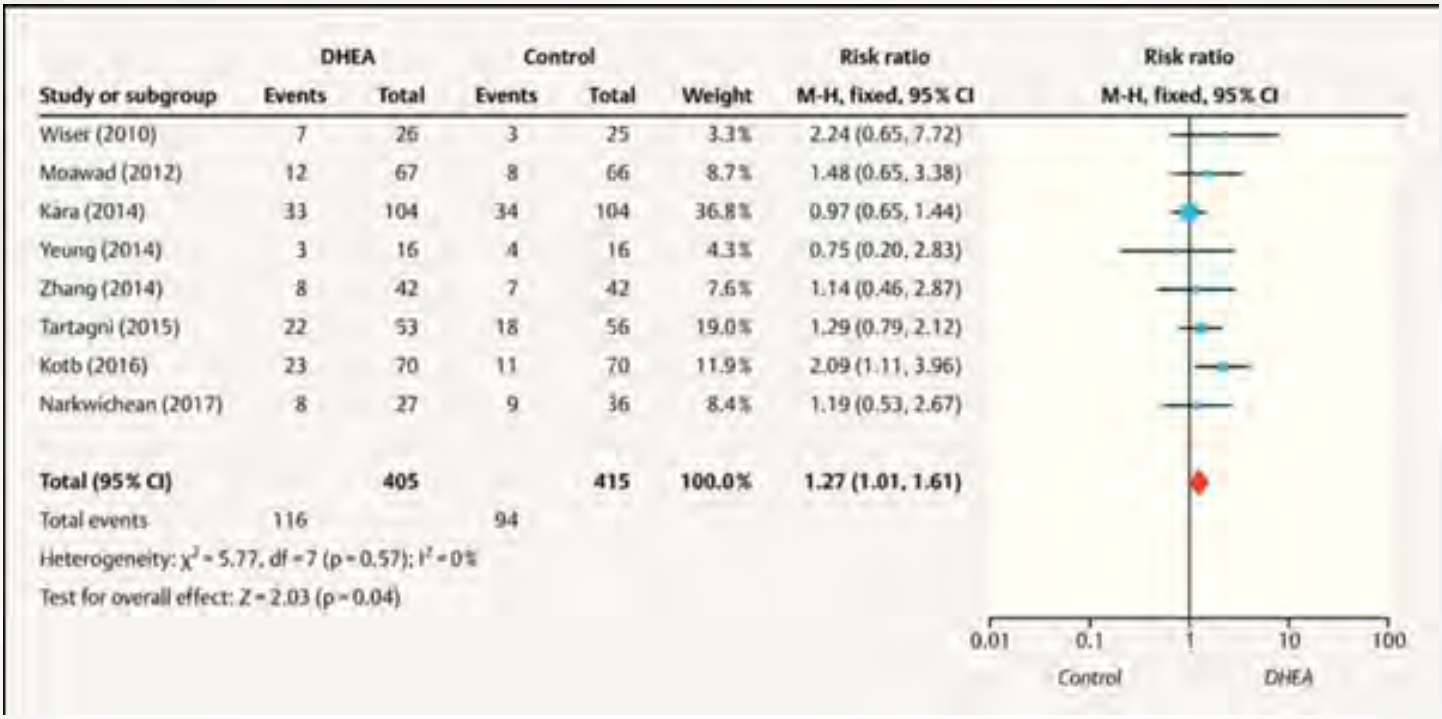

Fig 4 Meta-analysis of DHEA RCTs

Current literature indicates the existence of a tendency in DHEA supplementation increasing the number of oocytes retrieved and embryo implantation rates.[23]

Conclusions

Premature ovarian insufficiency is a complex condition arising from numerous possible aetiologies with multiple sequelae including infertility secondary to diminished ovarian reserve.

IVF and embryo or oocyte cryopreservation via vitrification are established methods with excellent pregnancy and live birth outcomes assuming proper methodology. Ovarian tissue cryopreservation is being increasingly practiced. It should be noted that these established methods of fertility treatments and fertility preservation are not readily available worldwide and are subject to legal regulations throughout the world. Several established methods of fertility preservation are available to women with POI. Further research on experimental methods is underway and the field of fertility preservation is rapidly expanding.

ART in these patients is challenging and presents multiple issues. Thorough counselling, modern Bologna criteria and POSEIDON group stratification based approaches, multidisciplinary care and good teamwork will ensure consistent success and reproducible results. DHEA pretreatment may improve clinical pregnancy rates and live birth rates and is currently the only relevant treatment which is widely available. Research based alternatives including in vitro activation and stem cell therapy require robust evidence based protocols before they can be widely accepted into clinical practice.

