

HYPERGONADOTROPIC OVARIAN INSUFFICIENCY IN WOMEN OF LATE REPRODUCTIVE AGE

NATALIA V. KHVORYK^{1 A-G}

• ORCID: 0000-0002-2901-7389

HAMED ASAAD ALJAZAA^{2 E-F}

• ORCID: 0000-0002-5350-7003

¹ Department of Obstetrics and Gynecology,
Grodno State Medical University, Grodno, Belarus

² Grodno State Medical University, Grodno, Belarus

A – study design, B – data collection, C – statistical analysis, D – interpretation of data, E – manuscript preparation, F – literature review, G – sourcing of funding

ABSTRACT

Background: At present, the increasing frequency of hypergonadotropic ovarian insufficiency in women of late reproductive periods is associated with various problems, which requires the development of new criteria and an integrated approach to solving these problems.

Aim of the study: To investigate the causes, clinical manifestations and diagnostic criteria of hypergonadotropic ovarian insufficiency in women of late reproductive age.

Material and methods: We examined 42 patients with clinical and laboratory criteria for hypergonadotropic ovarian failure. The causes and clinical manifestations of hypergonadotropism, as related to ovarian failure, in women of late reproductive age were revealed through this analysis.

Results: Women aged 36–42 years that have had previous surgery on pelvic organs often undergo changes typical of hypergonadotropism. Certain clinical indicators such as lability of follicle-stimulating hormone (FSH) levels and other direct and indirect signs of decreased ovarian reserves allow practitioners to prescribe appropriate therapy on time. Timely diagnosis and an individualized approach can help prevent symptoms of hypoestrogenia and related complications. The results of this study show that early detection of a luteal out-of-phase (LOOP) event, along with a more detailed history was diagnosed in 16 (38.1%) of cases. Early detection allows more timely changes in diagnosis, may noted signs that can reflect both the normal state and pathology.

Conclusions: Levels of Anti-Müllerian hormone, basal levels of FSH in two successive cycles, early detection of an LOOP-event and the use of ultrasound are significant factors that can help in the assessment of ovarian reserves.

KEYWORDS: reproductive age, ovarian reserve, damaging factors, surgical interventions

BACKGROUND

Significant reductions in the ovarian reserves of women of older reproductive age is an urgent problem that has been on the rise in recent decades. Increases in average life expectancy and the tendency to postpone the birth of offspring to a late reproductive period are factors that may contribute to current medical and social reproductive issues that women face today. Age is a significant determinant of the well-being of reproductive function. At the age of 27–28, the first signs of decreases in reproductive function appear. At this stage, basal levels of gonadotropins begin to rise. By 45 years, reproductive capacity approaches zero, and by 55 hormonal function starts to die out. The rate of aging of the reproductive system is determined by the interaction of genetic factors and the diverse influences of the environment [1,2].

Cessation of ovarian function in women under 40 is an indication of premature ovarian failure (POF) or hypergonadotropic ovarian insufficiency. The main clinical and laboratory symptoms of cessation of ovarian function are amenorrhea, an increased concentration of gonadotropic hormones in the blood and hypoestrogenism and its consequences [1–4]. Interestingly, in the case of viral infections, especially frequently recurrent variants, cellular immunity is activated. This includes the production of antigens of the major histocompatibility complex (MHC) class II, which is increased not only in cells of the immune system, but also in cells of the ovarian epithelium, which leads to the production of anti-ovarian antibodies that are associated with POF and other autoimmune disorders [1,4,5]. The consequences of surgical interventions on pelvic organs may

stimulate the development of problems associated with decreased reproductive and hormonal potentials. It is well known that surgical aggression may be one of the reasons for the development of POF [1,6,7]. Women with infectious processes in the reproductive system including paramyxovirus (mumps), human immunodeficiency virus (HIV) or pelvic inflammatory disease represent a risk group for the development of premature ovarian failure [1,5,8].

According to the recommendations of the American Society for Reproductive Medicine (2008), 3 reproductive periods are distinguished before menopause, which are characterized by an increased level of FSH and a reduced ovarian reserve. These stages include the so-called 'late reproductive period', perimenopause, which is divided into early and late stages. Clinically, menstrual transition is associated with hypoestrogenia in which woman may complain of dryness in the vagina, decreased libido, weight gain, deterioration in the condition of hair and nails, irritability, night sweats and increased blood pressure. Traditionally, the classification of the stages and criteria for the functioning of the reproductive system (Stages of reproductive aging workshop – STRAW) is based on the menstrual transition period which begins with changes in the duration of the menstrual cycle and a monotonous increase in FSH levels [9].

