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Optimizing Female Infertility in Premature Ovarian Insufficiency

Erken Yumurtalık Yetersizliğinde Kadın İnfertilitesinin Optimizasyonu

Pınar ÇAĞLAR AYTAÇ
0000-0003-0052-8000

Department of Obstetrics and Gynecology, Reproductive Endocrinology and IVF Clinic, Başkent University Adana Dr. Turgut Noyan Training and Research Center, Adana, Türkiye

Corresponding Author
Sorumlu Yazar
Pınar ÇAĞLAR AYTAÇ
pinarcag1976@yahoo.com

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ABSTRACT

Premature ovarian failure is a complex pathology with numerous etiologies and multiple system sequelae resulting for early deprivation of ovarian sex hormones. In the studies to determine the etiology, it is seen that many patients are in the unexplained group. On the other hand, genetic predisposition and autoimmune cause of premature ovarian insufficiency (POI) are the most common known etiologic causes. Early diagnosis and energetic treatment are important in order to prevent symptoms related to estrogen deficiency. Initiating hormone replacement therapy as soon as possible will prevent menopausal symptoms and reduce long-term complications in women. Another important problem in these patients is infertility, which occurs due to ovarian failure. In fact, fertility, which begins to decrease before menstrual irregularity, turns into infertility with a rapid decline in the number of follicles in the following period. Here, the detection of patients at risk and appropriately timed fertility preservation treatments (such as freezing of oocyte, embryo, or ovarian tissue) or assisted reproductive techniques can be offered. Besides this, studies like stem cell therapy, platelet-rich plasma (PRP), and in vitro activation of ovarian tissue in patients with POI are recent and still investigational but may be promising in the future. In the present review, the current pathophysiology and treatment options of premature ovarian failure were discussed.
Keywords: Premature ovarian insufficiency; infertility; diagnosis; treatment.

ÖZ

Erken yumurtalık yetmezliği, az bilinen etiyolojisi ile neden olduğu yumurtalık hormonlarının azalmasıyla saptanan, kadınlarda birçok sistemi etkileyen patolojilere yol açar. Etiyolojisini belirlemeye yönelik çalışmalarda pek çok hastanın açıklanamayan grupta olduğu görülmektedir. Diğer yandan genetik yatkınlık ve otoimmün nedenli erken yumurtalık yetersizliği (premature ovarian insufficiency, POI) bilinen en sık etiyolojik nedenlerdir. Temelde östrojen eksikliği ile ilgili semptomların önlenmesi amacı ile erken tanı ve tedavi önemlidir. Hormon replasman tedavisinin bir an önce başlanması, kadınlarda menopozal semptomların önlenmesini ve uzun dönemli komplikasyonların azalmasını sağlayacaktır. Bu hastalarda diğer önemli sorun ise over yetmezliği ile ortaya çıkan infertilitedir. Aslında adet düzensizliği ortaya çıkmadan önce azalmaya başlayan fertilite, ilerleyen dönemde folikül sayısının daha hızlı azalması ile ciddi bir infertilite sorunu haline gelmektedir. Burada özellikle risk altındaki hastaların tespiti ile uygun zamanda fertilite koruyucu tedaviler (oosit, embryo veya over dokusunun dondurulması gibi) ve yardımla üreme teknikleri önerilebilir. Bununla birlikte, infertilite yakınması olan POI tanısı alan hastalarda; kök hücre tedavisi, trombositten zengin plazma (platelet-rich plasma, PRP) ve over dokusuna in vitro aktivasyon gibi uygulamalar yeni ve deneysel aşamada olsa da gelecekte umut verici olabilir. Sunulan bu derlemede erken yumurtalık yetmezliğinin güncel patofizyolojisi ve tedavi seçenekleri tartışılmıştır.
Anahtar kelimeler: Erken yumurtalık yetersizliği; infertilite; tanı; tedavi.