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Adjuvant Therapy

Dr Jiteeka Thakkar
Member, MOGS Youth Council
Consultant Obs Gyn, IVF Specialist

Introduction

Worldwide 48.5 to 186 million people are affected by the inability to have children and delayed conception affects 10% to 15% of couples who are trying to conceive. Infertility or subfertility has been defined by the World Health Organization (WHO) as the "failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse". Poor ovarian responders (PORs) account for 9–24% of patients undergoing ovarian stimulation for in vitro fertilization (IVF).[1-5]

Oxidative stress and ROS

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to neutralize these toxic products. This imbalance leads to cellular damage. A certain amount of ROS is beneficial for the progression of normal cell functions, and this includes reproductive cells and tissue. Excessive amounts become pathophysiological and lead to DNA damage and even apoptosis. Increased levels of ROS could either be due to endogenous or exogenous factors. In reproductive cells the most common exogenous causes of oxidative stress are environmental pollution, smoking, alcohol, poor nutrition, and obesity. Infections and chronic and autoimmune diseases are also known to be endogenous causes.[6-8]

To prevent oxidative damage or stress, the body has developed an antioxidant defence mechanism. Antioxidants can directly scavenge ROS, inactive them, and repair the damage. Natural antioxidants present in the body include enzymatic and nonenzymatic forms. Antioxidant enzymes are catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase. Other nonenzymatic antioxidants include ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), ferritin and transferrin.[9-10]

It is suggested that the production of ROS is influenced by cytochrome P450 and the corpus luteum itself is also a main source. The process of oocyte maturation, meiosis I and II, is largely influenced by variable amounts of ROS and antioxidants. OS has a direct effect on the oocyte, embryo and implantation by causing cell membrane lipid peroxidation, cellular protein oxidation, and DNA damage. Supplementary antioxidants have several proposed mechanisms of action. The benefits for female fertility include improved blood circulation in the endometrium, lowered hyperandrogenism, decreased insulin resistance, fertile cervical mucus and an influence on prostaglandin synthesis and steroidogenesis.[11-13]

Women with diminished ovarian reserve tend to have a very small number of poor-quality eggs. Poor-quality eggs frequently fail to fertilize, and when they do fertilize, they often develop into poor-quality embryos that stop growing before embryo transfer, fail to implant, or stop developing in the uterus and end in miscarriages.

Dehydroepiandrosterone (DHEA)

DHEA is an androgen pre-hormone produced in the zona reticularis of the female adrenal gland and the ovarian theca cells. It is a precursor to the sex hormones testosterone and estradiol. It is first produced during fetal life, while serum levels of DHEA decrease markedly after the 45th year of women's age. Its anti-aging effects were described 30 years ago, which led to further investigation into the role of DHEA in improving ovarian reserve. It was first reported as a treatment in ART in 2000, being used as an adjunct to IVF in women with premature ovarian failure (POF), premature ovarian aging (POA) and diminished ovarian reserve (DOR).[14-16]

For women with DOR, the generally recommended DHEA dosage for female fertility purposes is 75 mg daily, which is split into three 25 mg doses. It has vastly improved pregnancy outcomes for women who suffer from premature ovarian aging (or POA) as well as women over 40 whose ovarian reserve is declining as a part of the natural aging process. The purpose of DHEA supplementation in hypo-androgenic infertile women is improvement of egg quantity and quality. Studies have demonstrated that taking a DHEA supplement for at least 6-8 weeks is required before statistically significant improvements in female fertility can be observed. Peak effectiveness is typically reached between 16 and 20 weeks. However, the length of time is not necessarily the best indicator and the woman's testosterone levels should rise to about the upper ⅓ of the normal range. Where time is of the essence, it is recommended that fertility treatments be initiated after 6-8 weeks of DHEA supplementation with the patients continuing supplementation uninterrupted until pregnancy or until patients decide to discontinue treatment attempts with use of their own eggs.

More recent recommendations suggest that the timing of the start of a post-DHEA IVF cycle should not only be based on a pre-fixed interval of time with DHEA supplementation, but also on measured improvements in androgen levels from pretreatment baseline levels. A small minority of women don't convert DHEA to testosterone very well and we cannot automatically assume that a sufficient length of supplementation always leads to satisfactory testosterone levels.[17]

Testosterone

Most commonly used in the transdermal form, testosterone has also shown to have beneficial effects on the poor ovarian reserve patients. It can be administered by gel or spray form. A dose of 10 mg of testosterone gel can be applied on external side of thigh for 21 days starting from first day of menstruation prior to initiation of ovarian stimulation.