In the updated STRAW + 10 system (2011), the functional phase is stage -3b, which is characterized by a regular menstrual cycle and a normal level of FSH in the early follicular phase, and the -3a stage is associated with shortening of the menstrual cycle and elevated levels of FSH [8]. The refined criteria determine the entry into the early menstrual transition period, which is characterized by menstrual cycles that are variable in length with a difference of 7 or more days, followed by the preservation of this difference at least once during 10 cycles. At the same time, additional criteria include elevated levels of FSH, volatile, low Anti-Müllerian (AMH) hormone levels, and low numbers of antral follicles [1,9,10].

AIM OF THE STUDY

This study was conducted with the aim to investigate the causes, clinical manifestations and diagnostic criteria of hypergonadotropic ovarian insufficiency in women of late reproductive age.

MATERIAL AND METHODS

Study design, setting and duration, study population

We examined 42 patients with clinical and laboratory criteria for hypergonadotropic ovarian failure. Ages ranged from 36 to 42 years, averaging 37.3 ± 2.2 years. A control group for comparison consisted of 18

women who were comparable in age and underwent preventive examinations.

Inclusion criteria

The criteria for selecting patients in the study were: menstrual irregularities and clinical indications of estrogen deficiency, FSH levels in serum of more than 25 mIU/L at least in a single definition (FSH study was conducted twice according to the criteria of the European Society of Human Reproduction and Embryology, 2015) and episodic or stable amenorrhea among women under 42 years old.

Exclusion criteria

Excluded from the study were patients with a diagnosis of polycystic ovary syndrome, hyperprolactinemia or amenorrhea of central origin. The diagnosis of ovarian failure was based on anamnestic, clinical and laboratory data and instrumental examination methods.

Methodology

The functional state of the hypothalamic-pituitary-ovarian system was determined and based on hormonal status, including levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol and Anti-Müllerian (AMH) hormone. The levels were determined by using enzyme immunoassays with measurements of plasma concentrations of the aforementioned hormones. A transvaginal ultrasound was performed to evaluate the volume of the ovary, the number of follicles and the pathology of the uterus.

Ethical considerations

The study was conducted after ethical approvals were obtained from the Grodno State Medical University – ethical Committee (no.: 23/2018).

Statistical analysis

Statistical analysis was performed using the software set Microsoft Excel and Statistica 6.0. To describe the obtained results of the studied phenomena, we calculated the frequency indices of the studied phenomena (p) with a statistical error (Sp), arithmetic mean (M) and arithmetic mean error (m).

Characteristics of the study group

Almost all examined patients had a higher education, (39 women, or 92.9% of all cases), or secondary special education (3 women, or 7.1% of all cases). In the group, 7 women (16.7%) had smoking habits. During treatment, patients' main complaints were menstrual irregularities, which occurred in 31 patients, or 73.8% of all cases. Oligomenorrhea occurred in 32 cases (76.2%), shortening of the menstrual cycle was noted in 37 cases (88.1%), while amenorrhea was diagnosed in 5 cases (11.9%). Subjective symptoms of ovarian function depletion in the form of hot flashes, decreased libido, headaches, fatigue, sleep disturbances and vaginal dryness were reported by 32 women (76.2%).

RESULTS

The average age of the onset of menarche was 13.4 ± 0.5 years. The onset of sexual activity of the patient was on average 19.1 ± 1.4 years. In most cases, i.e. in 39 cases (i.e. 92.9% of all cases), a regular menstrual cycle lasting 28.9 ± 2.5 days was observed after menarche. Analysis of reproductive function indicators showed that the majority of women, 40 (95.2% of all cases), had undergone childbirth, however, in 2 patients (4.8%) reproductive plans were not implemented. Of the women who had children, 36 (85.7%) had 2 births, 3 (7.1%) had three births and 1 (2.4%) woman had only one child. Abortions were observed in 12 (28.6%) women. Eight (19%) women had a history of unsuccessful in vitro fertilization (IVF) attempts. Of extragenital diseases, thyroid pathology was most often encountered, with autoimmune thyroiditis occurring in 5 women (11.9%). Other pathologies included childhood and acute respiratory infections, diseases of the cardiovascular system (9 women, or 21.4% of total cases), urinary tract infections (4, or 9.5%), gastrointestinal tract problems (5, or 11.9%), and endocrine-metabolic disorders (3, or 7.1%). Of particular relevance was the analysis of gynecological pathology. It was found that more than half of the patients (29, or 69.0% of total cases) underwent different types of treatments for different pathologies. The different gynecological pathologies found in the group of women studied is presented in Tab. 1.

