INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

The Role of Polycystic Ovary Syndrome in the Structure of Female Infertility

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Annotation: Polycystic ovary syndrome (PCOS) is a heterogeneous complex disorder characterized by oligo-anovulation, hyperandrogenism and/or hyperandrogenemia, and polycystic ovarian morphological changes. Interest in PCOS encompasses several specific aspects, including reproductive, cosmetic, and medical. Polycystic ovary syndrome (PCOS) is a heterogeneous and complex disorder characterized by both metabolic and hormonal disorders and is a major cause of infertility in women. Much information has emerged in recent years to define the diagnostic criteria for this syndrome. In addition to hormonal aspects and metabolic abnormalities such as insulin resistance and obesity, susceptibility to developing earlier than expected glucose tolerance, the idea that these aspects should be included in the diagnostic criteria in order to develop potential therapeutic strategies is being considered. In addition, family history of SPCJ in families and in both female and male relatives may demonstrate stigmata of the syndrome, suggesting a genetic background.

Keywords: PCOS, multicystic ovaries, infertility, pharmacotherapy, diagnosis, hormones.

Introduction

According to the World Health Organization, infertility is the inability of a sexually active couple not using contraception to achieve pregnancy within one year. This period is determined by current understanding that the cumulative conception rate among healthy married couples by the end of the first year is 85.0%, and by the end of the second year, it increases to only 8.0% [1, 2].

The incidence of infertility is 15-30% in the general population of married couples, with infertility lasting more than 5 years observed in 42% of infertile women of reproductive age, and approximately 30% of infertile couples requiring assisted reproductive technology (ART) [3, 4].

PCOS contributes significantly to the problem of infertility: it is the cause of endocrine infertility in 56.2% of cases, and accounts for approximately 20-22% of the causes of infertility [3, 4]. Infertility management in women with PCOS requires an understanding of the pathophysiology of anovulation. Figure 2 demonstrates possible causes of infertility in women with PCOS.

It should be emphasized that a diagnosis of PCOS does not necessarily mean the presence of PCOS. The last major unified document on infertility treatment in PCOS was published 20 years ago. This has prompted the search for new ways to overcome infertility in women with PCOS. International guidelines emphasize that PCOS is a risk factor for infertility in the presence of oligo-anovulation. Furthermore, accurate knowledge of the PCOS phenotype and comorbidities (e.g., obesity, insulin resistance, etc.) is particularly important in infertility patients to optimize and personalize treatment strategies. Furthermore, even if the presence of ovarian dysfunction and its impact on reproductive function in a patient with PCOS is certain, other subclinical dysfunctions, including endometrial changes and oocyte viability, cannot be ignored [3, 4].