In a systematic review performed with around 225 patients, it was observed that transdermal testosterone significantly increased live birth and reduces the doses of FSH required. These findings support a synergistic role of androgens and FSH on folliculogenesis but due to smaller numbers, they should be interpreted with caution.

The Cochrane board concluded that in women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates. However, the overall quality of the evidence is moderate and evidence still is insufficient to draw any conclusions about the safety of either androgen. Definitive conclusions regarding the clinical role of either androgen await evidence from further well-designed studies.[18-19]

Growth hormone

GH plays an important role in the functioning of the granulosa cells. It promotes ovarian steroidogenesis and follicular development in the ovary. A meta-analysis of 663 patients and 11 studies showed that GH supplements increased serum oestradiol (E2) level on human chorionic Gonadotropin (hCG) day, metaphase II oocyte number, 2PN number and obtained embryo number; however, there was no significant difference on clinical pregnancy rate.

GH-releasing hormones increase the sensitivity of ovaries to gonadotropin stimulation and thereby enhances follicular development. It enhances the oocyte quality by accelerating and coordinating cytoplasmic and nuclear maturation. There are some propositions that GH-releasing factor supplementation may improve pregnancy rates in poor responders. It is started concomitantly with gonadotrophins. The dose varies from 4 to 8 IU daily or 10 to 24 IU on alternate days in patients with diminished ovarian reserve.

Although the use of GH in poor responders has been found to show a significant improvement in live birth rates, they were unable to identify which sub-group of poor responders would benefit the most from adjuvant GH. According to the Cochrane review, the results still need to be interpreted with caution and the included trials were few in number and small sample size. Therefore, before recommending GH adjuvant in in vitro fertilisation further research is necessary to fully define its role.[20-21]

Platelet rich plasma

PRP (plasma rich in Platelets) is a natural product where a high level of platelets is concentrated but with growth factors concentration 3 to 5 times greater than plasma. Growth factors are stored in granules, and include platelet derivate growth factor (PDGFs), Transforming growth factor-beta (TGF-ß), vessel endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin growth factor (IGF), and some others. These cytokines play an important role in cellular proliferation, chemotaxis and differentiation of mesenchymal and other cells and promote angiogenesis.[22]

According to the protocol employed, PRP administration should take place during the early follicular phase of the cycle. For menstruating women with POR and perimenopausal women, PRP can be administered on day 3 of the menstrual cycle. For amenorrhoeic POI and menopausal women, PRP administration can be performed on a random day. Preparation of PRP is to be done immediately following blood sample collected from the median antebrachial vein. Approximately 20 to 60 mL of the patient's peripheral blood is required in order to prepare the required volume of PRP. The initial concentration of platelets in peripheral blood is 250,000 - 400,000 platelets/µL. The goal concentration of platelets in PRP is approximately 1,000,000 platelets/µL. Prepared PRP can be stored for one hour at a temperature of 4°C, if required.

Intraovarian infusion method

Patients if on hormone replacement therapy can undergo PRP after 6 months of stopping hormonal therapy and those not on any therapy can undergo PRP intraovarian instillation immediately after basic baseline investigations.

Following PRP preparation, the technique of injection can be an empirical approach, resembling the transvaginal paracentesis performed during the oocyte pick-up procedure. Both ovaries can be visualized via transvaginal ultrasound monitoring and under minimal inhaled sedation PRP can be infused intramedullary at multiple sites using a 17-gauge single lumen needle. Gradual infusion of 4 mL of activated PRP can be done via a syringe attached to the transvaginal probe transducer. Following the infusion procedure, the pelvis should be thoroughly examined via ultrasonography, in order to check total vascular integrity. Minor leakage can be observed following retraction of the needle employed. Patients are recommended to remain in supine position for 15 minutes. AFC, AMH levels, and oocyte yield in the ICSI-ET cycle, mature metaphase II (MII), number of resulting embryos, and cycle cancellation rate post treatment should be noted.

