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Review

*Corresponding author
Naina Kumar, MD
Associate Professor
Department of Obstetrics and Gynecology
Maharishi Markandeshwar
Institute of Medical Sciences and Research
Mullana-133207, Ambala, Haryana, India
Tel. +91-9552515600
E-mail: drnainakumar@gmail.com

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Premature Ovarian Insufficiency: Aetiology and Long-Term Consequences

Naina Kumar, MD*; Isha Manesh, MD Student

Department of Obstetrics and Gynecology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana-133207, Ambala, Haryana, India

ABSTRACT

Premature ovarian insufficiency (POI) is characterised by premature cessation of ovulation/menstruation for 4-6 months along with raised serum gonadotropin levels especially follicle stimulating hormone (FSH) (>40 IU/L) on two or more occasions >4 weeks apart. POI is a heterogeneous disorder resulting from various autoimmune, iatrogenic and metabolic factors, chromosomal or genetic mutations and infections. Premature loss of ovarian function in women with POI is associated with long-term psychosocial sequelae, infertility and major health complications. It is also associated with age-specific increase in mortality due to cardio-vascular diseases. Its occurrence has increased in recent years as more and more women now-a-days attain motherhood late, also there is increase in incidence of gynaecological malignancies and its successful management leading to increased risk of POI. This manuscript aims to highlight the recent advances in pathogenesis and management of POI. Literature regarding premature ovarian insufficiency, its incidence, pathogenesis, management and recent advances was searched from various English language journals, WHO, ACOG data, published peer-reviewed articles on PubMed, Medline, Embase and Google Scholar upto 2017.

KEY WORDS: Amenorrhoea; Menopause; Ovary; Ovulation; Stem cells.

ABBREVIATIONS: POI: Premature Ovarian Insufficiency; FMR1; Fragile X mental retardation 1; WHO: World Health Organization; AOAs: Antiovarian antibodies; APSs: Autoimmune Polyendocrine Syndromes; FSH: Follicle Stimulating Hormone; BMPs: Bone Morphogenetic Proteins; ESCs: Embryonic Stem Cells; MSCs: Mesenchymal Stem Cells; UCMSCs: Umbilical Cord Mesenchymal Stem Cells; ADSCs: Adipose-derived Stem Cells; FMR-1:Fragile X Mental Retardation 1.

INTRODUCTION

Premature ovarian insufficiency (POI) also known as Premature ovarian failure or Hypergonadotropic ovarian failure or Menopausa precoce[1] is defined as a primary ovarian defect, characterized by an absent menarche (primary amenorrhea) or premature loss of ovarian follicles before 40 years of age (secondary amenorrhea).[2,3] Characteristic features include cessation of ovulation or amenorrhoea for 4 months or more, hypoestrogenism (estradiol levels <50 pg/ml)[4] and high serum gonadotropin levels,[5,6] especially two serum follicle-stimulating hormone (FSH) levels (>4 weeks apart) in menopausal range[7,8] (>40 IU/l).[4]

POI was previously known as premature menopause, but this term is a misnomer, as all women with POI do not always stop menstruating, neither do their ovaries shut down completely.[8] In most women aged >40 years, there is a physiological decline in ovarian function with aging which is called as perimenopause/menopausal transition.[9] Ovarian ageing resulting in ovarian failure and menopause is a continuous process[5,10] and menopause is usually attained at 51 years (range 40-60 years).[11-13] The World Health Organization (WHO) defines menopause as permanent cessation of menstruation due to ovarian follicular activity loss.[13]

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POI differs from menopause as, in POI unpredictable and varying degrees of ovarian functions are still present in 50% of women, and about 5-10% can even conceive and deliver child after diagnosis and treatment.[7,8,14] It is a hypergonadotropic and hypogonadism state resulting from depletion/dysfunction of ovarian follicles due to either low initial numbers or accelerated loss.[15] Premature loss of ovarian function leads to significant long-term psychosocial sequelae and major health complications.[16] It also results in age-specific increase in mortality rate.[17,18]