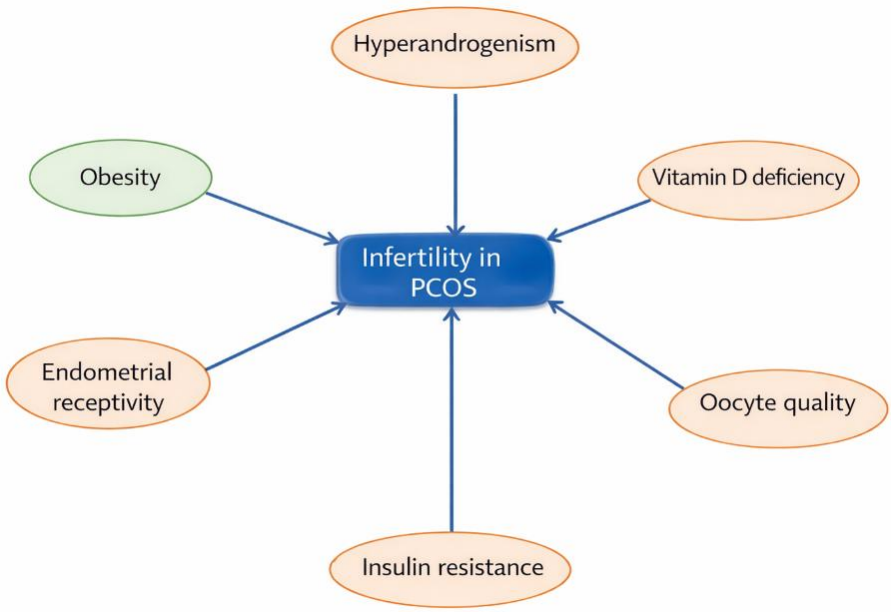

Figure 2. Main factors leading to infertility in women with PCOS

It is highly likely that severe metabolic changes may be closely associated with worse reproductive outcomes and vice versa. An analysis of 1,376 infertile women showed that younger age, lower baseline free androgen and insulin levels, shorter duration of fertility attempts, and higher sex hormone-binding globulin (SHBG) levels significantly impacted the final outcome of infertility treatment, namely, achieving at least one pregnancy [1, 2]. This study demonstrated that the prognosis of women with infertility due to PCOS is a combination of general prognostic factors and PCOS-specific factors. Therefore, a good clinician should consider a variety of factors when treating infertility in patients with PCOS. Studies of combined symptoms such as anovulation + hyperandrogenism and anovulation + polycystic ovarian morphology in PCOS have not shown significant differences in the development of infertility [2,4,6]

Anovulation in women with PCOS. Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility, affecting up to 10% of the female population. Given the high incidence of PCOS, much research has been conducted into its etiology and treatment. Despite numerous attempts, it has not been possible to determine the exact cause of anovulation in PCOS. Various features of PCOS can contribute to ovulation disorders. In 1935, Stein and Leventhal first described PCOS in their observations of seven women who had enlarged ovaries, amenorrhea, infertility, and hirsutism. Their hypothesis was that sclerocystic thickening of the ovarian cortex impedes egg expulsion and, therefore, leads to ovulatory failure [3,4,7].

This was apparently supported by the fact that wedge resection of the ovaries restored ovulation. Over time, it became apparent that the primary lesion of PCOS is an endocrinological disorder within the ovary itself—excessive androgen production. This is associated with various extraovarian hormonal disturbances, including insulin resistance, hyperinsulinemia, and elevated LH concentrations [5,6,8].

Despite these numerous endocrinological abnormalities in PCOS, none of them alone can explain the pathogenesis of this condition. It has been found that PCOS is more common in female relatives, leading to the hypothesis that this condition is inherited genetically, although environmental factors may also contribute to the risk. It was found that 22% of sisters of women with PCOS also met the diagnostic criteria for the syndrome [5,7,8].

Previously, PCOS was thought to follow an autosomal dominant inheritance pattern, but this data has not been confirmed by modern studies examining a more complex genetic structure [6,9,11].

Thus, the study of the causes of anovulation in PCOS continues to be of interest to many researchers.

Gonadotropin release abnormalities. PCOS is associated with increased LH pulse frequency and amplitude and normal or weakened FSH pulse frequency. Studies conducted in the daughters of women with PCOS during puberty have shown that hypothalamic-pituitary dysfunction manifests itself already at this early stage in the life of a PCOS patient. Instead of the usual increase in LH release pulsation observed during the night, an increase in LH pulsation is observed at the end of the day. Thus, it is clear that the GnRH pulse generator is altered very early in PCOS [7,9,12].

The LH pulsation frequency in women with PCOS does not correspond to the cyclical changes observed in women with ovulatory cycles. LH pulses are observed approximately hourly throughout the cycle. It is unknown whether this is due to the hypothalamus, pituitary gland, or peripheral feedback mechanisms [8,9,12]. Impaired gonadotropin release may also be one of the causes of anovulation in PCOS.

Hyperandrogenism. The ovaries produce all three classes of sex steroids: estrogens, progestins, and androgens. Two androgens are secreted by the ovaries: androstenedione and dehydroepiandrosterone (DHEA). Androstenedione is produced by the stromal and thecal cells of the ovaries under the influence of LH. About half of a woman's androstenedione production occurs in the ovary, and the other half in the adrenal glands. DHEA originates primarily from the adrenal glands. Androstenedione is normally converted to estradiol by the enzyme aromatase under the influence of FSH, but aromatase activity is reduced in women with PCOS. Excess androstenedione in the ovary is converted to estrone and testosterone. The ovary also secretes androstenedione into the blood, and it is partially converted to testosterone in peripheral tissues. Elevated concentrations of androstenedione, testosterone, estrone, and DHEA are observed in women with PCOS [7,9,14]

In vitro experiments have shown that hyperandrogenism accelerates follicular development from primordial to small antral follicles.

As a result, the density of pre-antral and small antral follicles in the polycystic ovary is six times higher than in a normal ovary. These follicles apparently do not undergo the expected progression into ovulatory follicles and also experience a reduced rate of apoptosis. This explains the typical appearance of the polycystic ovary.[5,6]

Anti-Müllerian hormone (AMH). AMH belongs to the transforming growth factor-beta (TGF-B) family and is produced exclusively by the gonads.[8] In women, it is secreted throughout life by the granulosa cells of the early primordial follicles. Its secretion increases and reaches a maximum in small antral follicles, and as the follicles progress to the preovulatory state, AMH secretion decreases. Once a follicle reaches 10 mm in size, the concentration of AMH secreted by this follicle becomes undetectable. There is a strong correlation between serum AMH and the number of small antral follicles, and therefore its quantity is widely used as a marker of ovarian reserve [5,8,9].