Autologous intraovarian PRP infusion may restore ovarian function, enabling reactivation of the folliculogenesis process, recovery of menstrual cycle, and the enhancement of the hormonal profile. This may in turn enable achievement of pregnancy—even via natural conception—for certain women that are still exploring options on employing their own gametes. Future studies are required in order to provide concrete evidence.[23]

Melatonin

Melatonin has been studied as an antioxidant, free radical scavenger and nutrient that can modulate gene transcription for antioxidant enzymes in the ovarian follicular fluid and is thought to improve egg quality. One study demonstrated that women who had failed their first round of IVF, were slightly more likely to get pregnant on their next round of IVF if they had been taking a melatonin supplement (3 mg/day) compared to women who received no melatonin. Women that received melatonin supplementation had modest improvement in the percentage of mature eggs retrieved during their IVF cycle, embryo quality and clinical pregnancy rate. Although the difference was not statistically significant, researchers believe that melatonin has a positive impact on egg and embryo quality.[24]

Coenzyme Q10

It has been suggested that CoQ10 counteracts physiological ovarian ageing by restoring mitochondrial function. CoQ10 functions as an electron carrier in the mitochondrial respiratory chain and has a key role in oxidative phosphorylation to produce adenosine triphosphate (ATP). CoQ10 also exerts a crucial role as antioxidant by inhibiting lipid peroxidation and DNA oxidation, strengthening the endogenous antioxidant system. Dose recommended is Oral CoQ10 administration (200 mg/day in two daily doses for 30 days) and results in improved follicular fluid oxidative metabolism and oocyte quality in over 35-year-old-women.

A controlled randomized trial with an oral CoQ10 supplementation of 600 mg for two months and for up to three cycles (if pregnancy did not occur) resulted in a lower rate of aneuploidy in post-meiotic oocytes retrieved from aged women, but no significant differences in IVF outcomes were detected between the CoQ10 and placebo groups. The beneficial effects of CoQ10 supplementation were also observed in young women. In young women with low ovarian reserve and supplemented with CoQ10 (200 mg thrice daily for 60 days), an increased number of retrieved oocytes, fertilization rate, and high-quality embryos transferred were noted. The clinical pregnancy and live birth rates per embryo transfer and per one complete stimulation cycle tended to be higher in the CoQ10 group.[25-26]

Vitamin C and E

Among all of the currently used antioxidants, vitamins C and E are commonly used as natural antioxidants. Vitamin C is the major water-soluble antioxidant, which can effectively reduce a-tocopheroxyl radicals and level of low-density lipoprotein (LDL) in cell membranes, thereby restoring a-tocopherol and inhibiting the generation of free radicals. Vitamin E is the main hydrophobic antioxidant protecting cell membranes from oxidative damage by reaction with lipid radicals produced in the course of the lipid peroxidation chain reaction. Vitamin E supplementation has been shown to be associated with reduced risk of atherosclerosis by reducing oxidative stress and inhibiting LDL oxidation.

Dietary recommendations

Maintaining a healthy and balanced diet helps improve fertility. A 'rainbow' diet, which includes a wide array of colourful fruits and vegetables, is one of the best ways to include a high amount of nutrition in your meals. Some products like wheatgrass, avocados, sesame seeds, nuts, berries and green leafy vegetables can be beneficial.

Conclusions

While there are several approaches to improve fertility with adjuvants in patients with premature ovarian insufficiency, they need more research and larger randomised trials. DHEA supplementation seems to clearly improve live birth rates while other strategies including transdermal testosterone, GH, platelet rich plasma and coenzyme Q10 need more robust evidence.

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Pregnancy Complications

Dr Ganpat Sawant MD DNB FCPS DGO DFP DICOG
Ex HOD and Prof Obs Gyn Dept, DY Patil Medical College, Navi Mumbai
Managing Council member, IAGE, MOGS, FPAI
Director Noble Plus Hospital

Introduction

Premature ovarian insufficiency (POI) is being encountered more commonly in current practice. The term 'premature ovarian insufficiency' is preferred over 'premature menopause' because it does not imply a total cessation of ovarian activity. Ovarian failure is not permanent, which differentiates this condition form menopause. POI is relatively rare, with an occurrence of one in 100 women before the age of 40 years, one in 1000 women before the age of 30 years and one in 10,000 before the age of 20 years.

Spontaneous pregnancy

Diagnosis of premature ovarian insufficiency is usually sudden and distressful for the patient in terms of facing infertility. Women with POI ovulate extreme rarely. However, 5% of such women conceive spontaneously and have a normal pregnancy after the diagnosis is established. Spontaneous pregnancy with idiopathic POI is not associated with increased risk of miscarriage and obstetric complications. In 25% cases, POI has an intermittent and unpredictable course. To date, no clinical test can accurately determine the potential for conception in patients with POI.

The age of the patient at the time of treatment or natural conception has a significant effect on the chance of pregnancy in women with POI. The mean age of those who conceived after a diagnosis of POI was 30 years. Oocyte quality is correlated with female age and hence, it is not surprising that a young patient affected by POI is more likely to conceive if ovulation is restored naturally, or through assisted reproductive technology.

