Occult form of premature ovarian insufficiency

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Abstract

Premature ovarian insufficiency (POI) is a life-changing diagnosis, with profound physical and psychological consequences. Despite the description of different genetic, immune and iatrogenic factors of POI, the etiology of most cases of this disease are unexplained, and optimal management strategies are still unclear. Recent data showed that POI may have a long period of oligomenorrhea before the fully developed form (complete ovarian failure stage), with the occurrence of amenorrhea and climacteric symptoms. The main problem in the recognition of early stages of POI is the lack of proper diagnostic criteria. Patients with an undiagnosed occult form of POI may present with menstrual irregularities, unexplained infertility or repeated IVF failures. We evaluated 23 patients with unexplained oligomenorrhea and/or infertility. After a proper evaluation of these patients, a low ovarian reserve was identified, and an occult form of POI was diagnosed.

Introduction

Premature ovarian insufficiency (POI) is the preferred term for the condition that was previously referred to as premature menopause or premature ovarian failure [1]. The condition differs from menopause in that there are varying and residual ovarian functions [2,3]. According to the new ESHRE guidelines, POI is a clinical syndrome defined by the loss of ovarian activity in a woman before the age of 40 [4]. The ESHRE guidelines recommend the following diagnostic criteria for POI: oligo/amenorrhea for at least four months and elevated follicle-stimulating hormone (FSH) level > 25 IU/l on two occasions > 4 weeks apart [4].

Most patients with POI will present with amenorrhea, but about 50% will have varying degrees of residual ovarian function with periods of oligomenorrhea and spontaneous ovulations [5]. It is estimated that approximately 5–10% of patients with POI are able to conceive spontaneously [5,6]. It seems that most of these patients have early stages of POI (occult form) with low ovarian reserve. The precise cause of most cases of primary ovarian insufficiency remains unknown. In most women, the disease develops after a normal puberty and established regular menses [6]. Occasionally, menses stop abruptly. In some women, menses fail to resume after a pregnancy or after they have stopped taking hormonal contraceptives [7]. However, most commonly, there is a prodromal period of oligomenorrhea. Occult ovarian failure, which may be an early stage of the POI, was first described by Cameron IT and colleagues in 1988 as the triad of infertility, regular menses and elevated plasma FSH concentrations [8]. Women with an occult form of POI may have spontaneous follicular activity, and if hormonal tests are performed during such episodes, levels of FSH and estradiol could be in the normal range, or FSH could be elevated only minimally. This may lead to missed diagnoses. In these cases, the earliest ovarian reserve assessment is very important. Well-known parameters of ovarian reserve are: a woman’s age, antral follicle count determined by pelvic ultrasound on days 4–8, day 3 FSH and estradiol, AMH and Inhibin B serum levels [1,2]. However, serum FSH and estradiol levels may fluctuate and could not be markers of precise ovarian reserve assessment in the occult form of POI. More reliable markers for POI diagnosis are AMH levels and AFC on days 4–8. A transvaginal ultrasound imaging of the ovaries is one of the relevant diagnostic tests in patients with POI. Findings of a normal ovarian size/volume and the presence of a high antral ovarian follicle count (> 6) make the diagnosis of POI less likely [9]. In patients with occult POI, spontaneous pregnancy and IVF programs with their own oocytes are still possible.

However, current studies have failed to determine specific biomarkers or signs/symptoms of POI that will accurately predict when the full clinical form of the disease (premature menopause) will occur [10]. In recent years, many studies have been conducted with women with fully developed POI (amenorrhea and climacteric symptoms). Some authors proposed screening programs to recognize early stages of POI by AMH levels and early screening for specific gene mutation carriers (fragile X chromosome) in a special population (familiar cases of POI), as causes of POI are limited and predictable (e.g. Turner syndrome or preexisting ovarian surgery) [11]. Today, only the low ovarian reserve associated with endometriosis has in the literature been proposed as a potential indication for early POI screening [12]. A large majority of women with occult POI are not recognized until their
presentation with infertility [11]. Studies in the literature involving patients with early stages of POI are lacking.

