

# Reality of premature ovarian failure in Argentina

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## SUMMARY

Premature Ovarian Insufficiency is defined as a decline in ovarian function that is accompanied by two biochemical determinations of Follicle Stimulating Hormone in hypergonadotropic values, in addition to low levels of circulating estrogens in women under 40 years old. Although some of its possible etiologies are recognized and diagnosed, most of the time, its cause remains unknown. It is a pathology with medical, psychological, and reproductive implications. Patients may experience climacteric symptoms, infertility, and emotional distress. In the medium and long term, cardiovascular and bone health can be affected, and some degree of cognitive deterioration can be evidenced. The therapeutic approach needs to be comprehensive for the patient and multidisciplinary. SAEGRE created in Argentina an interhospital network dedicated to gathering relevant statistical information regarding this and other pathologies in order to provide better assistance for these patients.

**KEYWORDS:** Premature ovarian failure, premature ovarian insufficiency, Infertility, Ovarian reserve, hypoestrogenism, Hypergonadotropic amenorrhea, Occult ovarian failure, Ovarian biochemical failure.

## INTRODUCTION

Premature ovarian insufficiency (POI), formerly known as “primary ovarian failure,” is characterized by an accelerated depletion of ovarian reserve with a decrease in the number of residual follicles and deficiency in sex hormones, which is manifested in women as subfertility and hypoestrogenism years and even decades before the normal age of menopause. The subtleties in the clinical presentation and the relative lack of knowledge of the population with respect to this condition may lead to a delay in di-

agnosis and subsequent treatment. The condition is defined as a hypergonadrophic amenorrhea that occurs before the age of 40 years. It is detected in 5% to 10% of women who are evaluated with amenorrhea. Its prevalence in the general population is estimated with oscillation between 0.3% and 0.9% of women<sup>1</sup>.

There are several causes described that can cause follicular atresia or dysfunction<sup>1</sup> Table 1.

The most common symptoms are changes in the cycle, amenorrhea, and consequent infertility. There

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**TABLE 1.** CAUSES OF PREMATURE OVARIAN INSUFFICIENCY

SPONTANEOUS	INDUCED
Genetic	Radiotherapy
Autoimmune	Chemotherapy
Infectious	Surgical
Idiopathic	
Environmental toxins	

may also be symptoms of hypoestrogenism as hot flushes, vaginal dryness, sleep disorders, and irritability.

Women with premature ovarian insufficiency left untreated have a higher risk of osteoporosis and cardiovascular disease and all the effects of menopause, reducing their quality of life and leading to early mortality <sup>2</sup>.

The diagnosis of these patients requires at least two determinants of FSH in the early follicular phase (between the 2nd and 5th day of the cycle). The presence of hypogonadotropic hypogonadism in a woman younger than 40 years old is consistent with a diagnosis of POI.

In Argentina, there are no studies on the prevalence in the population. For this reason, the Argentine Society of Gynecological and Reproductive Endocrinology (SAEGRE) has created the Interhospital Network of Endocrinology to build databases that allow us to improve the statistics on these matters.

**METHODS**

The SAEGRE Hospital Network of Gynecological and Reproductive Endocrinology proposed an epidemiological study with the purpose of learning the relevant aspects of POI in Argentinian women. A descriptive, observational, multicenter study collaborative in nature.

Public hospitals of the Autonomous City of Buenos Aires and the first sector of the province of Buenos Aires participated. We analyzed clinical histories of women who attended external offices of Gynecological Endocrinology from January 1st, 2011 to December 31st, 2016 (5 years analysis).

The inclusion criteria were women younger than 40 years with two determinants of FSH > or = 40 mUI/ml; other causes of primary and secondary of non-hypergonadrophic amenorrhea were excluded. The information of POI patients stored in the database was: sociodemographic factors (age, identification data, nationality, place of residence, occupa-

tion), family history (maternal age of menopause, POI in the family), personal history (pregnancies, autoimmune diseases, chromosomal alterations, gynecologic surgery, chemotherapy and radiotherapy, infections, smoking, alcoholism, drugs), reason for consultation.