Pregnancy outcomes

Pregnancy-related risks are associated with the cause of POI and to some extent, whether the pregnancy is spontaneous, or the result of oocyte/embryo donation. The risk of miscarriage is probably the same as in women with normal ovarian function. In women with POI who become pregnant spontaneously, the risk of transmitting some pathologies such as Fragile X syndrome, should be considered.

Turner syndrome

Patients with Turner syndrome have a greater risk of abortion due to transmission of aneuploidy. However, natural pregnancies occur in at least 2% of women with Turner syndrome. Not only are these pregnancies uncommon, but their rates of miscarriage (29%), stillbirth (7%) and birth malformations (20%) are significantly higher than those of other female populations. Researchers believe that these miscarriages are caused by chromosomal abnormalities in the fetus, particularly Trisomy 21 and Turner syndrome and live-born children of these patients exhibit a much higher rate than in the general population (4 vs 0.4% for Trisomy 21 and 15 vs 0.5% for Turner syndrome).[1]

Many authors have reported a higher miscarriage rate in Turner syndrome patients (40–60%). This suggests that miscarriages in Turner syndrome might be caused by uterine factors, such as a hypoplastic uterus or low uterine blood flow. It has been suggested that the endometrium of women with Turner syndrome responds suboptimally to steroid hormone stimulation; this may be related to a reduced concentration of steroid hormone receptors. Another group has shown that Turner syndrome patients have an early implantation failure and they suggest that an inherent endometrial abnormality, possibly associated with a deficiency in X-linked genes regulating endometrial receptivity, is the main cause. The anatomy of the uterus is altered in Turner syndrome patients and a hypoplastic uterus is a frequent finding that could be the cause of a higher rate of miscarriage in these patients.[2]

Owing to the short stature of women with Turner syndrome and their associated health problems that can complicate pregnancy, it is advisable for these women to avoid multiple pregnancies. Therefore, most centres opt to transfer only one or two embryos during IVF. It is estimated that approximately 25–50% of women with Turner syndrome also have an associated cardiovascular malformation. Deaths and aortic dissection have been reported in Turner syndrome patients who became pregnant through oocyte donation. Patients with Turner syndrome should be adequately screened using echocardiography prior to treatment.[3]

Cancer survivors

Cancer survivors may worry about transmitting genes that could result in an increased risk of cancer in the next generation. Another concern is for the oocytes, if ovarian function is recovered after chemotherapy (CT). Studies on pregnancy outcome in cancer survivors have found no significant increase in congenital malformations or malignant neoplasms in their offspring.[4]

A systematic review on the long-term follow-up of survivors of childhood cancer concluded that chemotherapy has no adverse effects on uterine function or pregnancy outcomes other than an increase in miscarriage rates in pregnancies conceived soon after chemotherapy (Scottish Intercollegiate Guidelines Network (SIGN), 2013). However, a large retrospective observational study of approximately 6,100 offspring of childhood/adolescent cancer survivors showed anthracyclines (doxorubicin or daunorubicin) were associated with low birth weight independent of exposure to radiotherapy.

In contrast, abdominopelvic radiotherapy is consistently reported to be associated with poor uterine function with increased risks of late miscarriage, prematurity, low birth weight, stillbirth, neonatal haemorrhage and postpartum haemorrhage. There are also case reports of uterine rupture as well as a possible increase in placental attachment disorders (placenta accreta and percreta). Not only is the effect on uterine function dose dependent, but also related to age at the time of exposure, the pre-pubertal uterus

being more susceptible. There are case reports of peripartum heart failure, which are probably due to exacerbation of pre-existing cardiac dysfunction originating at the time of exposure to anthracyclines or radiotherapy.

Oocyte donation avoids transmission of genetic material to the next generation, thus abolishing the possibility of transmitting hereditary cancer from the affected woman. The protocol of recruiting oocyte donors includes the declaration of the absence of any previous history of familial cancer.

Oocyte donated pregnancies

Oocyte (or embryo) donation is an established fertility treatment for POI and most IVF units report similar pregnancy, implantation and live birth rates as their cycles using women's own oocytes. Small case reports have suggested that these pregnancies may be obstetrically high risk. In the largest cohort study of 232 consecutive oocyte donation pregnancies, there was a high prevalence of miscarriage (40% after identification of a single gestational sac), pregnancy-induced hypertension (22%), prematurity (13%), low birth weight and small for gestational age (18% and 15%, respectively), caesarean section (61%), and postpartum haemorrhage (12%) with the quoted figures relating to singleton deliveries. Threatened miscarriage in the first trimester with subsequent live birth was also common (11%). Donor pregnancies should therefore be cared for in a high-risk antenatal clinic.