Table 1. Gynecological pathology of the examined women.

Gynecological pathology	Number of patients	
	absolute	%
Benign Cervical Disease	11	26.2
Cervical Dysplasia	1	2.4
Endometrial polyps	8	19.0
Uterine fibroids	6	14.3
Cysts and ovarian cyst (including endometriosis)	14	33.3
Ovarian apoplexy	12	28.6
Inflammation of the uterine appendages	14	33.3
Infertility	18	42.9
Ovarian Endometriosis	7	16.7
Adenomyosis	4	9.5
External genital endometriosis	4	9.5
Ectopic pregnancy	6	14.3
Atonic uterine bleeding after labor	1	2.4

As can be seen in Tab. 1, the most common gynecological pathology was infertility, both primary and secondary, which was found in 42.9% of all cases. To help treat this pathology, the women underwent diagnostic and/or therapeutic laparoscopy. Most of these patients (10, or 55.5% of all cases) were diagnosed with ovarian endometriosis and/or external genital endometriosis. Appropriate treatment was provided for these condi-

tions. Next in frequency of occurrence were ovarian cysts and cystoma, as well as chronic inflammatory diseases of the uterus (6, or 33.3%). Surgery for ovarian cysts was carried out on an emergency basis due to rupture and bleeding in the abdominal cavity. Cystomas were removed as planned by laparoscopic access. Most often (in half of the cases) these were endometrioid cysts. A hormonal study conducted in the early follicular phase showed that fluctuations in FSH levels ranged from 9 to 38 mIU/L. The average normal value is 28.6 ± 7.4 mIU/L. During a menstrual cycle, the study was conducted twice in succession and the hormone fluctuations during repeated determination ranged from 25 to 49 mIU/L. In cases when women had amenorrhea, a hormonal study was performed once and the levels of FSH corresponded to a hypergonadotropic state. Fluctuations in hormone levels ranged from 52 to 105.5 mIU/L. Comparing the FSH indicator with the levels in patients of the control group (8.6 ± 1.8 mIU/L), we obtained significant differences ($p < 0.001$). In women who had a clinical LOOP (luteal out-of-phase) event, we noted signs that can reflect both normalcy and pathology.

LOOP-event assessment in the studied objects

A LOOP event represents an atypical sharp increase in estradiol in the second phase of the menstrual cycle followed by a sharp decrease, which leads to a menstrual cycle of less than 21 days if ovulation occurs, with the subsequent cycle being abnormally long (more than 36 days) in cases where an LOOP event does not end with ovulation [11]. Therefore, clinically the LOOP-event with a more detailed history was diagnosed in 16 patients (38.1% of all cases).

In cases where the menstrual cycle lasted 21 days or less, the level of FSH did not exceed 12 mIU/L. However, in the subsequent anovulatory cycle, the duration of which was more than 36 days, the level of FSH in most women corresponded to hypergonadotropic values reaching 52 mIU/L. LH levels in the early follicular phase for women of the main group corresponded to 18.8 ± 8.1 mIU/L, whereas in the control group the values were 5.1 ± 1.9 mIU/L ($p < 0.001$). We did not notice any significant differences in the LH/FSH ratio between the main group (0.62 ± 0.2) and the control group (0.58 ± 0.5), which indicates interdependent hormonal fluctuations in the basal levels of hormones. We found that there were no significant differences in the levels of estradiol, which increased to 45.8 ± 8.8 pg/mL and 48.9 ± 8.1 pg/mL, in the main and control groups, respectively. The lack of difference is associated with the determination of basal levels of the hormone in the blood. There were also no significant differences when comparing prolactin levels in women of both groups ($p > 0.05$). The AMH level in all patients was reduced and corresponded to 0.26 ± 0.13 ng/mL, while in the control group, it amounted to 1.2 ± 0.86 ng/mL.

