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Review Article

Premature Ovarian Insufficiency; The Conventional and non-Conventional Fertility Options

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ABSTRACT

Premature ovarian insufficiency (POI) is defined as the cessation of normal ovarian function before the age of 40 years. It is associated with amenorrhea, signs of estrogen deficiency, and infertility. Furthermore, impacted women suffer from negative effects on personal health due to the influence on psychological, sexual, reproductive prospects, long-term bone, and cardiovascular health. Because of the complexities of POI and the scarcity of current information about recent breakthroughs in POI-related domains, we must update our understanding of the pathogenesis, diagnosis, and appropriate therapeutic choices. This review will discuss the most recent definitions of POI as well as the risk factors for both natural and iatrogenic POI. We will highlight the diagnosis process and treatment strategies provided to patients impacted, particularly in the fertility-related disciplines, via evaluating the efficacy of treatment for POI in both the conventional and by non-conventional approaches (complementary medicine). Taking into account all accessible alternatives that would optimize quality of life and long-term well-being regarding this distressing condition.

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INTRODUCTION

The discontinuation of normal ovarian function before the age of forty; is called spontaneous primary ovary insufficiency POI (also called hypergonadotropic hypogonadism, premature failure of the ovaries, and early menopause). It is coupled with amenorrhea, estrogen insufficiency symptoms, infertility, and overall health issues. It has different incidence based on the presenting age, showing a 1% incidence at 40 years old [1]. Though diagnostic criteria in POI is lacking, the following points were suggested to aid in the diagnosis: (i) oligo/amenorrhea for four months at the least, and (ii) elevated FSH level exceeding 25 IU/l four weeks apart. Many women with POI have a sporadic ovarian function that might linger for decades following the diagnosis. Most women realize they are infertile gradually after several failed efforts at pregnancy. In contrast, the acute identification of infertility with POI may happen while investigating other presenting problems such as amenorrhea [2]. POI carries multiple health risks to women; POI affects bone health by reducing bone mineral density and raising the risk of fractures. Therefore, women are advised to a healthy lifestyle, daily exercise, and maintain normal weight[3].Women with POI are at a higher risk of cardiovascular disease and must be informed about risk factors that may improve via behavioral change (e.g., quitting smoking, changing their diet, and engaging in regular exercise). Hormone replacement treatment, in particular, can help to reduce the risk [4]. Another health concern is psychological aspects. Patients with POI exhibit lower self-esteem, greater shyness, greater social anxiety and depression. These issues are likely to influence the quality of life negatively. Therefore, psychological care is incorporated in the management of women with POI, and that extra support channels ought to be provided [5]. POI can be natural in onset or iatrogenic; iatrogenic factors such as surgery, radiation, and chemotherapy were reported, particularly for malignant tumours; both have different fertility options that the patient needs to comprehend [6]. Due to the outstanding advance in fertility preservation and mesenchymal stem cells research, this review aimed to verify the main reproductive options for women with POI, both conventional and non-conventional. Introducing contemporary solutions that might lead to new prospects for women with POI in the future.

Natural Premature Ovarian Insufficiency; Cause and Workup

The aetiological factors behind POI are diverse. Enzymatic deficiencies like 17-α-hydroxylase and Galactosemia. Genetics was blamed in cases of turner syndrome, mosaicism and deletion and inversions defects were identified too. Gentic mutation manifested by FSHR gene on 2p and FRM1 gene on X. Autoimmunity was reported by some authors supposed to be mediated by cell-mediated or autoantibodies .some researchers hypothesized fetal infection by mumps or severe maternal pelvic inflammatory diseases. No specific aetiology was responsible. In fact, some advocate heterogenic factors to be the reason behind it, not to mention the idiopathic causes [7-10]. For that, a list of primary workups for women presented with POI was suggested; it included testing for genetic causes and autoantibodies [1]. The former will test for fragile X syndrome and for Y chromosome material. As for the latter, it will test for thyroid antibodies [1,2].