Based on the age of onset, POI can present itself as primary amenorrhea, without onset of menarche, or secondary amenorrhea after puberty.[3] It is a continuum of disorders with four clinical states which are not permanent. Patients usually budge from one state to another in an unknown manner.[19] These states are as follows:

1. *Occult POI* presents as unexplained infertility with normal baseline serum FSH levels.
2. *Biochemical POI* presents as unexplained infertility with elevated basal serum FSH levels.
3. *Overt POI* previously known as premature ovarian failure is characterized by elevated serum FSH levels with associated menstrual disorders like oligomenorrhea, polymenorrhea, and metrorrhagia.
4. *POI* is an extreme state of total primordial follicle depletion; an irreversible state characterized by anovulation, amenorrhea, infertility, and elevated gonadotropin levels.

Incidence

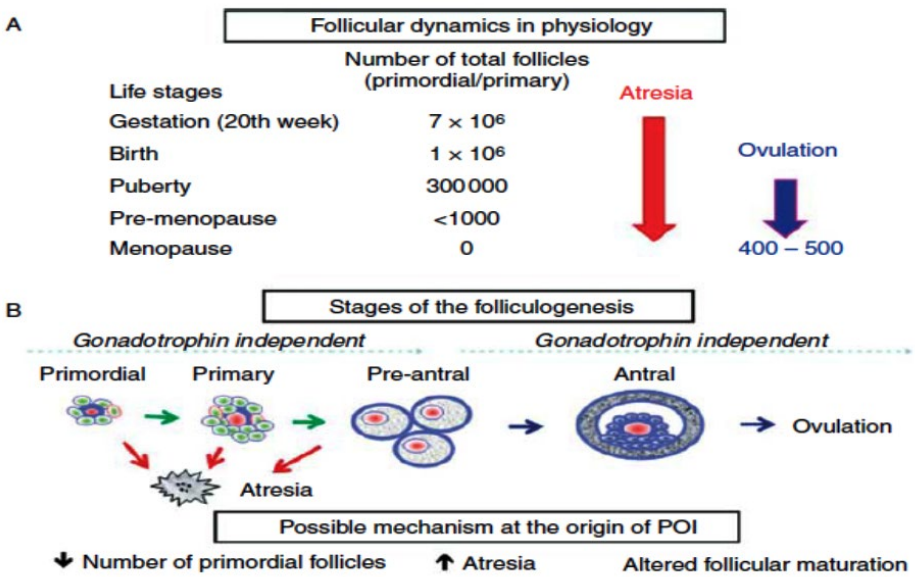
POI is relatively common, with an estimated occurrence of 1 in 100 by 40 years; 1 in 1000 by 30 years[11,12] and 1 in 10,000 by 20 years of age.[1,20,21] It affects around 1-3% of women in the reproductive age below 40 years and around 0.1% in women below 30 years of age.[2,10,18,22,23] Women with POI, around 10-28% experience primary amenorrhea and 4-18% secondary amenorrhea.[10,18] Incidence of spontaneous onset POI has increased due to increasing success rates of cancer treatment in girls and young women.[20,24,25] On the other hand, familial POI accounts for 15-30% of all cases.[1,12,26]

Pathogenesis

Process of human folliculogenesis being highly complex and organised, is characterised by progressive maturation of small primordial follicles to larger ovulatory follicles. This whole process occurs continuously, and can stretch over a period of a year.[27] Reproductive life span of human females start with a fixed number of primordial follicles,[28] of which only 400-500 develop and ovulate before physiological menopause (Figure 1).[29]

On the other hand, exact mechanism for development of POI is not known. It can be due to: a) Preliminary decrease in primordial follicle pool; b) Accelerated atresia of follicles; c) Defective maturation/recruitment of primordial follicles (Figure 1).[29] Furthermore, accelerated follicular atresia can be because of changed apoptosis rate, defective follicle maturation blocking and abnormalities in primordial follicle activation that causes decreased number of available functional follicles/accelerated