INTRODUCTION

Premature ovarian insufficiency (POI) is the depletion of ovarian reserve in patients before the age of 40. The diagnosis of POI is necessary for both menstrual irregularities (amenorrhea or oligomenorrhea) for more than 4 months and for follicle stimulating hormone (FSH) to be higher than >25 mIU/ml in two different measurements. Its incidence is about 1% of the female population and can be as high as 3.7% (1,2). Before the age of forty, POI is an unexpected condition in which women have to deal with its chronic consequences, such as reproductive, psychological, and sexual health, osteoporosis, and cognitive and cardiovascular defects. Infertility is one of the consequences of POI, which has genetic, autoimmune, chromosomal, and gonadotoxic treatment and often has idiopathic causes. Although follicles are detected in the ovary in 73% of POI patients, the probability of spontaneous pregnancy is very low (about 4.8%), which is unfortunately very low for their peers (3,4). In many countries, oocyte donation or adoption is recommended due to the very low pregnancy rates in these patients. Donations can give the POI population a chance of a pregnancy rate of up to 40-50% (5). In places where donations are prohibited, as in our country, there is little or no chance of having a baby for adoption. In this section, we address the fertility difficulties of patients diagnosed with POI rather than other disorders caused by POI.

Pathophysiology

Most of the etiology of POI is unknown, it is defined as idiopathic, in descending order, iatrogenic (secondary to ovarian surgery or chemotherapy or radiotherapy), genetic, autoimmune, and infection. The primary POI is acquired spontaneously, but the secondary POI depends on the pelvic region after ovarian surgery, chemotherapy, or radiotherapy. Ethnicity has a role because in some ethnic populations, such as Caucasian, African-American, and Hispanic, POI is observed at much higher rates than in Japanese or Chinese women (6). Smoking is a risk factor that increases POI (odds ratio, OR: 1.82, 95% confidence interval, CI: 1.03-3.23), late menstruation, longer breastfeeding may reduce the POI risk factor (7).

Genetic

Although most of the etiology of POI is idiopathic, genetic causes account for 10-15 cases of POI (1). In genetic causes, X chromosome defects are seen as monosomy X (Turner syndrome 45XO), trisomy X, or deletions in the X chromosome. There are many more chromosomal defects in the POI population in patients with primary amenorrhea than in secondary amenorrhea. FMR premutations for familial reasons may also play a role in etiology. The European Society of Human Reproduction and Embryology (ESHRE) POI guideline recommended chromosomal analysis and fragile X mutation test analysis in all non-iatrogenic POI patients. Autosomal mutations have not yet been noted, unless clinically suspected (such as blepharophimosis, ptosis, and epicanthus inversus syndrome, BPES). If the Y chromosome is detected, gonadectomy is recommended for malignancy (1). There are new studies investigating rare new variants that cause POI by whole exome sequence analysis (8). In the future, the idiopathic norms of POI can be explained by genetic studies with whole exome sequence analysis.

Autoimmunity

In patients with autoimmunity, the ovarian reserve decreased by 20%. Adrenal insufficiency or Hashimoto's disease can be seen mostly in this population. Therefore, in patients with POI, 21-hydroxylase (21-OH) autoantibodies or adrenal cortical antibodies should be checked during the diagnosis of POI. The anti-TPO antibody should also be screened annually for autoimmune thyroiditis (1).

Iatrogenic

Iatrogenic causes are the second most common etiology after idiopathic. In bone marrow malignancies, radiation therapy after autologous stem cell transfer, especially pelvic radiation therapy, can cause 90% POI. After chemotherapy with alkylating agents, the ovarian reserve is also irreversibly reduced. In addition, benign surgery for the ovary also leads to a decrease in the ovarian reserve. Viral infections that can invade the ovary also cause premature ovarian failure. Ovarian surgeries should not be recommended in POI patients unless there is a risk of malignancy.

Fertility and Reproduction

Patients with POI have 25% ovulation during their reproductive years, that is, they still have follicles in their ovaries that give them a chance of pregnancy with their own germ cells. Although they have a very low spontaneous pregnancy rate, 5-10%, the highest pregnancy rate is 1-2 years after the diagnosis of POI (9). This period is the time to bring patients to the doctor in search of a remedy for menstrual irregularity or infertility, and just before the depletion of all oocytes. Therefore, this period may be the precious period when the probability of pregnancy with autologous oocytes is the highest. After the diagnosis of POI has been made, patients should be informed about infertility and menopause for fertility treatments or fertility preservation as soon as possible. This is an unexpected pathology. Most patients are young, and fertility is not their priority. Suddenly they face this early menopause and its burden can upset them and increase their anxiety. Accurate guidance and information play an important role in referencing this population.

Fertility Treatments

In fertility clinics, when attending POI patients, the first reflex is to recommend in vitro fertilization (IVF) for these patients. Because of the limited time and low spontaneous pregnancy rates, clinicians recommend IVF, which has higher pregnancy rates, for the treatment of infertility, and also gives a chance to reduce the time to get pregnant. However, there is still not enough data on the ways of infertility treatment, such as expectation management, ovulation induction, or IVF. The spontaneous pregnancy rate in expectation management is very low, such as 4-5% (1). Since the follicular phase is shortened in POI patients, the luteal phase is not always followed after follicular growth and ovulation. Therefore, the endometrium is not ready for an ovulating euploid embryo. The low rate of spontaneous pregnancy may be a consequence of these cases in POI.

