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Mini Review

Pathophysiology of polycystic ovarian syndrome: Mini-review

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Between menarche and menopause, the female reproductive system undergoes regular cyclic changes called the menstrual cycles. The maintenance of the cycle affects the biologic and sociologic aspects of women's life including fertility and reproduction. Menstrual cycle results from complex interactions among the hypothalamo-pituitary-gonadal axis. A woman with irregular periods is likely not ovulating. Polycystic ovarian syndrome is the most common cause of anovulation/oligoovulation. The prevailing stage of follicular development reflects the female reproductive function at the particular time of menstrual cycle. Antimüllerian hormone produced by growing follicle is the most recent circulating factor to be analyzed as a predictor of ovarian reserve. The basic denominator of polycystic ovarian syndrome is disturbance in selection of a dominant follicle. This results in a significant production of antimüllerian hormone, arrested follicular growth, and ovulatory dysfunction. The integral pathogenic factor of Polycystic ovarian syndrome is insulin resistance and obesity which explains menstrual irregularities, hyperandrogenism, infertility and other associated metabolic manifestations. There is still no standard definition of the diagnosis of polycystic ovarian syndrome. The exact pathophysiology of PCOS remains to be elucidated.

Keywords: Polycystic ovarian syndrome; Antimüllerian hormone; insulin resistance; Luteinizing hormone; hyperandrogenism

INTRODUCTION

Menarche refers to the onset of menstruation, which normally occurs between the age of 12-14 years (1). Menarche is an indicator of female physiological development, health, and nutritional status (1). Menopause refers to cessation of menses, which usually occurs between the age of 44-45 years (2). Between menarche and menopause, the female reproductive system undergoes regular cyclic changes called the menstrual cycles. The maintenance of the cycle affects the biologic and sociologic aspects of woman's life, including femaleness and sexuality (3); fertility (4); and reproduction (5). Menstrual cycle results from complex interactions among the hypothalamus; which produces gonadotropin-releasing hormone (GnRH); the anterior pituitary gland which synthesizes and releases follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin hormone (PRL); the ovaries which synthesize and release estrogen, progesterone, and androgens; and associated target tissues such as (endometrium, cervix, and vaginal mucosa (6). In most women in the middle reproductive years, menstrual bleeding occurs every 24-32 days. Only 15% of women have perfect 28-day-cycle (7). A cycle of 4 ± 1 week is considered to be normal. Intervals often vary for an individual woman of different times at her reproductive life. Menstrual cycle intervals are most irregular in the two years following menarche and the three years preceding menopause (8,9). Menstrual cycle is least variable between the age of 20 and 40 years. Menstrual flow lasts 4 ± 2 days with an average blood loss of 20-60 mL (10).

Any amount greater than 80 mL is considered to be abnormal (10). By convention, the first day of the vaginal bleeding is considered day 1 of the menstrual cycle. For most women, the luteal phase of the menstrual cycle is stable, lasting 13 to 14 days. Thus, variations in normal cycle length generally result from variations in the duration of follicular phase (11). Regularly predictable periods that occur every 24-32 days likely reflect ovulation. A woman with irregular period is likely not ovulating or oligo-ovulating (12). The most common causes of anovulation/oligoovulation are: Polycystic ovarian syndrome (PCOS) which represents up to 90% of ovulatory disorders; functional hypothalamic amenorrhoea (FHA); diminished ovarian reserve (DOR); premature ovarian failure (POF); and premenopause (13). Other causes include (changes in diet, exercise, and environmental changes (14); emotional changes (15); and following abortion and parturition(16).

During fetal life, germ cells populate the cortical stroma of the ovary. The ovary of childbearing cycling woman contains follicles at different stages of development. It is the prevailing stage of development which reflects the female reproductive function at the particular time of the menstrual cycle: resting primordial follicle; growing preantral follicle (primary and secondary); growing antral follicle (tertiary); Dominant preovulatory (graafian); dominant periovulatory follicle; corpus luteum of (menstruation or pregnancy); and atretic (apoptotic) follicle.

Primordial germ cells can be identified in the yolk sac as early as the third week of gestation (17). The cells begin their migration into the gonadal ridge during the sixth week of gestation and generate the primary sex cords.