Figure 1: (A) Normal Physiology of Foloocular Development. (B) Mechanism of Origin of Premature Ovarian Insufficiency.[29]



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atresia.[30,31]

Hence, factors that initiate such mechanisms are highly heterogeneous and can be a result of, genetic mutations, chromosomal, infectious, autoimmune, metabolic and iatrogenic factors.[18,29]

AETIOLOGICAL FACTORS

Genetic Factors

Genetic factors are most commonly responsible for POI accounting for 7% of all cases.[3,5,32] X chromosome is most commonly affected, but autosomal involvement is also common.[18,33] Aneuploidies and rearrangements are most commonly reported with POI[34] (Figure 2).[29]

X CHROMOSOME

Monosomy (45 X)

Terminal deletions of long arm of X chromosome result in primary amenorrhea and absence of breast development in all cases.[12,35] Total or near total absence of single X chromosome,[18] known as Turner's syndrome affects around 1 in 2500 live female births and is usually associated with ovarian dysgenesis leading to primary amenorrhea. However, 3-5% of such females with Turner mosaic karyotype can menstruate and even develop secondary sexual characteristics. Turner syndrome is associated with 4-5% POI cases.[12,36,37]

Trisomy

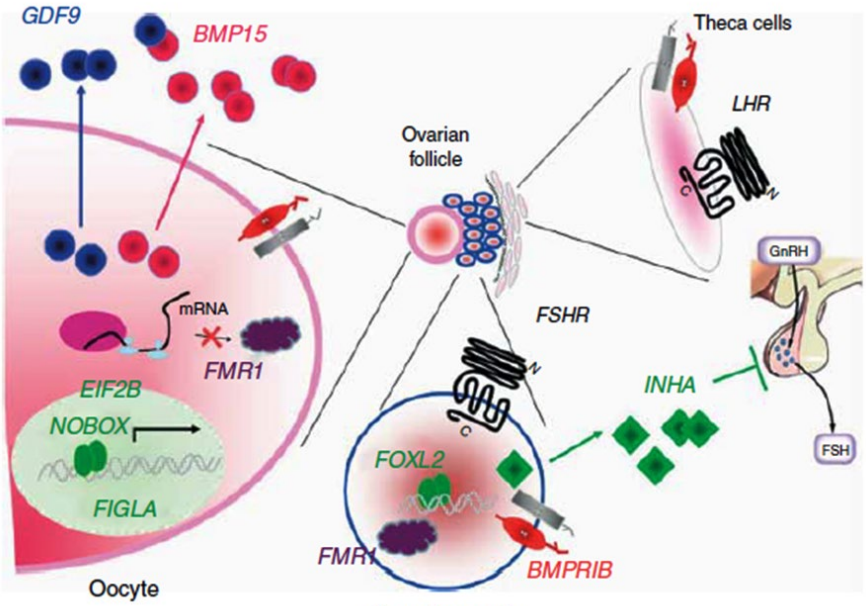
Trisomy affects 1 in 1000 women.[12,18] Trisomy X females usually have normal ovarian function, but in some, it may manifest as early menopause, secondary amenorrhea, oligomenorrhea.[10,38] Around 10% of females have mosaicism with 46, XX/47, XXX or 45, X/47, XXX karyotypes. Manifestations depend on time at which causing events occurred.[10] Ovarian failure in females with 47, XXX (mosaic/non-mosiac) can be due to meiotic inadequacy of three X chromosomes, which is still unproven.[10,34] However, cytogenetic studies in women with POI have shown that trisomy X (mosaic/non-mosaic patterns) have very low incidence of POI.[10,39,40]