Analysis of the UK HFEA database indicates that oocyte recipients have an almost two-fold increased risk of preterm birth and low birth weight compared to women using their own oocytes after adjusting for other maternal confounders. The risk of aneuploidy is related to the age of the donor, not the recipient, and should be taken into consideration during antenatal aneuploidy screening.

Autoimmune disorders

Patients with POI and the presence of autoimmune activity may respond to ovulation induction and have the best chance of conceiving using their own oocytes. As miscarriage has been associated with autoimmune mechanisms, the crucial questions are:

Do the antibodies affect the oocyte inside the ovary?

Does the autoimmune mechanism diminish the chance of implantation only if the oocyte has been affected previously?

Will the embryos in the pregnant woman be attacked regardless of the origin of the oocytes?

If the answer to the last question is affirmative, we should expect to see more miscarriages in the group with autoimmune processes. The answers remain elusive.[5]

Discussion

Pregnancies and live births are uncommon in patients diagnosed with POI but are not impossible. Indeed, POI is not always an irreversible condition and resumption of ovarian function can occur in karyotypically normal patients.

Analysis of the reproductive outcome of patients with idiopathic POI in oocyte donation program compared with those of patients with true menopause shows that there were no differences in pregnancy, implantation or miscarriage rates between these groups. POI is a syndrome with different causes and pregnancy can be achieved with a woman's own or, more commonly, with donated oocytes. Specific considerations should be made in women with POI according to the aetiology, miscarriage risk and cardiac risk in Turner syndrome and the transmission of genetic abnormalities in women with genetic POI.

Conclusion

It is crucial to underline the importance of educating and reassuring patients that spontaneous pregnancies in women with POI are not associated with higher obstetric morbidity or neonatal risk as compared with the general population and may lead to the birth of a healthy child, especially where the woman's age is less than 30 years. In oocyte donor pregnancies, there is a high prevalence of miscarriage, PIH, prematurity, fetal growth restriction, caesarean section and postpartum haemorrhage with singleton deliveries.

Many questions remain unsolved in the evolution of pregnancy in patients with POI. The majority of studies have been retrospectives with patients. Until we are able to identify the cause and understand the pathogenesis of POI, the therapeutic options remain elusive. Further studies are needed to answer the questions that still remain about pregnancy and reproductive health in patients with POI.

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Metabolic Issues

Dr Sujata Dalvi
Managing Council member, MOGS
Asst Editor JOGI – Journal of Ob Gyn of India
1st Joint Secretary of AMOGS

Introduction

Premature Ovarian Insufficiency (POI) is term used to include diagnostically similar conditions like hypergonadotropic hypogonadism, premature ovarian failure and ovarian dysgenesis. This condition can be transient or progressive and will eventually result in premature menopause. POI is a heterogenous disorder affecting women below the age of 40 years. Conceptually, POI is characterised by ovarian follicular dysfunction or depletion of functional primordial follicles before the age of 40 years.

The incidence is 1% and causes are genetic, autoimmune, environment, metabolic, iatrogenic and cancer therapy. In most cases, cause is unknown – idiopathic POI. It has long term metabolic comorbidities like cardio-vascular disease (CVD), diabetes, cognitive impairment and osteoporosis. These women are at high risk of developing metabolic syndrome. The management is hormone replacement therapy (HRT) until the natural age of menopause.

The term POI has been adopted by ESHRE- European Society of Human Reproduction and Embryology as POF - Premature Ovarian Failure is considered as final stage of POI. The diagnosis is confirmed by 2 FSH levels in post-menopausal range (> 30 U / L) at least 1 month apart in duration of 4–6 months of amenorrhoea.

Genetic metabolic abnormalities associated with POI

Galactosemia Toxic accumulation of galactose during infancy. Defects in ocular, renal, hepatic system. Requires treatment in childhood to prevent mental retardation.

CHO deficient glycoprotein deficiency Neurological abnormalities
17 alpha hydroxylase/ desmolase deficiency – XX females with no secondary sexual characteristics – responds to external hormones.

Aromatase mutation No conversion of androgens to estrogens – has clitoromegaly/ primary amenorrhoea – responds to external estrogens.

Metabolic syndrome

Defined as those with 3 or more of following components:

1. Abdominal obesity (waist circumference > = 88 cm)
2. High triglycerides (> = 150 mg/ dL)
3. Low HDL (< = 50 mg/ dL)
4. Elevated blood pressure (syst BP > = 130 / diast BP < = 85 mm Hg)
5. High Fasting (FBS > 100 mg/ dL)

Criteria for abdominal obesity is adopted from cut off from European region.

