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Editorial

Polycystic Ovarian Syndrome and Endometriosis as Two Evil Extremes of Health Continuum

Endometriosis is a common, benign, inflammatory, and generally reproductive tract disorder that significantly aggravates the quality of life in affected women; moreover, evidence shows that endometriosis has a heritable component as a result of its high familial incidence and roughly 10% of women at reproductive age are suffering from the disease. The hallmark of endometriosis is proliferation of the endometrial tissue outside the uterus, typically on the ovaries, pelvic cavity, fallopian tubes, or rectovaginal area. Such "ectopic" tissue drives estradiol-induced growth and destructive changes similar to the "entopic" inner lining of the uterus during menstrual cycles. The estrogen-induced changes during menstrual cycle cause severe pelvic pain and chronic inflammation that culminate in reduced fertility and infertility. In fact, there is no cure and effective treatment for endometriosis prior to the decline in estrogen levels at menopause. Currently, the gold standard treatment is surgical exicion of endometrial lesions, or hysterectomy (1).

Menstrual blood and tissue discharge during menstruation is a rare physiological phenomenon in mammals that is restricted to humans and few other mammals. From the past to present, two main hypotheses are propounded for the etiopathogenesis of endometriosis. The first attributes the development of endometriosis to non-Müllerian stem cells, the Sampson's theory, due to retrograde flow of menstrual blood and the second is related to Müllerian stem cells, caused by altered differentiation and movement of Müllerian remnants over the early development of the uterus. However, current evidence approves the multifactorial nature of endometriosis as a result of combined contribution of anatomical, hormonal, immunological, estrogenic, genetic, epigenetic, and environmental factors in women; yet, other pieces of evidence confirm that endometriosis occurs due to changes in intrauterine conditions during prenatal development (1, 2).

Polycystic ovary syndrome (PCOS) is another common gynecologic disorder, affecting up to 20% of women during their reproductive age. PCOS is accompanied with anovulation, polycystic ovaries, hyperandrogenism, hirsutism, abdominal obesity, insulin resistance, and increased body mass index (BMI) and waist to hip ratio (WHR). The exact etiopathogenesis of PCOS symptoms is still quite unclear. As of today, genetic, environmental, nutritional, and metabolic factors have been identified as the main causes of this syndrome. However, similar to endometriosis, new evidence supports the association of PCOS with changes in intrauterine environment during prenatal development (3, 4).

The endocrinopathy is a general risk factor for endometriosis and PCOS, but the pattern of hormonal changes is quite opposite. In endometriosis, the levels of LH, testosterone, and anti-Müllerian hormone (AMH) decrease whereas the levels of follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), and oxytocin increase. On the other side, women with PCOS have increased levels of LH, AMH and androgens while decreased levels of FSH, SHBG and oxytocin are detected among them. By evaluating these patterns of hormonal changes, it seems that the causes of two disorders may be the same; therefore, endometriosis and PCOS appear to be typical instances of diametric diseases such as osteoporosis and osteoarthritis, preeclampsia and postpartum hemorrhage, and cancer and neurodegeneration (2, 4, 5).

Anogenital distance (AGD) is defined as the distance between the anus and external genitalia which is measured in men from the base of the scrotum to the anus and in women from the end of the vagina to the anus. AGD in men is longer than women. Another difference between men and women is the ratio of the 2nd to the 4th finger length (2D:4D) that is lower in men than women. The difference in AGD and 2D:4D indices in men and women are the result of the exposure of embryos of each sex to different levels of testosterone during prenatal development. The pattern of these two indices is completely different and opposite in PCOS and endometriosis. In PCOS, these two parameters show values close to the male pattern while in endometriosis, the lowest values of female pattern indicate the role of testosterone levels in development of reproductive organs during intrauterine growth of the female fetus and the probability of occurrence of these two diseases after puberty (3, 4).

Recent evidence confirms that occurrence of PCOS and endometriosis during reproductive age is related to disruption of utero development of hypothalamic–pituitary–ovarian (HPO) axis in female fetus. The HPO axis organizes the neural and hormonal network of reproductive system throughout the life before the fetus is born and subsequently after puberty, in particular secretion of GnRH, FSH, and LH to control ovarian and uterine

functions. Thus, PCOS is a developmental disorder of the HPO axis that results from relatively high levels of prenatal testosterone, while endometriosis is caused by relatively low levels of prenatal testosterone (2, 3, 5). In the experimental model of rodents, the symptoms of PCOS can be established through administration of testosterone at an initial stage of prenatal development in these animals (2-4). In addition, epidemiological studies show that the prevalence rates of endometriosis are higher in Asian and European women in comparison with African populations. In contrast, the incidence of PCOS among Asian and European is lower than African women. Measurement of serum testosterone during pregnancy in these three populations of women confirmed the above hypothesis; accordingly, higher level of testosterone in African pregnant women increases the risk of PCOS and reduces the risk of endometriosis in their daughters and lower level of testosterone in Asian and European women increases the risk of endometriosis and reduces the risk of PCOS in their daughters (4).

Despite the above evidence, there are conflicting findings for which further research should be conducted, such as coexistence of PCOS and endometriosis in one woman which is probably an exception to the finding on the effect of prenatal testosterone on female fetus or the discrepancies are due to inaccuracy of previous studies (6).

All in all, these findings can be regarded as valuable milestones in prevention and treatment of these two diseases. The occurrence of the diseases is connected to changes in testosterone levels in the prenatal period. However, the actions for modifying or reducing the serum levels of testosterone in pregnant mothers to prevent the diseases are extremely risky and unsafe. Each hormone has a variety of roles and functions in a complex network with other hormones and growth factors that their imbalance may have tremendous consequences for the fetus and mother. Though the above cited valuable approach has provided a brilliant opportunity for preventing polycystic ovary syndrome and endometriosis, extensive research should be conducted to validate these findings and use the outcomes for clinical application.

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