It is not possible to distinguish the ovary from the testicle by histologic criteria until approximately 10-11 weeks of fetal life. After primordial cells reach the gonad, they continue to multiply by mitosis and differentiate into oogonia. At 12th week of gestation, a subset of oogonia (in pools), enters a process of meiosis to become primary oocytes. During this process, most of the cells in each pool undergo atresia (apoptosis). Primary oocytes are surrounded by a single layer of flattened granulosa cells creating a primordial follicle. The formation of primary oocytes continues until the time of reproductive maturity (18). At the 20th week of gestation, oogonia reach their maximum number of six to seven million (17). At full term, the number of oogonia will be about 1-2 million. Fewer than 400.000 oogonia are present at the onset of puberty, of which fewer than 500 are destined to ovulate (19). Most germ cells are lost through atresia (20).

To assess an individual's ovarian reserve (ovarian aging), early follicular phase serum levels of follicle stimulating hormone (FSH), Inhibin B, and estradiol (E_2) have been measured. Inhibin B and E_2 are produced by early antral follicles in response to FSH, and contribute to the classical feedback loop of the pituitary-gonadal axis to suppress FSH secretion. With the decline of the follicle pool, serum levels of inhibin and E_2 decrease and subsequently serum FSH levels rise (negative feedback mechanism) (21). Because these factors are part of a feedback system, their serum levels are not independent of each other. Furthermore, changes in serum levels of FSH, inhibin, and E_2 occur relatively late in the reproductive aging process. Substantially elevated serum levels of FSH are not found until cycles have become irregular (22). So far, assessment of the number of antral follicles by ultrasound, the antral follicle count (AFC), best predicts the quantitative aspect of ovarian reserve (23). However, measurement of AFC requires an additional transvaginal ultrasound examination during the early follicular phase. The number of primordial follicles is indirectly reflected by the number of growing follicles (24). Hence a factor primarily secreted by growing follicle, and that is not controlled by gonadotropins, will reflect the size of primordial follicle pool. Since anti-Müllerian hormone (AMH) is expressed by growing follicles up to selection (25), not influenced by pituitary gonadotropins and reflects only the follicle population (26) , and can be detected in serum (27) ; may fulfill this role.

AMH has been mainly studied for its regulatory role in male sex differentiation. The developing Sertoli cells begin to secrete AMH during developmental weeks 7-8. This gonadal hormone causes regression of the ipsilateral paramesonephric (Müllerian duct) system, and this involution is completed by 9-10 weeks' gestation (28). Hence AMH is known as Müllerian inhibiting substance (MIS) or Müllerian regression factor (MRF) (29,30). AMH also controls the rapid gebernacular growth necessary for the tansabdominal descent of the testis. Serum AMH levels remain elevated in boys during childhood and then decline at puberty to the low levels seen in adult men (31). In contrast, girls have undetectable AMH levels until puberty, when serum levels become measurable (31).

AMH is the most recent circulating factor to be analyzed as a predictor of ovarian reserve (32). Recent studies suggest that The AMH levels correlate with ovarian primordial follicle number more strongly than FSH or inhibin levels (33). Serum levels of AMH can be used as an early (when cyclicity is still normal) marker of ovarian aging (ovarian reserve). The latter should be assessed before entering an assisted reproduction program, an in vitro fertilization (IVF) program for instance, to predict the success of controlled ovarian hyperstimulation (34). AMH serum levels were shown to be highly correlated with number of antral follicles before treatment and number of oocytes retrieval upon ovarian stimulation (ovarian induction) by gonadotropins (35).

Ovarian aging (DOR) is characterized by decreased ovarian responsiveness to exogenous gonadotropin administration and poor pregnancy outcome (36). Thus, in situations where accurate ultrasound data cannot be obtained, AMH can be used as a surrogate diagnostic marker in patients with PCOS (37).

As a diagnostic marker of PCOS, AMH offers relatively high specificity and sensitivity (92% and 67%) respectively (38).