**RESULTS**

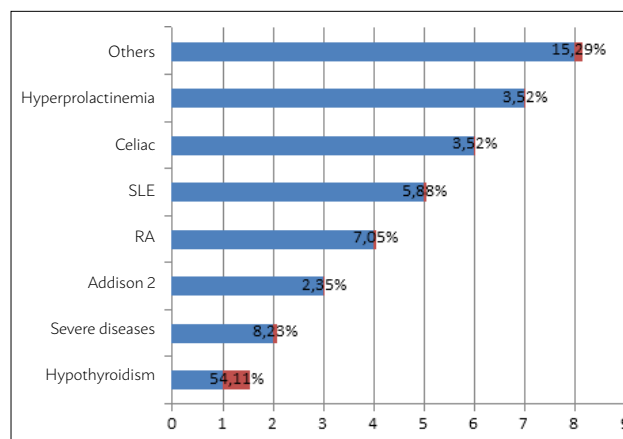
We studied 302 patients treated at the Endocrinology clinics of hospitals members of the SAEGRE Interhospital Network who met the inclusion criteria. The average age of our population was 33 years, with two cases of 19 years old as the younger age with a POI diagnosis. A total of 11.9% of the patients had a history of POI in their family.

As to his personal history, 50.3% did not have any previous pregnancy, were nulliparous, and of the remainder 49.7%, 6.9% had had previous abortions, with no pregnancies to term.

Of the total patients, 28.1% had an associated medical pathology, of which 27.5% of the total (83 patients), presented associated autoimmune diseases (among which autoimmune thyroid diseases predominated). A total of 54.11% were patients with hypothyroidism, followed by patients with Graves-Basedow diseases at 8.23%, and rheumatoid arthritis in 7.05%. There were other pathologies in smaller percentages, such as Systemic Lupus Erythematosus, hyperprolactinemia, Celiac, Addison. See Figure 1

A total of 7.6% of the 302 patients had received chemotherapy/radiotherapy due to prior oncologic diseases. A percentage of 8.20% had had gynecolog-

**FIGURE 1.** PATHOLOGIES ASSOCIATED WITH POI IN OUR POPULATION.



ical surgeries, of which 52% had been subjected to bilateral oophorectomy, 24% to total anexohysterectomy, 12% to bilateral adnexectomy, and 8% to unilateral oophorectomy.

Of the total number of patients, 2.3% had had some type of infection, most of them (57.1%) had had tuberculosis, followed by HIV infection (28.5%).

Among the changes in the cycle that were the main reason for consultation, 55.6% had amenorrhea, followed by 40.3% who presented oligomenorrhea; only 0.33% had regular normal cycles.

Regarding the causal pathology of POI, 49.33% had idiopathic causes, followed by 27.1% in which the cause was not specified (due to an incomplete study of the causes), with equal percentages of 8.2% were causes due to gynecological surgery and previous chemotherapy/radiotherapy. A total of 3.3% of the POI causes were genetic; in smaller percentages, there was infectious pathology, galactosemia, fragile X syndrome. See Figure 2.

## DISCUSSION

As mentioned earlier, the evidence of hypogonadotropic hypogonadism in the context of a change in the cycle of women younger than 40 years old is consistent with a diagnosis of POI<sup>2</sup>. It is important to note that unlike women with menopause, which marks an irreversible state of ovarian senescence, women with POI continue with some degree of ovarian function. Therefore, fluctuations in the ovarian hormones, as well as occasional spontaneous ovulations may be found in a small proportion of women with POI, which adds complexity to the clinical picture.

A comprehensive review of medical and family history can provide certain information and guide

doctors in the process of reaching a timely and correct diagnosis. Special attention should be given to the chronology of events, individual exposures, and personal and family history. In our population, 12% presented a history of first-degree ovarian failure. A detailed menstrual history containing the age of menarche, as well as the frequency and the menstrual pattern is useful to determine any change in the menstrual period at the beginning of the course of events. It is noteworthy that about 50% of our patients had a history of oligomenorrhea cycles during the years prior to diagnosis. Medical conditions, medications prescribed, or previous gonado-toxic exposures should be considered since they can directly affect the ovarian function and reserve. In these cases, the patient must be advised of different techniques to preserve their future fertility, that is why different medical specialties should know the impact of certain drugs and perform a multidisciplinary work on fertile women.