Fragile X Syndrome

Fragile X syndrome is an X-linked dominant genetic condition characterised by expansion of trinucleotide repeat[41] with prevalence of 1/6000 in females and 1/4000 in males.[42,43] It is a common cause of hereditary mental retardation and developmental delay.[43,44] Fragile X mental retardation 1 (*FMR1*) gene is located on X chromosome at Xq27.3. There is expansion of CGG trinucleotide repeats in 5′ untranslated region of first exon of *FMR1* gene. Affected females show >200 CGG repeats, as compared to normal (5-54 CGG repeats). This expansion of >200 repeats causes methylation-coupled silencing of *FMR1* gene resulting in loss of FMR-protein which is important for brain development in prenatal and postnatal period.[41,43,45]

Recently, it was reported that higher number of CGG

Figure 2: Genes involved in Pathogenesis of Premature Ovarian Insufficiency.[29]



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repeats (>30-40) can be used to detect premature ovarian aging and POI in infertile women.[43,46] An estimated 16-26% of female with *FMR1* premutation carriers develop POI,[43,47,48] whereas only 2% of normal women develop isolated POI.[49] They are also known to develop tremor-ataxia syndrome,[50] mild neuro-cognitive dysfunction.[51] It was also reported that paternally inherited Fragile X premutations were more likely to be associated with POI as compared to maternally inherited permutations.[52]

Bone Morphogenetic Protein 15 Gene (BMP15)

Bone morphogenetic proteins (BMPs) are proteins belonging to transforming growth factor-β (TGF-β) superfamily, which play an important role in oocyte-specific growth/differentiation factors that help in follicle maturation and granulosa cell growth.[18,29,53,54] BMP15 gene is located on the short arm of Chromosome X (Xp11.2) within 'POI critical region'.[18,29,55] *BMP15* mutations are associated with 1.5-12% of POI cases.[1,56-60] This defect is an unusual example of X-linked disease in which affected females inherit mutation from their unaffected father.[1,56]

Autosomal Genes

Genetic studies have shown various isolated gene defects associated with POI, which are:

a) Estrogen receptor (ER-α and ER-β) mutations,[12,35]
b) FSH receptor mutations (FSHr),[61,62] associated with <1% POI cases.[1,32, 60,63]
c) LH receptor mutations (LHr)[64] associated with <1% POI cases.[1,32,60,63]
d) FOXL2 mutations: Occurs with either blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) type 1 (without POI) or BPES type 2 (with POI), known as POI-3.[1,65,66]
e) Steroidogenic factor 1 (NR5A1) mutation.[12,35]
f) CYP19A1 mutation.[12,35,67,68]
g) *Inhibin A* gene mutation associated with 5% of POI cases.[60,69]
h) *NOBOX* gene: Newborn ovary homeobox gene (*NOBOX*) plays role in initial phases of follicular maturation[70] and is rarely associated with POI.[71,72]

Despite several genes shown to be associated with POI, the exact mechanism still remains uncertain.[54,56,65,73]

Autoimmune Factors

Autoimmunity is characterized by auto-reactive lymphocytosis, organ and non-organ-specific autoantibodies.[74,75] It accounts for 4-30% of POI cases[1,8,76-82] and is characterised by presence of antiovarian antibodies (AOAs), lymphocytic oophoritis on histopathological examination, in association with other autoimmune conditions.[82-86] Exact mechanism of autoimmune POI remains obscure and may be due to genetic and or environmental factors that are responsible for initiating immune response.[43,75,83,87,88] Important factors involved are: Major histocompatibility complex antigen (HLA), cytokines, cell-mediated immunity, antibody-mediated immunity, etc.[43,75,83,87,88]

There are three main types of autoimmune POI: Adrenal autoimmune POI, non-adrenal autoimmune POI and isolated idiopathic POI.[43,88,89] Autoimmune causes in pathogenesis of POI is characterised by presence of autoantibodies directed towards the ovarian tissue.[84,90,91] These AOAs can be detected in the serum of affected females before clinical onset of POI.[92] These antibodies bind to various steroid hormone-producing cells[8,14,82,93,94] like adrenal cortex cells, theca cells of ovary, placental syncytiotrophoblast cells, and are known as steroid cell antibodies (StCAs).[82] They also bind to gonadotropins and their receptors,[95-97] zona pellucid,[98] oocyte,[99] corpus luteum,[84,100] and can act as markers of ovarian autoimmunity.[82]