**The study**

The main clinical question of the study was whether menstrual cycle irregularity and low AFC accessed by routine transvaginal sonography may be early symptoms of POI. We assessed ovarian reserve by cycle day 3 FSH and estradiol levels, AMH and transvaginal ultrasound-determined antral follicle count on cycle days 4–8. We consider AFC < 6 small follicles (diameter 3–9 mm) as a low ovarian reserve indicator.

We evaluated 23 reproductive-age women (25–39 years). Twelve women initially presented with oligomenorrhea (at least three menstrual cycle lengths more than 40 days during the last year), and 11 patients presented with primary unexplained infertility. There was no history of pelvic surgery, any cancer or chromosomal abnormalities existed and antibody measurements could be diagnosed by low ovarian reserve accessed by low AFC, and oligomenorrhea may be the earliest clinical symptom. However, day 3 FSH/estradiol levels have no clinical significance.

**Table 1. Main characteristics of patients with the occult form of POI.**

| Characteristics                        | Oligomenorrhea (n = 12) | Infertility (n = 11) |
|----------------------------------------|-------------------------|---------------------|
| Age of POI diagnosis (years)           | 30.4 ± 2.7              | 34.5 ± 3.9          |
| BMI (kg/m²)                            | 20.3 ± 0.02             | 21.5 ± 0.03         |
| Age of menarche (years)                | 12.4 ± 1.29             | 12.6 ± 0.8          |
| Menstrual cycle length (days)          | 21–90                   | 24–67               |
| Length of menstrual disturbances (years)| 0.9 ± 0.1               | 1.8 ± 0.2           |
| Pregnancy (n)                          | 0                       | 0                   |
| Day 3 FSH (mU/ml)                      | 5–37                    | 8–30                |
| Day 3 estradiol (pmol/l)               | 13–300                  | 30–259              |
| AMH (ng/ml)                            | 0.4 ± 0.7 (0.13–1.0)    | 0.3 ± 0.6 (0.13–0.9) |
| AFC (numbers)                          | 4.2 ± 0.9 (3–5)         | 3.8 ± 0.8 (1–5)     |

**Figure 1. Transvaginal sonography of the ovaries with AFC = 1 37 years old infertile patient with oligomenorrhea.**

The mean AFC in the oligomenorrhea group was 4.2 follicles and 3.8 follicles in the infertility group (p > 0.05).

The results of this small study showed that the occult form of POI in women with unexplained oligomenorrhea and infertility could be diagnosed by low ovarian reserve accessed by low AFC, and oligomenorrhea may be the earliest clinical symptom. However, day 3 FSH/estradiol levels have no clinical significance.

**Conclusion**

Most cases of spontaneous POI remain undiagnosed at early stages, and women progress in the disease until becoming clinically symptomatic at advanced stages. Women with a missed POI diagnosis may suffer from occult primary ovarian insufficiency for a long period of time. They usually present with menstrual irregularity (oligomenorrhea) or infertility, and after proper evaluation, their poor ovarian reserve can be confirmed and an occult form of POI established. Although the duration of the prodromal period as well as premature menopause age in patients with POI could not be predicted, we believe an earlier recognition of POI has great clinical significance for reproductive-age women. Early POI recognition may help to make a decision about reproductive goals and would offer this patient population the opportunity to preserve fertility, with even a chance of spontaneous pregnancy in rare cases. Thus, we support the idea that the occult form of ovarian failure exists, may have unpredictable duration and should be actively diagnosed. We suggest a diagnosis of occult POI should be taken into account in every woman with oligomenorrhea and low antral follicle count accessed by routine pelvic sonography. Day 3 FSH and estradiol levels cannot be markers for occult POI. In our small-sized clinical study, women who presented with only oligomenorrhea were younger than infertile patients; therefore, menstrual irregularity may be the earliest clinical symptom of occult POI. A new approach to managing women with primary ovarian insufficiency is needed, as the POI has a chronic course.
Declaration of interest
The authors declare that they have no competing interests.

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