Communication

Endocrinology of Primary Ovarian Insufficiency: Diagnostic and Therapeutic Clues

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Endocrinology of Primary Ovarian Insufficiency: Diagnostic and Therapeutic Clues

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Abstract: This paper briefly reviews the most important endocrine features of primary ovarian insufficiency (POI) and shows their relevance for diagnosis and treatment of this condition. Endocrine disturbances in POI cause problems both for fertility and for general health status of the affected women. Subfertility or infertility results from depletion of growing ovarian follicles and is, in its turn, the causative factor of hypoestrogenism responsible for general health problems, including hot flashes, dyspareunia, genitourinary syndrome of menopause (vulvovaginal atrophy and urinary incontinence), decreased sexual desire, dry eyes, night sweats and insomnia, as well as the risks for cardiovascular health, metabolic abnormalities, diabetes, obesity, chronic inflammation, hypertension, and autonomic nervous system dysfunction. A combination of high serum FSH and low estradiol concentrations is a key feature charactering POI and the decisive element for POI diagnosis. The treatment of the general health problems, based on correcting hypoestrogenism by hormone replacement therapy (HRT) with 17β-estradiol, is relatively easy. On the other hand, resolving infertility is a much more difficult task, and oocyte donation is the only really efficient instrument. Fertility preservation strategies, are suitable alternatives in cases of early POI diagnosis, in which some viable follicles are still present in the ovaries. In patients who refuse oocyte donation, intraovarian injection of autologous platelet-rich plasma may be considered. Other innovative treatments, such as stem cell therapies or nuclear transfer, are currently under investigation.

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1. Introduction

Primary ovarian insufficiency (POI), sometimes also referred to as "primary ovarian failure", is a condition characterized by the appearance of insufficient ovarian function before the age of 40 years [1,2]. Though not very frequent, POI is important to be looked for because of its multiple negative consequences, not only for the fertility status but also for the patient's health in general. The estimated global prevalence of POI is 3.7% [3], but it has been steadily increasing over the past years [4]. The negative consequences of POI for the general health of affected women have been extensively reviewed recently [1,2,5,6] and include an increase in the long-term risk for cardio-metabolic disease, type 2 diabetes, hyperlipidemia, coronary heart disease, stroke, centripetal obesity, chronic inflammation, hypertension, vasoconstriction, endothelial dysfunction, autonomic nervous system dysfunction, skeletal fragility, neurocognitive disorders, and total and cancer-related mortality. Improvement of the diagnostic and therapeutic methods to be employed in cases of POI is thus an important challenge for future research, and the analysis of the endocrine profile of the affected patients is fundamental to achieve this goal.

2. Causes of POI

Causes of POI have been extensively reviewed recently [2,5,6]. They may be related to either genetic or non-genetic factors.

The genetic factors casing POI include chromosomal abnormalities, mainly those concerning the X-chromosome, genetic polymorphism, and single-gene mutations [2,5,6]. Mutations of the newborn

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ovary homeobox (NOBOX), the factor in germline alpha (FIGLA), genes located in forhead box L2 (FOXL2), nuclear receptor subfamily 5 group A member 1 (NR5A1), bone morphogenetic protein 15 (BMP15), growth differentiation factor 9 (GDF-9), transforming growth factor-β superfamily, the FSH and LH receptor, steroidogenic factor 1 (SF-1), cytochrome P450 family 19 subfamily A polypeptide 1 (CYP19A1) and inhibin alpha subunit (INHA) genes were all demonstrated to cause infertility and loss of follicles [2,5,6]. Alteration of non-coding RNAs (ncRNAs) expression, leading to epigenetic dysregulation, was also found in women with POI.

The non-genetic causes of POI can be related to autoimmune, iatrogenic, or metabolic, factors [2,5,6], autoimmune thyroiditis, adrenal insufficiency, polyglandular syndrome and Addison's disease being the most common immune factor associated with POI. Chemotherapy and radiotherapy are the most common iatrogenic causes of POI, while the most known metabolic causes of this disease are galactosemia, mytotonic dystrophy, and hydroxylase deficiency [2,5,6].

The knowledge of possible non-genetic factors causing POI is essential since, once POI is diagnosed, their involvement can be investigated, and the underlying pathology can be treated adequately.

3. Hormonal Regulation of the Ovarian Function

Most of biologically relevant ovarian activity is exerted by different cells of ovarian follicles. Ovarian follicles are dynamic structures that undergo important changes over time, related to their growth, cell differentiation, and hormonal dependence. At birth, only small primordial follicles are present. During further life, primordial follicles grow and sequentially transform into growing pre-antral, early antral and preovulatory follicles [7]. Individual primordial follicles have different fates: some enter the growth phase while others fall prey to atresia.

Two phases of follicular growth can be distinguished: a gonadotropin-independent one and a gonadotropin-dependent one. The gonadotropin-independent phase is characterized by multiplication of granulosa cells, begins before puberty and is driven by PI3K/AKT/mTOR activation and PTEN inhibition, while the activation of specific transcription factors, such as NOBOX, in the oocyte is essential for its growth [2]. After puberty, the growing blood levels of pituitary gonadotropins, namely follicle stimulating hormone (FSH) and luteinizing hormone (LH), take over the main control of follicle development, namely the formation of follicular antrum, through increased follicular fluid production by granulosa cells, and initiation of meiotic maturation of the oocyte [7]. Pituitary synthesis of FSH and LH is stimulated by secretion of GnRH and inhibited by estradiol and inhibin released from growing follicles [8]. Ovulation is triggered by preovulatory LH peak which, in turn, is provoked by a sudden switch from an inhibitory to a stimulatory action of estradiol when persistently increasing estradiol concentrations reach a critical point [9]. The LH peak is also responsible for resumption of meiosis and its progression to metaphase II in preovulatory oocytes [10].