Furthermore, it was observed that POI has strong association with autoimmune Addison's disease. Around 60-87% cases of POI have Addison's disease.[14,82,90,93,101] There are two types of autoimmune polyendocrine syndromes (APS)[5,74,75] strongly associated with POI. Type 1 APS [autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)] characterized by combination of hypoparathyroidism, adrenal failure, and chronic mucocutaneous candidiasis. It is usually seen in children and is associated with POI in 60% cases presenting as primary amenorrhoea. Type II APS is characterised by autoimmune Addison's disease with adrenal insufficiency and other autoimmune illnesses without hypoparathyroidism.[5,74] It usually occurs between the third to fourth decades of life and is associated with POI in 25-40% cases.[14,82,90,93,101] Other autoimmune conditions commonly associated with POI are: hypothyroidism,[102-104] autoimmune adrenal insufficiency,[105] hypoparathyroidism,[79] type 1 diabetes mellitus, hypophysitis, autoimmune haemolytic anaemia, celiac disease, inflammatory bowel diseases, glomerulonephritis,[5] Sjogren's syndrome[106] and myasthenia gravis.[89]

Iatrogenic

Iatrogenic causes for POI are increasing due to rise in incidence of various gynaecological cancers and their successful treatment.[107,108] Oocyte is highly radiosensitive and responds to even 2 Gray dose of radiotherapy.[43,109] Hence, an ovarian radiotherapy dose of ≥6 Gray results in ovarian insufficiency in almost all females over 40 years of age.[110] Effect of radiotherapy on ovaries is dependent on dose, age, and radiation therapy field.[43,111,112] Chemotherapy also causes ovarian insufficiency but exact mechanisms are not clear; however, it is well known that chemotherapeutic agents affect granulosa cell functions and oocytes, ultimately causing ovarian insufficiency.[43,113] Major predictive factors for development of ovarian insufficiency after chemotherapy are; age, class, dose of chemotherapeutic agent, concurrent use of radiotherapy, etc.[43,108,114] It has been reported that use of alkylating agents (N-mustard, L-phenylalanine mustard, Chlorambucil, Busulfan, and Cyclophosphamide) are strongly associated with POI (40%).[12]

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Furthermore, it has been reported that ovarian drilling for polycystic ovarian syndrome and chocolate cysts removal for endometriosis are associated with early menopause.[12,115] Recent literature reports that uterine artery embolization also leads to POI by affecting ovarian vascular supply.[43,116] Hence, it was observed that almost any pelvic surgery, be it ovarian cyst removal or hysterectomy–can affect ovaries and lead to POI, by affecting vascular supply or by causing inflammation in pelvic area.[117] Studies have shown that in some cases of POI, ovarian function may return spontaneously many years after chemotherapy and/or radiotherapy[118,119] and many successful pregnancies can also occur in such women.[43]

Infectious and Toxic agents

Till date there are no direct evidences available that suggest correlation between infections and POI, but studies report that Mumps oophoritis may be related to development of POI. True reason of post-oophritis ovarian failure is unknown.[5,43,120] In vast majority of affected women, return of ovarian function occurs following recovery.[18,43] Another infectious agent and its treatment that can be linked with POI is HIV infection.[5,121] It has been reported that around 3.5% of females with POI have a history of infections like varicella, tuberculosis shigellosis, malaria and cytomegalovirus.[7,43,80]

Amongst the various toxins that are strongly associated with POI, smoking is one major toxin. It was found that there is an inverse relationship between number of cigarettes smoked per day and age at menopause.[43,122] Smoking causes alteration of ovarian function, and leads to early menopause in female who smoke as compared to non-smokers.[43,123]