Considering that women with PCOS have an increased number of small pre-antral and antral follicles, AMH concentrations in them are significantly elevated compared to women with normal ovaries. This has been confirmed by several studies [7,10].

However, an increased number of follicles is not the only explanation for elevated AMH levels in patients with PCOS. It is possible that the higher the AMH level, the more severe the PCOS. AMH concentrations in PCOS patients are clearly higher in women with amenorrhea compared to women with oligomenorrhea, who, in turn, have higher AMH levels than women with regular menstrual cycles [6,5].

Thus, the higher the AMH level, the more severe the ovulation disorder. AMH also appears to interact with other hormones within the hypothalamic-pituitary-ovarian axis. These mechanisms are illustrated in Fig. 2.

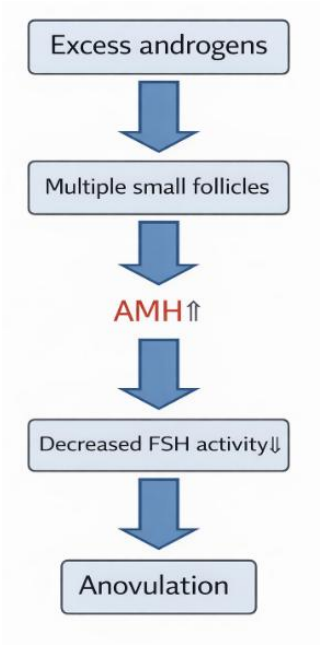

Fig. 2. The possible role of AMH in anovulation in PCOS

FSH and AMH. Finding low FSH concentrations in patients with PCOS would help understand the anovulation in this condition. However, serum FSH levels are usually within the normal range, albeit at the lower end of the normal range. However, there is evidence of endogenous inhibition of FSH action, likely due to high AMH concentrations in antral follicles [3,4,5]. Clearly, this inhibitory function of AMH can be overcome exogenously.

FSH or by stimulating an FSH surge, as with ovulation induction with clomiphene. Treatment with clomiphene restores ovulation in approximately 80% of patients. Even low doses of exogenous FSH have been shown to stimulate the development of dominant follicles [4,6]. This is an encouraging discovery for those facing the common clinical manifestation of infertility in patients with PCOS.

LH and AMH. AMH and LH concentrations show a positive correlation, as evidenced by numerous studies [4,5,6,7]. The exact mechanism of this association has not yet been described, but there are various plausible explanations. Disruption of the LH pulsation frequency is an early abnormality in PCOS and leads to elevated LH concentrations in the blood. LH receptors are found only on theca-luteal cells. LH acts on these cells, stimulating the conversion of cholesterol to androstenedione and testosterone. These androgens promote the development of primordial follicles into pre-antral follicles, which then produce increased amounts of AMH. Based on these associations, an obvious method for restoring ovulation would be to reduce the number of follicles in the ovaries, which would then lead to a decrease in AMH concentrations. This is consistent with the initial findings of Stein and Leventhal, who demonstrated that wedge resection of ovarian tissue [4,5,6] restores ovulation, as does follicle destruction during laparoscopic ovarian diathermy. Accelerated follicle loss occurs after age 40, and therefore, it is not uncommon for women with PCOS to regain regular menstrual cycles as they reach this age [8,11,12].

However, waiting until a woman reaches age 40 or removing part of her ovary is not a panacea in the list of therapeutic methods for patients with infertility due to PCOS. Several ovulation induction methods are available. The choice of treatment method depends on the AMH concentration. Weight loss of less than 5% of body weight has been shown to restore ovulation in 60% of patients with PCOS [4,7,8]. A study comparing AMH levels in PCOS patients undergoing laparoscopic ovarian diathermy found that women with higher pre-procedure AMH levels were less likely to restore spontaneous ovulation after surgery, with an AMH cut-off value of 7.7 ng/mL above which spontaneous ovulation was unlikely [9,10,11].

Thus, although the exact etiology of anovulation in PCOS remains to be determined, the various risk factors described above, particularly the role of AMH, insulin resistance, obesity, hyperandrogenism, endometrial receptivity, and oocyte quality, help us understand the nature of ovulatory disorders and define parameters on which to base treatment decisions.

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