Risk Factors

Cardiovascular Disease

POI has significant risk factors for health and disease susceptibility. Loss of ovarian function and subsequent deficiency of endogenous estrogen leads to high risk of cardiovascular disease and mortality. This is due to endothelial and autonomic dysfunction, abnormal lipid profile and insulin dysfunction.

POI leads to abnormal lipid metabolism, impaired glucose tolerance and elevated cardiovascular risk. HDL/ TC/ LDL levels are found to be high whereas triglycerides, glucose, insulin, HOMA IR and BP did not differ significantly in some study groups. Some metabolic factors persisted after correction of age and BMI, hence more research is advisable. Meta-analyses from various studies shows POI with increased incidence of ischemic heart disease. Atherogenic lipid profile changes lead to increased CVD risk.

POI is also associated with decreased circulating androgen levels, leading to increased dyslipidemia and atherosclerosis further impairing CVD risk. Mortality rate in IHD increases by 80% in POI group.

Increased waist circumference reflects central obesity which is a risk factor for CVD. Some studies have proposed fat distribution to be better indicator of adiposity than BMI. Menopausal transition is associated with increased accumulation of abdominal visceral fat. Visceral fat is metabolically active, produces inflammatory markers and is associated with increased CVD risk in post-menopausal women.

CRP levels are associated with increased CVD due to promotional atherothrombosis. Raised CRP, insulin levels and dyslipidemia is reported in pre-menopausal women with diminished ovarian reserve, suggesting impaired CVD risk with decreased ovarian reserve.

Increased risk of hypertension and decreased kidney function is potentially seen in women with POI. Hypertension is a well-known risk factor. Decreased GFR could be a risk factor in patients with diabetes/ HT. Decreased GFR itself could be a marker for vascular disease. No co-relation between subclinical atherosclerosis and healthy, slender, non-smoker, non-diabetic POI has been found.

Management

Cardiovascular evaluation should consist of regular BP monitoring, weight, smoking status, physical activity status, ECG and blood investigations like lipid profile, sugar, insulin levels at regular intervals.

Women at increased risk of CVD can modify with behavioural changes like stopping smoking, regular weight bearing exercises and maintaining healthy weight. HRT has beneficial effect on plasma lipids, blood pressure, insulin resistance and endothelial function. It should be continued till natural age of menopause.

Carbohydrate metabolism

Glucose metabolism may be abnormal in women with POI and autoimmunity may lead to Type 1 diabetes. Women with Turner syndrome have 50% risk of developing impaired glucose tolerance and four-fold increase in Type 2 diabetes. This is due to insulin deficiency and resistance.

Bone health

Estrogen deficiency results in bone remodelling. Increased osteoclastic activity leading to bone resorption which in turn induces bone formation but resorption exceeds formation. There is net loss of bone by 2–3% per year early after menopause. Slow mineralisation of new bone is much less as compared to old bone. Increased bone remodelling is reversible in short term but with time there is perforation of cancellous bone with loss of bone micro architecture and is irreversible. The rate of bone loss slows down after 10 years of menopause. Women with POI have reduced BMD, associated with estrogen deficiency. Prevalence of osteoporosis is in range of 8 – 14 %. Later, it leads to increased fracture risk.

Management

Regular BMD evaluation should be done. A balanced diet with adequate calcium, vitamin D, weight bearing exercise, healthy body weight, cessation of smoking and decreasing alcohol intake should be followed to reduce fracture risk.

Calcium 1000 mg/ day and Vit D 800 IU/ day should be taken.

HRT- Estrogen replacement Oral/ transdermal with cyclical progesterone (dydrogesterone) is more effective. Estrogen replacement therapy has more beneficial effect in reducing BMD. COCs are also helpful.

The bisphosphonates, alendronates, etidronates and risedronates, SERMs and parathyroid – all help in reducing fracture risk.

Quality of life

POI is not homogenous and quality of life varies with individuals. Health problems like cancer risk, unrelated health issues, vasomotor problems and type of treatment have an impact on QOL with addition of social and economic impact. POI is associated with increased risk of depression, anxiety, stress, low levels of self-esteem and life satisfaction. Psychological well-being is of immense importance.

Group intervention is encouraged to reduce social isolation and overcome self-esteem. Referral to special psychiatry center for further treatment if needed should be done. Non hormonal therapy like SSRIs, SNRIs, clonidine and gabapentin have effect on quality of life with vasomotor symptoms. There is also increased risk of dementia and may be associated with neurological dysfunctions.