Restoring Fertility; Interventional Trials

Many researchers seek therapies to restore the reduced fertility and the menstrual cycle for those affected, Some tried cyclic HRT hormone replacement therapy; followed by Human menopausal gonadotrophins HMG triggering drug or HMG combined with estrogen; others sought different combinations of hormonal treatment. Some tested Danazol value to restore reduced sexual drive and improve climacteric symptoms. Even corticosteroids were used combined with HMG. Sadly non of this intervention was statistically significant to reach the level of recommendation [7]. Interestingly it was reported that 5-10% of POI women did have spontaneous pregnancies regardless of any therapeutic intervention; some have proposed an ovarian biopsy to predict spontaneous fertility relapse. However, the biopsy showed luteinized and dormant follicles [1].
Others suggested an ovarian ultrasound to predict subsequent pregnancy; still, it showed negative antral follicles in those who achieve subsequent spontaneous conception. Some women with POI have sought assisted reproductive technique either by implanting ova of a relative or sister, yet it showed high failure [11]. In fact, options for preserving fertility in women with POI is lost once they reach the diagnosis. This was the gloomy reality for those patients until recently where a breakthrough occurred that raised the hope again [6]. The utilization of mesenchymal stem cell-derived from diverse sources, such as bone marrow, placental tissue, cord blood, and menstrual blood cells. These appear to be effective in experimental animals but through unknown pathways, the latter being investigated for the activation of residual primordial follicles [12].

Mesenchyme Stem cells Therapy

Stem cells are special in that they have the potential to self-renew and specialize into specific tissues based on their surroundings and signals. Numerous research is being conducted to investigate their use in treating reproductive problems[6]. Stem cells treatment SCT is frequently paired with the introduction of platelet-rich plasma, which can be a rich-media of growth factors. platelet-rich plasma (PRP) is made from autologous human plasmas with a higher platelet content. Platelets' higher concentrations of growth factors and cytokines are added to platelets [13,14]. Thus, PRP has the ability to speed up the healing process at an injured site and, in the case of POI, boost cellular regeneration and renewal. Human SCT obtained from several adult tissue was evaluated in a chemically induced rat model of POI, thereby matching the effects of chemotherapy in women. Experiments on animal models of POI have confirmed the therapeutic potential of MSC transplantation [15].
The POI does not imply the full disappearance of primordial follicles in the ovary; in fact, it is estimated that roughly 1000 such follicles persist in the ovary until natural menopause.Stimulation of these seemingly inactive follicles is thus a possible therapeutic avenue. In human experiments, women in perimenopause or menopausal were treated with intra-ovarian platelet-rich plasma to see if it improved ovarian function. As a result, 18/30 women with POI had some menstruation restored, as well as a substantial improvement in blood levels of anti-Mullerian hormone(AMH) and Follicle-Stimulating hormone(FSH), as well as increased Antral follicle counts (AFC) [16,17]. Given the massive favorable results from human-derived SCT, a handful of studies has been published, and the majority of study in this field has been preliminary and non-controlled. Furthermore, ethical concerns have been raised, and legislation is required to guide these studies [18].

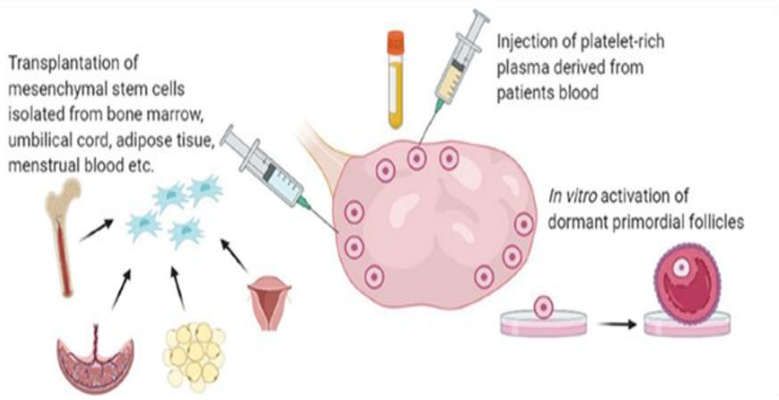

Figure1. The basis of Mesenchyme Stem cells [6]

Iatrogenic Premature Ovarian Insufficiency

Numerous oncologic and nononcologic disorders can have an impact on reproductive potential, either directly or indirectly through the disease or its fertility-threatening medication. Fertility preservation (FP) is a critical concern for people whose ongoing fertility may be jeopardized. Any FP intervention should aim to reduce or eliminate primary illness burden while also maintaining or sustaining reproductive health. A collaborative, interdisciplinary approach is required in the management of cancer patients, with whom FP choices should be explored prior to beginning [19]. Cancer treatment, surgical interventions and sex affirmation procedures, can all impact fertility potential. Because of advancements in cancer detection and treatment have evolved a paradigm shift concentrating on quality-of-life concerns and long-term survivorship [20]. Ovum and embryonic cryopreservation are well-established FP methods in post-pubertal women.