In some observational studies after ovulation stimulation (OS) with gonadotropin, the pregnancy rate was around 6.3% (4). In controlled studies in which

gonadotropin suppression was performed with gonadotropin releasing hormone (GnRH) agonist suppression cycles, the pregnancy rate did not differ from placebo-controlled cycles (4).

In a randomized controlled trial by Tartagni et al. (10), 25 POI patients were given ethinyl estradiol (EE) for two weeks before and during OS, and 25 POI patients did not receive EE, as a control group. Only eight of the study group with FSH levels below 15 mIU/ml in the early follicular phase ovulated, and four of them became pregnant. In another randomized controlled trial, 29 POI patients were given dexamethasone before OS, while 29 POI patients in the control group did not receive steroids. The study group had a higher pregnancy rate compared to the control group (11). These results may indicate that autoimmunity plays a role in the etiology of POI.

Check et al. (12), in their study, suggested that gonadotropin suppression with estrogen replacement and GnRH agonides with longer OS periods with recombinant FSH or human menopausal gonadotropin (hMG) may have better ovulation and pregnancy rates if patients have longer periods of amenorrhea.

In a comparative study by Ishuzuka et al. (13), they compared pregnancy rates in POI patients who underwent hormone replacement therapy (HRT) with or without ovarian stimulation between 2014 and 2020 in a clinic. OS was applied to 429 patients with 6891 cycles, 48.5% of patients had follicular growth, 5.8% had a live birth rate (LBR) in the IVF group, and 1.3% had an LBR in the intrauterine insemination group. The only group waiting for treatment without OS (37 patients with 117 cycles) observed follicular growth at a rate of 5.4% on HRT and no pregnancy was detected. In the same study, they reported that the pregnancy rate was higher in patients with an age of <35 years and an amenorrhea duration of less than 4 years before IVF treatment than in other POI patients in the same group (13).

Abnormal karyotype of patients may interfere with pregnancy rates in IVF in POI patients. In the study by Grin et al. (14), 49 POI patients with abnormal karyotype underwent IVF programs, with follicular growth in 57%, oocyte retrieval in 47%, and fertilization rate with 6.1% LBR in 70.7%. Patients with mosaic turner syndrome had longer amenorrhea intervals and a lower rate of follicular growth. In another study, by Jiao et al. (15), 955 POI patients were evaluated, 30% in the primary amenorrhea group had genetic etiology, and 11% in the secondary amenorrhea group had genetic etiology. In their studies, the pregnancy rate in the genetic group was 7.2%, the autoimmune group was 21.1%, the iatrogenic group was 34.8%, and the idiopathic group was 19.5%, so the lowest pregnancy expectancy was in patients with POI with genetic abnormalities. POI patients with a genetic etiology may interfere with pregnancy rates, but this is not sufficiently clear with current studies. Also, these patients are concerned about the penetration of pathology into their offspring. This is another issue that can be explored in the future.

DHEA and Testosterone

The ovarian reserve is irrevocably decreasing due to increasing age. The cause of the primordial follicular loss is not yet known, but this definite result has been tried to slow down with some adjuvant treatments such as dyhydroepiandrostenodione (DHEA) or testosterone. These molecules are synthesized by the ovary and the adrenal gland and enhance the effect of gonadotropin on follicle development through insulin-like growth factor 1 (IGF-1) (16,17). Some authors have concluded that the use of DHEA before IVF can increase ovarian reserve markers and ovarian response to ovarian stimulation (18-21). However, in many studies, the use of DHEA supplements in ovarian reserve or pregnancy rates before IVF treatment has not been observed (16,17). Qin et al. (17), in a meta-analysis of pretreatment with DHEA, have shown that the pregnancy rates could increase (OR: 1.47, 95% CI: 1.09-1.99), but decrease (OR: 1.08, 95% CI: 0.67-1.73) if only randomized controlled trials (RCTs) were included, which reveals that pretreatment with DHEA has no effect on pregnancy rates, number of eggs, fertilization, and miscarriage rates. These results suggested that we need more RCTs, not meta-analysis, to reach a more reliable conclusion about DHEA supplementation for POI patients.