Annual screening

It is needed to assess thyroid, adrenal function and other routine preventive health care. Suspected cases should be identified and management should be individualised.

Conclusion

Premature Ovarian Insufficiency represents a continuum from impaired ovarian function with intermittent ovulation to premature menopause as end point with permanent loss of ovarian function. Because of potential long-term consequences of hypoestrogenism, including cardiovascular disease, neurocognitive decline, menopausal symptoms and osteoporosis, it is important to establish correct diagnosis and identify medical conditions. Management should include comprehensive approach with HRT, physical and emotional support. The POI population needs long-term follow up with preventive maintenance therapy and periodic surveillance.

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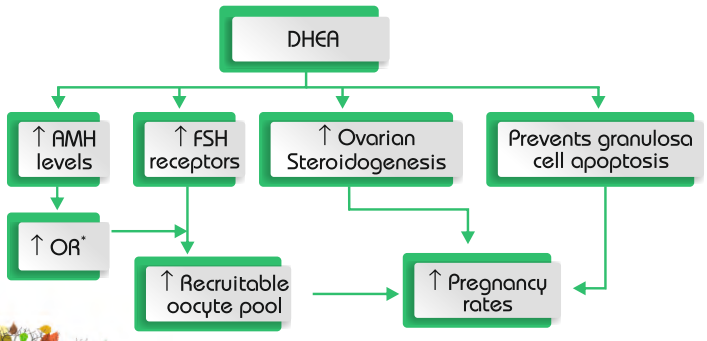

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*Animal Study

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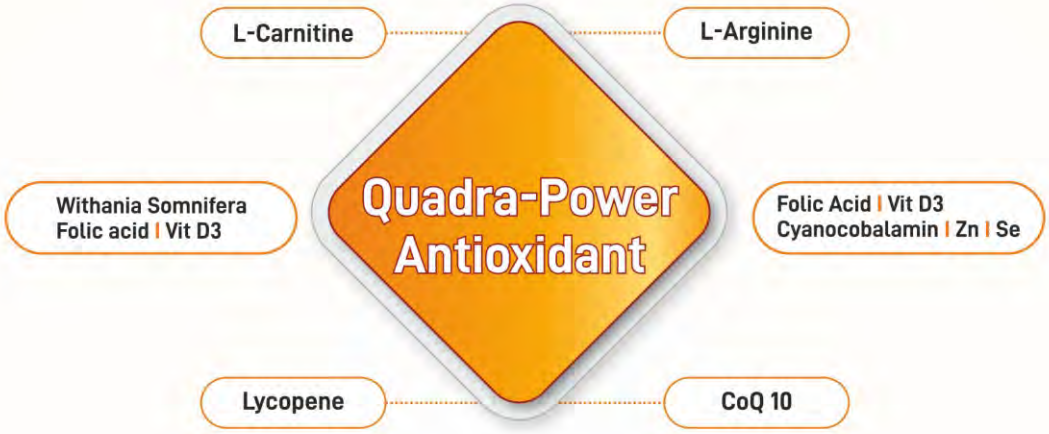

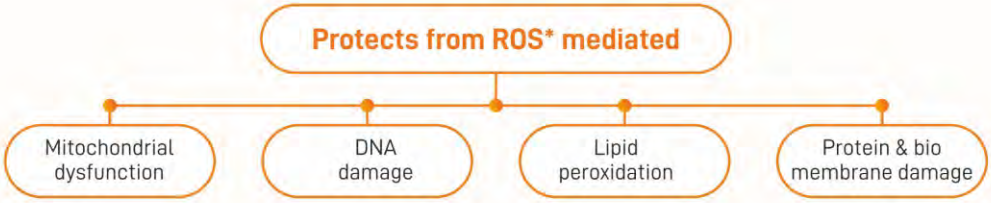

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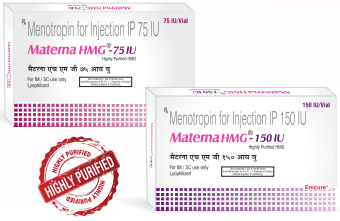

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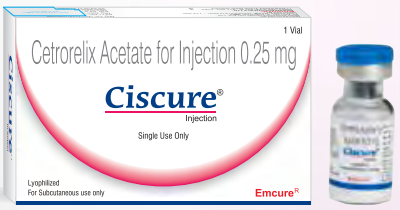

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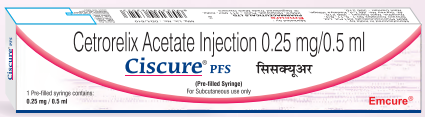

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