Other toxins that commonly affect ovarian functions and can lead to POI are: Polycyclic aromatic hydrocarbons (PaHs), toxic chemicals in tobacco, heavy metals, insecticides, plastics and industrial chemicals, but exact underlying mechanism is unclear.[5,18]

Clinical Course

Women with POI are typically observed with secondary amenorrhea/menopause, many a times preceded by irregular menstrual cycle at age <40 years.[20,78] In few women with primary amenorrhea, the cause can be an underlying chromosomal abnormality.[20] Other characteristic symptoms include hot flushes and night sweats[20,124]; these are mainly due to estrogen deficiency.[118,125] Vaginal symptoms include dyspareunia and dryness, which can be distressing for women.[125,126] In addition to these, women also suffer from sleep disturbances, mood swings, lack of concentration, depression, loss of libido, dry eyes,[127] altered urinary frequency and lack of energy.[117,125] These symptoms are usually transient and are mainly due to changes in ovarian functions (estrogen withdrawal rather than deficiency) that result from spontaneous onset of POI.[125,128] Furthermore, it was observed that in women with surgically induced POI, symptoms are more severe and persistent.[125]

Diagnosis and Assessment

Diagnosis of POI can be easily made on clinical presentation, in woman <40 years of age with amenorrhea or oligomenorrhea of 4-6 months with two measurements of elevated FSH levels. Final diagnosis can be made on certain investigations which include[125]:

Gonadotropin Levels: Both FSH and LH are elevated in women with POI (hypergonadotropic amenorrhea). Elevated FSH levels are more significant than LH. High FSH levels are considered as gold standard for diagnosis of POI and values >25 U/L on two occasions, more than 4 weeks apart is indicative of ovarian insufficiency.[125]

Low Estrogen levels: Estradiol (E2) levels <50 pg/ml is typically observed in women with POI.[78] Low estradiol levels in combination with high FSH and LH levels are diagnostic of POI.

Antimullerian Hormone (AMH): AMH is homodimeric glycoprotein consisting of two subunits,[129,130] and is produced by granulosa cells of growing follicles.[131] It regulates early follicular recruitment from primordial pool[132] and is a good reflector of ovarian reserve.[133-135] AMH levels are usually very low or undetectable in women with POI.[136] Hence, AMH testing may become important diagnostic tool for assessment of ovarian reserve before and after chemotherapy in young women with pelvic cancers, before and after ovarian surgery, and for females at high risk of POI.[137,138]

Inhibin B: It is produced by granulosa cells of growing follicles,[139] but its levels show significant variability between menstrual cycles. Hence, it is usually not recommended for diagnosis of POI.[138]

Once diagnosis of POI is made, other investigations include:

- Karyotyping and fragile X mental retardation 1 (FMR-1) premutation for genetic cause[8]
- Screening for autoimmune diseases like anti-adrenal, anti-21-hydroxylase,[8] anti-thyroid peroxidase, anti-thyroglobulin antibodies[125] and AOA are recommended.

Future Fertility

Around 5-10% of women with POI conceive spontaneously due to fluctuations in ovarian functions.[12,125,140] Till date no clear guidelines or drugs are available that can cause follicular development or increase fertility in women with POI.[125] Various studies have tried to examine the role of ovulation inducing drugs, gonadotrophins, glucocorticoids, GnRH agonists and antagonists,[141] but no clear advantage has been observed.[12]

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However, fertility preservation techniques can be considered for women at risk of developing POI due to disease or its management. Considerably high rates of natural pregnancies were reported in such women who underwent fertility preservation pre-treatment.[125,142] Another way of improving fertility in women with POI due to sterilizing surgeries is replacement of cryopreserved ovarian tissue, but this has been studied in very few cases.[125,143]

Recent advances have shown that oocyte donation is another option for women with POI desiring pregnancy.[125] Such a successful pregnancy was first reported in 1984[144] and since then it has become a 'routine' treatment.