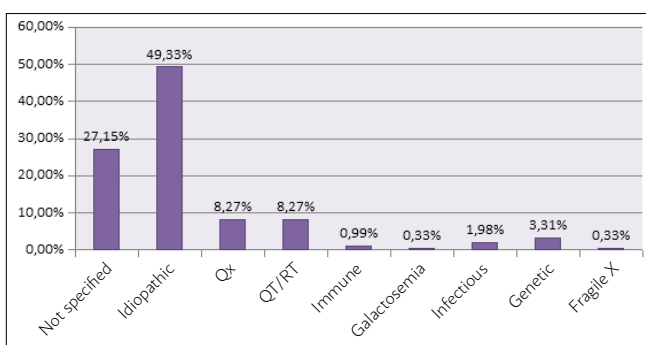
It is important to consider the documentation of any endocrinopathy (such as type 1 diabetes mellitus and hypothyroidism associated with Hashimoto's thyroiditis) since it is common for these conditions to occur in patients with POI<sup>3</sup>.

To determine the causes, it is useful to perform certain studies such as karyotype; genotyping for FMR (if there is a family history of POI); thyroid and adrenal glands antibodies. In most cases, the cause may not be evidenced; therefore, it is considered idiopathic. However, it is vital that these women are studied to demonstrate a possible cause, which can result in a specific treatment and assistance that is personal, familiar and includes possible future offspring.

Women with POI are subject to the entire range of symptoms experienced by women in menopause due to the presence of hypoestrogenism. Among these are the classic symptoms of menopause such as hot flashes, night sweats, sleep disorders, unstable state of mind and sexuality problems derived from dyspareunia, vaginal dryness, and decreased libido. These symptoms may be particularly intense in cases of iatrogenic POI, and the severity of the disease is often so great that it significantly affects the woman's quality of life, psychological well-being, and the intimate relations.

These women have a reduced life expectancy, in large part due to cardiovascular mortality and cerebrovascular accidents, changes in cognition, and low bone mass with an increased risk of fracture<sup>4,5</sup>.

**FIGURE 2.** CAUSAL PATHOLOGIES ASSOCIATED WITH POI IN OUR POPULATION 2011-2016



The adequate systemic replacement of hormones is critical to the control of symptoms, while local estrogens may be required to treat local symptoms such as dyspareunia or other genitourinary symptoms<sup>6-11</sup>. One thing that should be considered is that hormone therapy should be administered until the age of physiological menopause, i.e., around 51 years. This therapy is recommended by International Medical Societies, and its use does not present the same risks as the hormone therapy used during the climacteric.

Regarding the fertility, there are markers of ovarian reserve such as the FSH, FSH-estradiol binomial, HAM and recount of antral follicles, which can predict a low response to controlled ovarian stimulation and, therefore, a greater number of cancellations and lower response to treatments of IVF<sup>12-14</sup>. Nonetheless, none of them can predict the rate of pregnancy. The age of the patient is the most important marker to predict pregnancy rate since it usually is an indicator of oocitary quality<sup>15</sup>.

There is a certain hormonal transition that is identified until the definitive establishment of the premature ovarian insufficiency diagnosis or primary ovarian failure, both biochemically as clinically.

It is the general gynecologist's job to detect this transition and timely forward the patient to a reproductive specialist and offer alternatives for her reproductive present or future.

There are two phases between the normal class and the establishment of a definitive diagnosis of POI:

- Occult ovarian failure, in patients who have values of FSH <10 UI/ml in the early follicular phase (FFT), but Estradiol > 60pg/ml in FFT, regular menstrual cycles, and normal or decreased fertility according to age. The younger the age, the higher the possibility of pregnancy.
- Biochemical ovarian failure, in patients who have values of FSH > 10 UI/ml, but < 25 IU/ml in FFT, regular or irregular menstrual cycles, or frequent polymenorrhea. The fecundity in these patients may be reduced compared with women of the same age and preserved ovarian reserve, but not necessarily reduced in comparison with older patients<sup>16</sup>.