PCOS described since 1935 by Stein and Leventhal (39). As Stein-Leventhal syndrome. The basic denominator of this syndrome is disturbance in selection of a dominant follicle. The defective selective mechanism results in accumulation of small antral follicles which contribute significantly to the production of AMH. This results in arrested follicular growth and ovulatory dysfunction (anovulation/oligo-ovulation). The ovulatory dysfunction is manifested as amenorrhoea or oligomenorrhoea and elevated levels of circulating androgens. Hence the syndrome is also known as hyperandrogenic anovulation. Women with PCOS have reduced fertility. Infertility is 10 times more common among women with PCOS in comparison to healthy controls (40). PCOS-associated persistent periods of anovulation are positively correlated with infertility (41). Up to 50% and 25% of women with PCOS have primary and secondary infertility respectively (42). PCOS is characterized by uncontrolled ovarian steroidogenesis. Theca cells secrete high levels of androgens due to intrinsic activation of steroidogenesis even in absence of trophic factors (43). Androgens stimulate the proliferation of granulosa cells which produce up to four times higher levels of AMH in comparison to healthy controls (44,45). Fallat et al (46) was the first to report that serum AMH levels were correlated with antral follicle number. There have been several clinical studies that have confirmed this fact (38,47,48). Interestingly in follicles beyond the stage of small antral follicle, AMH expression diminishes (49).

Therefore, it is not surprising that serum AMH levels positively correlate with the number of 2-5 mm, but not 6-9 mm follicles in PCOS women (50). A defect in apoptotic process in some maturing follicles further increase their count in PCOS patients (51).

The finding that AMH levels are also increased in the follicular fluid of PCOS women (52) suggests that the increase in serum AMH level is not only due to an increase in the number of growing follicles, but may also result from increased AMH production per individual follicle compared to their size-matched counterparts of normal ovary. It has been suggested that aromatase activity in PCOS patients might be decreased because follicles from PCOS women do not produce large amount of E_2 (53). AMH also inhibits aromatase activity, suggesting that AMH contributes to the severity of PCOS which is manifested in high level of hyperandrogenism (53). Androgens again stimulate AMH production. Therefore, there is a positive feedback loop between AMH and androgens. The exact mechanism behind this positive feedback mechanism requires further studies, in particular, since in males during puberty, an inverse relationship between AMH and testosterone levels was found (54). So far, little is known about the factors that regulate expression of AMH in the ovary.

A remarkable feature of PCOS is decreased insulin sensitivity (55,57). A post-receptor binding defect in the insulin signaling pathways has been identified as an intrinsic component of PCOS, independent of obesity (55). There is also an alteration in gene expression of some players in insulin signaling pathways by microsomal gene analysis (56). A substantial population of PCOS women has compensatory hyperinsulinemia (55). Insulin resistance is the main pathogenic factor responsible for metabolic disturbance in PCOS (57). Insulin resistance can explain menstrual irregularities, hyperandrogenism, and other metabolic manifestations of PCOS (58,59). Hyperinsulinemia and hyperandrogenism act synergistically with increased LH to induce the following pathophysiologic sequences: First, triggering the arrest of follicular growth which continues to anovulation and hence the name hyperandrogenic anovulation (HA) for PCOS (60).second, inducing alterations in GnRH pulsatility lead to preferential production of LH compared with FSH (61, 62).

LH:FSH ratios are elevated and rise above 2:1 in 60% of patient with PCOS (63). Third, Suppression of sex hormone binding globulin (SHBG), a glycoprotein produced in the liver which binds most sex steroid hormones (64). Low SHBG levels also, for unexplained mechanisms, have been linked to impaired glucose control and a risk for developing type 2 diabetes mellitus (65). Fourth, Potentiation of androgen production by theca cells (66,67).

Administration of metformin in patients with PCOS is associated with reduction in both AMH serum levels and antral follicles, suggesting that measurement of AMH could be used to evaluate the treatment efficacy with insulin sensitizers (68).

PCOS has been associated with increased glycol-oxidative stress (69) secondary to mitochondrial dysfunction (70). Oxidative stress can itself induce insulin resistance and hyperandrogenism in patients with PCOS (70).

After four consensus workshops consisting of many of the world's experts on PCOS, there is still no standard definition of the diagnosis of PCOS (71). Diagnosis of PCOS follows three different guidelines (72,73): National institute of health criteria: hyperangrogenism, menstrual irregularities; Androgen excess-PCOS society criteria: hyperandrogenism which means biochemical evidence of elevated androgen (hyperandrogenemia) with clinical features of excess androgen (hirsutism, acne, androgenic alopecia, and acanthosis nigrigans. PCOS accounts for 70-80% of cases of hirsutism. Idiopathic hirsutism is the second most frequent cause (74)), menstrual irregularities (oligomenorrhoea or amenorrhoea) or polycystic ovaries on ultrasonography (at least 12 follicles in each ovary, follicle size between 2 and 9 mm and/or ovarian volume in at least one ovary exceeds 10 mL (75,76). ; Rotterdam criteria (two out of three criteria): hyperandrogenism, menstrual irregularities, polycystic ovaries on ultrasonography. PCOS is divided into four

