Premature ovarian insufficiency: current progress and future prospectives

Sara Pinelli
Giovanna Simi
Elena Rosa Obino Maria
Vito Cela
Paolo Giovanni Artini

Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynecology Oncology, University of Pisa, Pisa, Italy

Address for correspondence:
Sara Pinelli
Division of Obstetrics and Gynecology Oncology,
Department of Clinical and Experimental Medicine,
University of Pisa
Via Roma 67
56126 Pisa, Italy
E-mail: sara.pinelli@live.com

Summary

Premature Ovarian Insufficiency (POI) is defined as the occurrence of hypergonadotrophic hypoestrogenic amenorrhoea in patients younger than 40 years (1). POI represents the end of a gradual process of loss of primordial follicles earlier than expected for age. The disease evolves silently and finally leads to premature menopause. The term POI has replaced the previous “Premature Ovarian Failure”, which suggested more a sudden event than a gradual process (2, 3), but there is yet some confusion regarding the definition of the disease.

In fact, according to European Society of Human Reproduction and Embriology (ESHRE), the diagnosis of POI is based on two criteria in women younger than 40 years (2-4):

- menopausal symptoms, including no or infrequent periods;
- elevated levels of Follicle-Stimulating Hormone (FSH) on 2 blood samples taken 4-6 weeks apart (2).

However, there is no established cut-off of FSH level to define the disease, as it is rather consid-
ered a progressive process, with a transitional phase, when potential fluctuations of hormonal levels due to intermittent recovery of ovarian function are possible (3). During this transitional phase, menopausal symptoms and amenorrhea have not established yet, and often the only symptom of these patients is infertility, associated with an high level of FSH, fluctuating during months. In view of the above, there is a certain level of overlapping in definition between POI, reduced ovarian reserve (ROR) and “poor ovarian response” (POR) (5).

According to ESHRE consensus, the diagnosis of POR is made with 2 of the following (6):
- age above 40 years old or other risk factors for POR;
- a previous low response to ovarian controlled stimulation;
- a scarce ovarian reserve test (for instance, AFC <5-7 follicles o AMH <0.5-1.1 ng/ml).

Thus, to define a “poor responder”, a woman under 40 years old must have been undergone at least a cycle of COH (5).

Concerning RRO, there is not a precise definition in literature (5). Published research on the topic has been conducted with different cut-off of instrumental and laboratory parameters of evaluation of ovarian reserve. Besides, RRO patients could be POI patients in the transitional phase of the disease (5).

The estimated prevalence of POI is 0.5-3.0% of women of childbearing potential (7-9), and the disease calls for lifetime follow-up.

**Causes**

POI can be spontaneous (primary POI) or induced by radiation, chemotherapy or surgery (secondary POI). The majority of spontaneous POI (90%) is idiopathic (3, 4, 10).

Possible causes of spontaneous POI are divided in two groups: chromosomal and non-chromosomal abnormalities. Chromosomal anomalies are found in around 50% of POI patients referred for primary amenorrhea (11-13), while they are much more unusual in women with secondary amenorrhea. X chromosome abnormalities are most commonly found in those women with a family history of POI. Deletions and translocations within the X chromosome, such as Turner syndrome (X monosity) and Fragile X syndrome, have been related with POI (14, 15).

Additional important genetic alterations include those coding for enzymes crucial to reproduction [e.g. 17α-hydroxylase deficiency, FSH and luteinising hormone (LH) receptor mutations] and others such as gut-associated lymphoid tissue (GALT), euukaryotic translation initiation factor 2B (EIF2B) and forkhead box protein L2 (FOXL2). Recently a groups of Italian researcher found a frequent depletion of mitochondrial DNA in the blood cells of POI patients, suggesting that a mitochondrial defect may activate POI (16).

Non chromosomal abnormalities can be categorized in four groups: iatrogenic causes (surgery, chemotherapy and radiations) (17-19), autoimmunity (20), infections (herpes virus, cytomegalovirus, mumps) (21) and idiopathic form. The risk of idiopathic POI varies by ethnic origin (7). Luborsky founds that Caucasian ($p=0.02$), African-American ($p=0.004$) and Hispanic ($p=0.004$) women had significantly increased risk of POF compared to Japanese women (7).