The ASRM presently recommends only embryo and egg freeze as FP techniques. However, females who are not coupled or do not want to employ donor sperm or embryo freezing, and premenopausal girls; ovary cryopreservation is the technique of choice for FP. Even though it is deemed experimental with about 100 live births documented, it holds promise in the future. In addition, multiple methods, including ovarian transposition and GTRH agonists, have been suggested to decrease the impact of cancer therapy on reproductive potential, which warrants additional research [21]. In females who are not coupled or who do not want to employ donor sperm or embryo freezing, oocyte cryopreservation has been the technique of choice for FP. Although the ASRM Committee considers ovarian tissue cryopreservation to be experimental, it may hold promise in the future.

The Non-Conventional (Alternative Medicine) Options For POI

Even though HRT can alleviate certain clinical symptoms, it does not restore ovarian activity or fertility or might raise the risk of cancer, breast, ovary and endometrial cancer, and other disorders. To lessen the adverse effects caused by standard western medical treatment, it is vital to find an alternative therapy to augment or replace it. "complementary and alternative medicine are set of various medical and health systems, strategies, and products which are not commonly recognized to be part of traditional medicine" [22].

Herbs Remedies; the prescription of these therapy by chinses researchers offers numerous advantages; a better control the physical and mental diseases. One of these herbs was Bushen Huoxue which acts by adjusting FSH levels and FSH/LH ratio, raising AMH levels and modifying ANA-ACA-AOA, ACT-INH-FS, and clinical randomized controlled trials confirmed its value. Huoxue decoction can significantly enhance the clinical signs of patients with POI [23].

Another herb that can help in POI is Maca via enhancing sexual function, sperm production, women's reproductive function, cognition, depression, stress, energy, benign prostatic, bone loss, and metabolic disorders. Acupuncture medicine has been widely accepted in the treatment of POI and has proven superior to conventional western medicine. Its value was extensively assessed by RCT and Meta-analysis [24]. Traditional Chinese medicine mixed with massage has a very good curative impact in clinical settings [25]. Psychotherapy discovered that combining traditional medical treatment with psychological treatment dramatically boosted the cure rate of POI patients, which can relieve not only clinical signs but also reduce subjective load and mental stress and improve life quality [26]. Diet treatment can not only heal illnesses, but it can also fulfil hunger as mentioned by Xichun Zhang a modern therapist,Furthermore, food therapy is more appealing, has no damage

for treating if the chosen diet therapies are matched with the condition, the duration of recovering from a disease will be reduced, and even if it is not, the illness will not worsen." Nansha ginseng, yam, lotus seeds, and Dendrobium candidum are a few examples, see figure 2.

Fig.2 Some types of dietary therapy useful for POI

In the therapeutic food of POF, the soybean, radish, and mushroom have guiding relevance and practical usefulness [27]. Soybeans and green tea) were utilized to treat adult ovariectomized mice. In older mice, it improves immunological function. Some foods are ovarian function protectors, such as legumes, which can lower blood follicle-stimulating hormone levels in women and so preserve ovarian function [28,29].

CONCLUSION

In the treatment of POI, CM will continue to be widely employed and conventional medicine to effectively regulate the physical and mental disorders caused by POI, such as avoiding deterioration, lowering symptoms, and ensuring a healthy lifestyle. Although the effectiveness of herbal medicine and acupuncture therapy has been thoroughly demonstrated, most of these researches is hampered by a small sample size or are restricted to a single ethnic group. Still, the lack of bad effects, suggesting that safe treatment alternatives are worth pursuing. It is expected that CM therapy coupled with conventional medicine will develop a novel therapeutic strategy for POI.

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Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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