phenotypes (72) representing a wide spectrum of disease and requiring different treatment: a. Frank (classic) PCOS which have all three criteria associated with more profile of metabolic and cardiovascular risk factors (77,78). b. Classic non-polycystic ovaries. c. Non-polycystic ovulatory PCOS (with regular menses). d. Non-classic mild or normoandrogenic PCOS. The disparity between the guidelines, although minor, has been associated with a variation in the diagnosis and treatment of PCOS (79). Moreover, diagnosis in adolescent females is highly debatable (57). Although obesity and insulin resistance are considered intrinsic to PCOS, none of the two is induced in the guidelines and therefore should be used for diagnostic purposes (80). The prevalence of obesity in PCOS varies between 50-80% depending on local environment, ethnicity, and lifestyle, and not on the mere presence of PCOS (42,81). On the other hand, PCOS is at high risk of developing obesity (82). This may be explained by increased androgen which deposits fats in viscera and subcutaneous tissue leading to central obesity (83). The amount of visceral fat correlates with insulin resistance (84). Obesity plays a significant role in expression of metabolic features of PCOS. However, obesity is not the sole arbiter. This evident in lean women with PCOS who demonstrate the same metabolic features as those who are obese (42). Diagnosis of PCOS in children and adolescents confronts several challenges. The normal pubertal physiological events tend to mimic the manifestations of PCOS (85). This overlap between normal puberty and diagnostic pathological criteria of PCOS may cause an over-diagnosis of PCOS among adolescent girls (80). Puberty is characterized by physiological hyperandrogenism (86) and testosterone levels rise during puberty and reach a peak adult level within a few years after menarche. This can confound with pathological hyperandrogenism of PCOS (87,88,89,90). Measurement of testosterone level does not resolve this uncertainty because testosterone concentrations are highly influenced by the stage of puberty and menstrual cycle along with other factors (80). In addition, no well defined cutoff values for androgen levels in female adolescents (76). Moreover, acne which is largely seen during puberty is not correlated with hyperandrogenism (91).

Furthermore, hirsutism is a subject of high ethnic variation (92).

Adolescents frequently exhibit physiological anovulation, usually during the first two years after menarche, due to lack of maturation of hypothalamic-pituitary-ovarian axis (79). Menstrual irregularity is an unreliable criterion for diagnosis of PCOS in adolescents (93, 94, and 95). Normal physiologic changes and variations in the volume and size of the ovaries during puberty make ultrasonographic findings controversial for the diagnosis of PCOS (96).

Females with PCOS who conceive might suffer from pregnancy-related complications such as gestational diabetes(97); preeclampsia (98); miscarriage (99,100); ; small birth for gestational age (98); increased offspring morbidity and mortality (71). The influence of PCOS phenotype, whether classic or non-classic, on female infertility remains poorly comprehended. Data describing the effect of PCOS on pregnancy outcomes are also limited and based on small trials. Thorough studies are needed to assess the degree of infertility in PCOS various phenotypes and to understand the reasons for increased negative pregnancy outcomes in this group of women (101).

Weight loss is often recommended as the first line of treatment for obese women with fertility problems (102). Moderate weight loss has been repeatedly shown to improve menstrual regularity, ovulation , and infertility (103). Similar improvement has been shown for women with polycystic ovary syndrome (104).

A weight loss of 5% or more of initial body weight appears necessary to improve markers of infertility in most women (105). Weight reduction of this magnitude is attainable for the majority of women treated in behavioral weight-loss programs or with pharmacotherapy (106). Few studies like (107) have examined the effect of bariatric surgery on markers of infertility. At least one investigator (108) has found that 70% of females who were anovulatory prior to bariatric surgery reported regular menstrual cycles postoperatively.

In conclusion, PCOS is the most common cause of infertility due to anovulation. The diagnosis of PCOS remains one of the most challenging issues in endocrinology and reproductive medicine. AMH has an inhibitory effect on primordial follicle recruitment as well as the responsiveness of growing follicle to FSH. Further studies are needed to elucidate the exact interaction between increased AMH, hyperandrogenemia, increased LH, and insulin resistance with consequent better understanding of pathophysiology of PCOS.

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