Other factors predisposing to POI have been determined in a cross sectional study by Chang et al. (22) that observed that while an increased risk of idiopathic POI was associated with cigarette smoking, oral contraceptive use was linked to a reduced risk of spontaneous early menopause. Other factors, such as later menarche, irregular menstruation and longer breast feeding cumulatively reduced the risk of early menopause and POI. About 5-30% of POI is estimated to have an autoimmune aetiology (1).

No clear etiopathogenic mechanism is known regarding environmental factors like viral infections and toxins determining premature cessation of ovarian function (23).

**Current prospectives**

No guidelines have been established regarding management of infertility in POI patients. Currently no interventions have shown to remarkably increase the prospective of spontaneous conception, while egg donation is considered the most reliable opportunity to achieve pregnancy (2). Certainly, early diagnosis is crucial to counsel POI patients about their future prospective of childbearing and possibly address them to oocytes cryopreservation. A proper diagnostic workup has to be made in young patients affected by primary ammenorrhea, trough evaluation of possible autoimmune, endocrine or chromosomal anomalies.
Often the diagnosis of POI in western countries is made during the transitional phase, before the establishment of menopausal symptoms and amenorrhea, when unpredictable recovery of ovarian function may occur. During this phase, even if sporadic ovulation is possible (8, 24, 25), the chance of spontaneous pregnancy in women with POI is as low as 5-10% (2, 24). Also the outcomes of ovulation induction treatments are often below expectations (26-29). The only change for these patients to have still a chance to conceive with their own gametes is that the diagnosis is made during the “transitional phase”, when amenorrhea and menopausal symptoms have not yet arose. As a consequence, in the majority of these patients, the only opportunity of childbearing is eggs donation or adoption (2).

When approaching a patient suspect for POI, firstly a careful family history should be taken in order to identify genetic forms and refer patients to genetic counseling (23).

Then, it is necessary to rule out possible autoimmune or endocrine causes, which could be managed by treating the clinical disease. Indeed, spontaneous pregnancies have been obtained after thymectomy in patients affected by myastenia gravis, or during hormonal replacement therapy, in patients with Addison disease and hypothyroidism (23). Some Authors have reported occasional pregnancies in POI patients with polyglandular autoimmune syndromes treated with corticosteroids (23). It is notable, however, to take into consideration the cost-effectiveness of this therapies and potential side effects of immunosuppressive treatments.

A FSH level higher than 15 IU/l is generally related with a scarce ovarian reserve (6, 30), while a serum FSH level >40 mIU/mL is associated with infertility (31, 32).

In view of the above, it was hypothesized that the persistently elevated circulating level of gonadotropins could be a cause of reduced ovarian responsiveness itself (33, 34).

In an open, nonrandomized study Check, et al. (35) assessed the efficacy of a protocol including gonadotropin suppression and controlled ovarian stimulation with human menopausal gonadotropins (hMG) in women with hypergonadotropic amenorrhea. The hypothesis of the researchers was that the decrease in circulating FSH may improve ovarian response, by stimulating the expression of FSH receptors in ovarian granulosa cells.

The report of spontaneous pregnancies during cyclic estrogen and progestin treatment (36, 37), support this hypothesis. In these cases the estrogen induced decrease in circulating gonadotropins seem to improve the responsivness of remnant ovarian follicles.

In 1996 Taylor reported the occurrence of spontaneous ovulation in 46% of POI patients undergoing estrogens treatment (38).

In 2007 Tartagni et al. (39) evaluated the efficacy of a pre-treatment with estrogens before ovarian stimulation with gonadotropins in POI patients. The study group was randomized to receive short-term pretreatment with 0.05 mg ethinyl-E₂ three times a day for 2 weeks, while the control group received placebo. Levels of FSH, at the beginning of the ovarian stimulation, were significantly lower in the study group than in placebo group and the rate of ovulation in study group was significantly higher than in controls (32% vs 0%). Remarkably, ovulation induction was satisfactory only in women whose FSH levels after pre-treatment were <15 mIU/mL. The same group of researcher reported in 2011, a case of pregnancy in a woman with POI undergoing in vitro fertilization (IVF)/intracytoplasmic semen injection (ICSI) after pre-treatment with ethinyl-E₂, followed by therapy with estrogens associated with ovarian stimulation with gonadotropins. In this patient initial FSH was 47.5 mIU/mL (menopausal range, >40 mIU/mL), and they started ovarian stimulation with recombinant FSH when serum FSH was below 13 mIU/mL (40).