Long-term Consequences of POI /Premature Menopause

Bone Health

Estrogen is known for its beneficial effects on bone growth. It is responsible for increased bone remodelling and hence its deficiency is associated with bone loss, decreased mineral density and fracture risk, as seen after natural menopause.[145,146] Net bone loss after menopause is usually 2-3% per year.[147] Effect of estrogen deficiency on bone in women with POI is one of most clearly recognized adverse effects of POI. It usually remains asymptomatic for many years, until fragility fracture happens. Furthermore, depending on degree and duration of estrogen deficiency, women with POI develop reduced bone mineral density earlier as compared to normal females.[148,149] An estimated 8-14% of women with POI suffer from osteoporosis[148] as compared to normal females.[150]

Cardiovascular

Estrogen has cardio-protective effects and its early loss leads to increased risk of cardio-vascular mortality.[138,151] Hence, women with POI are associated with high risk of cardio-vascular mortality.[78,125,138,151] Various researches have proven that women with spontaneous POI suffer early onset coronary heart disease[152] and are at increased risk of dying from coronary vascular diseases (CVDs).[125,153,154] Furthermore it has been observed that women with pre-menopausal estrogen deficiency develop signs of endothelial dysfunction[155] and premature atherosclerosis very early.[125,156] It is well proven that estrogen plays an important role in ventricular contractile function,[125,157] decreases insulin resistance[125,158] and protects against lipid peroxidation, thereby playing an important role in cardio-protection.

Cognitive and Neurological Health

Few studies have observed the effects of POI on neurological health of women.[125] POI, especially the one resulting from bilateral oophorectomy before onset of natural menopause, increases risk of cognitive impairment/dementia. This risk is found to be inversely proportional to the age at which oophorectomy is performed.[12,159,160] Such women are also prone to develop Parkinsonism later in their life.[12,159,160] Hence, it is very important to explain all possible detrimental effects on neurological health before planning for hysterectomy and/or oophorectomy in women <50 years, especially for prophylactic reasons.[125]

Sexual and Genito-urinary Functions

In most women with POI, sexual problems are due to physiological stress, or secondary reaction to emotional stress of diagnosis and infertility resulting from the disease.[161] Furthermore, fertility treatment has unpredictable outcomes which leads to emotional stress and affect sexual functions in the long run.[125,162] Hence, to hold POI as the sole cause for sexual dysfunction may be incorrect, also there are no direct evidences to evaluate effects of POI on sexuality.[163]

Most common symptoms are those related to estrogen deficiency, which include vasomotor symptoms, sleep disturbances, depression, fatigue, loss of libido, vaginal dryness and dyspareunia.[125,164]

Endocrine Diseases

Women with POI are prone to develop endocrine disorders later in their life. Around 20% with idiopathic POI develop hypothyroidism and most commonly Hashimoto thyroiditis.[23] They also carry high risk of developing adrenal insufficiency.[138]

Future Perspectives

Most recent studies have shown the role of stem cells in the treatment of POI and have reported that oocytes can be generated from embryonic stem cells (ESCs).[165,166] These ESCs are induced into primordial germ cells which are then aggregated with somatic cells of female embryonic gonads for fertilisation.[166,167]

Other pluripotent cells that have been studied for use include, mesenchymal stem cells (MSCs) used for repairing damaged ovaries induced by chemotherapy.[168] Umbilical cord mesenchymal stem cells (UCMSCs) can also be used with advantage of little or no immune rejection.[169] Adipose-derived stem cells (ADSCs) are another type of MSC that can be differentiated into multiple cell types.[170]

Bone marrow transplantation has also been studied for use in women with poor ovarian function after long-term chemotherapy.[166,171] Hence, it is possible that with the latest research and advancement, ovarian aging may become reversible in the future, especially in women with POI.[172]

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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