Similarly, testosterone administration before IVF treatment has better oocyte count and pregnancy rates in those with a poor ovarian response, but there is limited data on testosterone supplementation in POI (22-24). However, these studies were heterogeneous and the study population was not uniform. Studies are underway on testosterone in weak responders (T-Transport group of Researchers), which may reveal better results that can guide us next year (NCT02418572).

In Vitro Activation

Kawamura et al. (25), suggested disruption of the hippo pathway and in vitro activation of AKT by laparoscopically derived oocyte cortex fragments. These parts of the ovarian cortex were made both mechanically and chemically to disrupt the hippo pathway and AKT activation, then laparoscopically translated into the ovary in 27 patients. A live birth can be performed. 37 patients were included in their second study, nine patients had follicular growth, four patients had embryo transfer, and two patients (%5.4) had an LBR (26). Hippo and AKT (protein kinase B) are signaling pathways that regulate the activation of primordial follicles. Activation without drugs can disrupt hippo signaling and cause activation of the primordial follicle and ovarian regeneration, follicle growth and ovulation may be possible. The breakdown of the ovarian cortex can now biomechanically activate the ovarian follicle pool. They removed the ovarian cortex, and a small sample was measured for stiffness and re-transplanted into the peritoneal fold. Activation of the ovarian cortex without drugs was performed in 19 patients, 52.6% of them continued ovarian function, and two of them gave live birth. Therefore, mechanical intervention can now also ensure the regeneration of the ovary (27).

Intra-Ovarian PRP Infusion

In recent case series, platelet-rich plasma (PRP) is a concentrated platelet plasma component of the autologous blood of patients injected into the ovary to regenerate folliculogenesis. The growth factors, cytokines, and chemoattractives of this plasma stimulated

angiogenesis and cell proliferation, enabling the primordial and primary follicles to transform into preantral follicles. Hosseini et al. (28), in an in vitro PRP injection study, was proposed to the primordial or primary follicles of the ovary at the preantral stage. Of the 311 patients diagnosed with POI, spontaneous pregnancy was present in more than 7.4% of the patients who received intraovarian PRP injection, and at least one cleavage embryo was present in 23.6% of them (29). Barad et al. (30) in recent studies, suggested that intrauterine PRP injection can give a 4.7% chance of pregnancy only in pregnancies with the option of oocyte donation. In the last study of Cakiroglu et al. (31), autologous PRP intrauterine injection of 510 patients with a poor ovarian response; spontaneous pregnancy was found to be 4.3%, the IVF program was 92.9%, the pregnancy rate was 20.5%, and the LBR was found to be 12.9%. These studies were before or after studies or observational studies, so we need randomized controlled trials to obtain more reliable results.

Stem Cell Therapy

Another experimental study is autologous stem cell transfer to the ovary. Bone marrow stem cell precursors were excreted through the colony-stimulating factor. Then the stem cells were collected through apheresis and injected into the ovarian artery through catheterization. Three out of 17 POI patients became pregnant spontaneously after autologous stem cell injection into the ovary (32). Mesenchymal stem cells can treat POI by performing a "home effect" for follicles. They can promote the growth and development of follicles, vascular formation, and immunomodulatory effects (33). In this study, animal preclinical and human clinical studies were reviewed. Follicular development, menstrual resumption, and spontaneous pregnancies have been reported after stem cell injection into most ovaries. With the very low success rate of having spontaneous pregnancy in POI patients, stem cells may offer a promising future for the health and reproduction of POI patients.

Fertility Preservation

Fertility preservation can be done by freezing oocytes, embryos, or ovarian tissue for future use. Embryos can be frozen to delay their development in couples who are not currently considering pregnancy. In single POI patients or menstruating adolescents, oocytes can be frozen. Limited follicle pools also make it difficult for mature oocytes to freeze. However, in adolescents who are expected to have POI after cancer treatments or ovarian surgeries in the future, ovarian tissue preservation should be recommended to preserve ovarian tissue. The preservation of ovarian tissue is no longer experimental. Since 2019, the American Society for Reproductive Medicine (ASRM) has established that patients treated with ovarian freezing gonadotoxic drugs preserve fertility (34), and in this way preserving future fertility may be their only chance for reproduction.

CONCLUSION

POI patients are still the most difficult infertility patients today. Although many treatment methods are proposed, there is no treatment algorithm. It is important for patients to individualize their treatment methods. However, the most important step in the treatment is the follow-up of the POI infertile patient by a specialist physician.

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