Moreover, Popat, in 2008, demonstrated that the treatment with 100 mcg transdermic estradiol reduced circulating levels of LH in 50% of patients affected with POI (41).

A recent study by Check et al. (42) assessed IVF results in menopausal women submitted to estrogen pre-treatment. Interestingly, they showed that the live pregnancy rate per embryo transfer was 20%, while the pregnancy rate per retrieval was 9.3%.

A randomized controlled study conducted by Yeung et al. tested the effects of supplementation with Dehydroepiandrosterone (DHEA) for 16 weeks on ovarian reserve markers. Researchers found an increase in antral follicle count (AFC), ovarian volume and circulating estradiol levels, but no differences regarding antimullerian hormone (AMH) or FSH (43).

Regarding iatrogenic POI, published data about the use of GnRH agonists (GnRH-a) during chemotherapy for cancer are conflicting. The ra-
tionale of this therapy is that the inhibition of the hypothalamic-pituitary axis by GnRH-a may protect the ovary by cytotoxic effects of oncologic treatment (44). Moreover, GnRH-a may reduce blood flow to the gonads hence suppressing ovarian function. While it seems quite well demonstrated that GnRH-a cotreatment during chemotherapy may lead to a resumption of menstrual cycle, on the contrary data regarding protective effect on fertility are far less promising (43-45).
In pre-puberal patients at risk of POI, nowadays the only prospective of future homologous pregnancy is cryopreservation of frozen-thawed ovarian tissue and subsequent transplantation. This technique acts by cryopreserving intact tissue containing small non-growing follicles, and despite being a relatively new procedure, it seems now expanding beyond the experimental stage, with numerous successful pregnancies published in literature (46, 47).
Today oocyte cryopreservation is the main fertility preservation technique in post-puberal women, especially in countries where embryo cryopreservation is forbidden. There is still the limitation due to timing, as oocyte cryopreservation needs time for ovarian controlled stimulation. However, nowadays we have improved “emergency protocols” to begin COH randomly, in every phase of menstrual cycle, (19) reducing the need to delay oncologic treatments.

Future prospectives

Past knowledge regarding ovarian ageing had always considered that each woman is provided at birth with a definite primordial follicles pool (48, 49).
Neo-oogenesis interrupts at birth, when primary oocytes start to undergo meiosis I. At this stage, meiosis arrests until puberty, when one or more primary oocytes complete the prophase of the first meiotic division each menstrual cycle. The follicular pool is destined to decrease progressively starting from fetal development as a consequence of the continuous process of oocyte selection and consequent atresia (48, 49).
Firstly in 2004, Johnson et al. (50) tried to demonstrate the presence of proliferative germ cells maintaining the folliculogenesis in mammalian ovary.
After this first attempt to contradict the traditional paradigm about ovarian physiology, several studies on the topic investigated the possibility to challenge this model, by studying the potential existence of female germline stem cells or oogonial stem cells.
Even if some researchers showed the persistence of meiosis and primordial follicles replenishment even during postnatal life in mouse model (48, 49), other researchers reported less optimistic results (51-53).
A recent study evaluated the potential effects of menstrual-derived Stem Cells (MenSC) in chemotherapy-induced mice with premature ovarian insufficiency (54). MenSC transplantation demonstrated to have a beneficial effect against ovarian damage by reducing apoptosis of granulosa cells and limiting interstitial fibrosis.

Conclusions

Even if great debate is present in literature about the real chance of application of these preliminary results to humans, future research should focus on this topic and on the possibility to stop, or at least to slow down, ovarian ageing.
In the meantime, we should spread our knowledge on fertility among young women in order to refer them to fertility specialists as soon as possible in the case of POI.
Moreover, clinicians should absolutely increase their skills in early diagnosis of POI during transitional phase, in order to give POI patients the chance to try to conceive spontaneously or to be referred to oocyte cryopreservation.

Conflict of interest

The Authors declare they have no conflict of interest. No financial affiliations to disclose.

References


39. Tartagni M, Cicinelli E, De Pergola G, De Salvia MA, Lavopa C, Loverro G. Pregnancy in a woman with premature ovarian insufficiency undergoing intracytoplasmic sperm injection after pretreatment with estrogens followed by...