The reproductive specialist must identify the moment in which the patient is to offer therapeutic alternatives available, according to the desire of the patient.

If the patient still has regular cycles, she may or may not express a desire to get pregnant:

- If pregnancy is not desired at the time of diagnosis, it is of the utmost importance to inform her of the possibility of postponing maternity through the cryopreservation of oocytes and/or embryos, always when the patient is younger than 35 years, and genetic causes such as fragile X syndrome or Turner have been discarded. It is essential to provide clear and accurate information about the minimum number of oocytes required for cryopreservation to achieve a reasonable rate of pregnancy. Once the diagnosis of POI is established, it is not possible to use cryopreservation in oocytes. Once this treatment is finished, the patient should be advised about a contraceptive method.
- If pregnancy is desired, ovulation monitoring can be offered for a few months, if the patient has not had yet time for a search or IVF/ICSI, for patients older than 35 years, or searching for more than 6 months. If the patient "qualifies" for IVF, different schemes of stimulation can be used.

If the patient already has no regularity in their menstrual cycles or amenorrhea:

- If there is no desire for fertility, advise on a contraceptive method.
- If there is a desire for fertility, without a doubt, the treatment of choice in these patients is oocyte donation, with pregnancy rates of 45-60%<sup>17,18</sup>.

It is essential to mention the importance of preserving fertility in cases in which, for reasons such as cancer or other non-malignant systemic diseases, the patient must be exposed to treatments such as chemotherapy, radiotherapy and/or surgery, which can affect the ovarian reserve.

The methods currently available are:

- *Ovarian transposition*: for cases of Radiotherapy, oophorectomy or external shielding of the ovaries can be performed<sup>19</sup>.
- *Use of analogs of GnRH*: There are two reviews and a meta-analysis that demonstrate a significant benefit in reducing the risk of ovarian failure<sup>20,21</sup>.
- *Vitrification of oocytes and/or embryos*: by means of controlled ovarian stimulation and with cur-

rent techniques that facilitate the recovery of such cells and/or embryos.

- **Freezing and implantation of ovarian tissue:** proposed for children or adolescents even if it is still an experimental procedure.
- **Obtaining immature oocytes and in vitro maturation:** does not require stimulation but has a lower yield of fecundity.

It is of utmost importance to know that this entity has a high emotional impact on women, therefore, in addition to the recommendation of hormone therapy and advice on fertility, psychological support must be provided to promote acceptance and the best response during follow-up.

## RESUMO

*Insuficiência ovariana primária é definida como um declínio da função ovariana acompanhado por dois determinantes bioquímicos do Hormônio Folículo Estimulante em valores hipergonadotróficos, além de baixos níveis de estrogênios circulantes em mulheres com menos de 40 anos de idade. Embora algumas das suas possíveis etiologias serem reconhecidas e diagnosticadas, na maioria das vezes sua causa permanece desconhecida. Trata-se de patologia com a implicações médicas, psicológicas e reprodutivas. Os pacientes podem vivenciar sintomas climatéricos, infertilidade e problemas emocionais. A médio e longo prazo, a saúde cardiovascular e óssea pode ser afetada, e algum grau de deterioração cognitiva pode ser observado. A abordagem terapêutica precisa ser abrangente para o paciente e multidisciplinar. A SAEGRE criou na Argentina uma rede interhospitalar dedicada a reunir informações estatísticas relevantes sobre esta e outras patologias, a fim de proporcionar uma melhor assistência para esses pacientes.*

**PALAVRAS-CHAVE:** *Insuficiência ovariana primária, falência ovariana precoce, infertilidade, reserva ovariana, hipoestrogenismo, amenorréia hipergonadotrófica, insuficiência ovariana oculta, insuficiência ovariana bioquímica.*

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