4. Endocrine Disturbances in POI and Their Clinical Consequences

Depletion of growing follicles in the ovaries of women with POI leads to extremely low levels of circulating estradiol and inhibin. This, in turn, causes abnormally high levels of pituitary gonadotropins, mainly FSH. The POI-related hypoestrogenism is also the cause of most clinical symptoms concerning the patients' general health status, such as hot flashes, dyspareunia, genitourinary syndrome of menopause (vulvovaginal atrophy and urinary incontinence), decreased sexual desire, dry eyes, night sweats and insomnia, as well as the risks for cardiovascular health, metabolic abnormalities, diabetes, obesity, chronic inflammation, hypertension, ant autonomic nervous system dysfunction [1,2,5,6,11]. Most POI patients are subfertile or infertile, depending on the duration of the POI condition, and some of them show symptoms supposedly related to the genetic background of the disease, such as Turner syndrome-like phenotype [5]. In fact,Turner syndrome (45,X) and other abnormalities of X chromosome, such as mosaicisms, partial loss of critical terminal regions of the long arm of the X chromosome, and X-autosomal translocations, are well-known chromosomal abnormalities causing POI [2].

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5. Diagnosis of POI

Diagnosis of POI is mainly based on the evaluation of endocrine parameters. Patients usually present with irregularities of the menstrual cycle and symptoms related to hypoestrogenism (see section 3). The diagnosis of POI is dependent on evidence of hypergonadotropic hypogonadism in a woman younger than 40. In particular, serum concentrations of FSH and estradiol are the most important parameters. When a POI diagnosis is suspected, serum levels of FSH and estradiol should be measured twice, at least one month apart, and persistently elevated FSH levels greater than 25 IU/L confirm the diagnosis of POI [12,13].

6. Treatment of POI

6.1. General Health Problems

Since virtually all of the general health problems associated with POI are caused by hypoestrogenism, hormonal replacement therapy (HRT) with estrogenic preparation is the treatment of first choice to restore physiological estrogen levels, in line with patients' age [14]. Among available formulations, preparations based on 17β-estradiol are preferable, as compared with those based on ethinyl-estradiol or conjugated equine estrogens [14]. Transdermal administration is more suitable than oral treatment because it bypasses the hepatic first-pass effect, reducing liver exposure to supraphysiologic doses of estrogen and thus avoiding the resulting increase in pro-coagulant factors, SHBG, triglycerides, and markers of inflammation [15].

Adding progestin is recommended in women with uterus to prevent endometrial hyperplasia and minimize irregular bleeding, micronized natural progesterone, taken orally or vaginally, showing greater efficacy than traditional synthetic progestins regarding breast cancer risk, metabolic impact, and thromboembolic events [16]. In addition to these specific treatments, patients should be advised to observe a well-balanced diet with adequate physical activity, to avoid smoking and to minimize alcohol consumption [17], with supplementary calcium and vitamin D treatment in cases with inadequate dietary intake [18].

6.2. Infertility

The probability of a spontaneous pregnancy is very low in women with POI. It is estimated to be 5% [19]. The reason for which pregnancy still may occur is that POI is not always permanent, and some POI patients can ovulate from time to time [6]. However, even in those women who can ovulate (about 25%) only 5-10% can conceive [20]. This is likely to be due to impaired oocyte quality. Oocyte donation is the recommended treatment for infertility due to POI, as it has been proven to achieve a 70–80% successful pregnancy rate in patients suffering from this pathology [6]. Fertility preservation strategies, such as the cryopreservation of oocytes, embryos and ovarian tissue, are suitable alternatives in cases in which some viable follicles are still present in the ovaries [21]. Hence, the possibility of preserving fertility strongly depends on an early diagnosis.

It is important to note that women who undergo infertility treatments, both those who had not received HRT before these treatments and those who interrupted it in the context of these treatments, should resume HRT after the attempt to conceive. If they did not, the general health problems associated with POI (see section 4) would reappear.

6.3. New Therapies

Stem cell therapy is a new exciting advance in POI [22]. Therapies with stem cells,such as, mesenchymal stem cells (MSCs), stem cells from extra-embryonic tissues, induced pluripotent stem cells (iPSCs), and ovarian stem cells, are currently being tested in amimal models. Intra-ovarian injection of platelet-rich plasma, prepared from autologous blood, has been shown to support the viability and growth of preantral follicles and to increase the number of retrieved oocytes, presumably through the release of different growth factors including platelet-derived growth factor, epidermal growth factor, insulin-like growth factor β-I, vascular endothelial growth factor,

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hepatocyte growth factor, and basic fibroblast growth factor [23]. Successful conception and a live birth in a patient with POI with the use of this technique have been reported [24]. Administration of growth hormone during ovarian stimulation with gonadotropins is known to enhance both the quantity and the quality of oocytes recovered by ovarian puncture in poor-prognosis patients [25], but it has not yet been specifically evaluated in women with POI. Other innovative techniques, based on nuclear transfer from patients' oocytes or somatic cells into enucleated donor oocytes [26], are under investigation but still not clinically available.

7. Conclusions

A specific pattern of endocrine disorders, characterized by high serum FH and low estradiol concentrations, is a typical feature of POI and decisive for POI diagnosis. Low serum estradiol is responsible for most of the negative impact of POI on the patiets' general health status, while the depletion of growing ovarian follicles is the cause of infertility. Restoring normal estradiol levels is the main therapeutic action to combat the general health problems of POI patients. Oocyte donation is an efficient method for the treatment of POI-associated infertility. Other treatments, aimed at achieving pregnancy with the patients' own oocytes can be considered but are much less reliable. Innovative treatment alternatives are currently under investigation.

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