Ultrasonographic criteria

Ultrasound scanning of the pelvic organs showed normal or reduced size of the uterus in patients. The total volume of the ovaries was $2.1 \pm 0.86 \text{ cm}^3$, indicating a poor prognosis for ovarian reserve according to ultrasound criteria. In the control group, this indicator corresponded to $6.1 \pm 2.3 \text{ cm}^3$, which was significantly different from the main group. In 16.7% of cases, one of the ovaries was not visualized. These ultrasound results were of patients that had undergone removal of a cyst larger than 8 cm in diameter, as well as two surgical interventions performed on one ovary.

Counting the number of antral follicles is a more accurate method for assessing ovarian reserve. A decrease in their number (i.e. less than 5) was recorded in 12 patients (28.6% of cases), a weakly expressed follicle count was registered in more than half of patients (26, or 61.9% of cases) and the absence of a follicle count was diagnosed in 4 patients (9.5%). The monotone pattern of the endometrium, which is when the anteroposterior size of the endometrium corresponds to 5 mm or less during the menstrual cycle, was observed in a third of patients (13 or 31.0% of cases). The absence of growth of the dominant follicle was recorded in the majority of women examined (37 or 88.1% of cases).

DISCUSSION

There is a “theory of burnout” when there is an accelerated growth of follicles, with subsequent depletion in the cortical layer of the ovaries with endometriosis. At the same time, a decrease in the pool of early follicles is observed, which can occur due to various reasons such as exhaustion of the pool of primordial follicles, activation of the early development of follicles, an increase in the number of atresized follicles or dysregulation of the selection of follicles [10,12]. Thus, there is a violation of folliculogenesis in the ovaries of women with endometriosis, characterized by a decrease in the total number of follicles at all stages of development. The extent of decrease in the number of follicles depends on the stage of spread of the pathological process and the age of the patient [12]. It was found that patients with ovarian endometriosis of various stages of distribution have a low level of AMH, and lower values are observed in cases that have bilateral endometrioid ovarian formations compared to unilateral formations [7,13]. Therefore, ovarian endometriosis in combina-

tion with age is a significant risk factor for follicular reserve depletion.

Excisional surgery has been questioned as an ideal surgical approach for endometriomas because it is associated with potential reduction of ovarian reserve [6]. Another significant factor is ovarian apoplexy, both as a result of organ trauma and pathology leading to surgery – 28.6%. Currently, laparoscopic surgery in gynecology occupies a leading position among gynecological procedures. More than 70% of surgical interventions are performed by laparoscopic access. It is well known that it is necessary to differentially approach the use of high surgical energies when working on the ovaries. The goal of surgery should be effective hemostasis and reducing morbidity associated with exposure to tissues. Other gynecological pathologies in women included benign diseases of the cervix, endometrial polyps, uterine fibroids, adenomyosis, surgical interventions for ectopic pregnancy and postpartum hemorrhage. A study by V.A. Guriev showed that patients with low ovarian reserves underwent bilateral ovarian resection in 25.3% of cases, while a cystectomy was performed in 19.8% of cases – for the latter, the cystectomy was performed on the right, which increased the odds ratio of reducing the ovarian reserve since the right ovary is functionally more active and therefore its loss, or a decrease in the primordial pool due to surgical interventions, is more significant [8]. It is well known that surgical intervention may be a major reason for the development of premature ovarian failure [1,6,7]. It has been found that uterine artery embolization increases the risk of premature ovarian failure [9].

Limitations of the study

The present study was conducted over a short period of time and had a small sample size. In future studies, a larger population size would be ideal.

CONCLUSIONS

In today’s modern times, issues such as the increasing incidence of diseases and tendencies towards late reproductive periods requires the development of new criteria and an integrated approach to solving these problems. Early detection of LOOP syndrome, assessment of AMH after gynecological interventions and ultrasound criteria for ovarian reserve will allow timely diagnosis and appropriate treatment of hypergonadotropic states in women of late reproductive age.

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Correspondence address:

Hamed Asaad Aljazaa

Clinical Resident

Grodno State Medical University

290000, Grodno, Gorky Street, 80

Phone: +375 33 325 64 01

E-mail: kafedra2.bsmp@mail.ru

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