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Editorial

Does polycystic ovary syndrome independently affect oncologic and reproductive outcomes in patients with endometrial cancer receiving fertility-sparing treatment?

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▸ See the article "Fertility-preserving treatment outcome in endometrial cancer or atypical hyperplasia patients with polycystic ovary syndrome" in volume 32, e70.

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among reproductive-age women and the most common cause of anovulatory infertility [1]. The pathophysiology of PCOS is complex, reflecting interactions among various factors, including disordered gonadotropin secretion, insulin resistance, androgen excess, and ovarian dysfunction associated with an abnormal follicular environment [2,3]. The risk of endometrial cancer has been shown to be two to six times higher in women with than without PCOS. Recent international guidelines have recommended that health professionals set a low threshold for assessing the presence of endometrial cancer in women with PCOS who have persistently thickened endometrium and/or risk factors, including prolonged amenorrhea, abnormal vaginal bleeding, and excess weight [4]. Although prolonged endometrial exposure to unopposed estrogen in anovulation is thought to be related to the increased prevalence of endometrial cancer in women with PCOS, it is unclear whether PCOS itself or its comorbid conditions, including obesity, insulin resistance, and metabolic syndrome, is responsible for the development of endometrial cancer.

Despite the increased risk of endometrial cancer in women with PCOS, little is known about the efficacy of fertility preservation treatment in PCOS patients diagnosed with endometrial cancer. In this issue, Wang et al. [5] retrospectively compared the oncologic and reproductive outcomes of fertility-sparing treatment in 285 patients, including 103 with and 182 without PCOS, diagnosed with atypical endometrial hyperplasia (AEH) or well-differentiated endometrioid endometrial cancer (EEC) G1 at a single center. AEH or EEC was histologically diagnosed by examination of endometrial biopsy samples obtained during dilatation and curettage. PCOS was diagnosed by the Rotterdam definition, which requires at least two of the three following characteristics: clinical and/or biochemical hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology (PCOM) [6]. Fertility-sparing treatment consisted of oral megestrol acetate (MA) (160 mg/d) in most patients, with the remainder treated with a levonorgestrel-releasing intrauterine system (LNG-IUS) alone or LNG-IUS plus MA, with some patients also receiving metformin. Therapeutic efficacy was evaluated every 3 months by examination of endometrial biopsy samples obtained under hysteroscopy. Patients who achieved a complete response (CR), followed by several months of consolidation treatment,

attempted to conceive or took progestins to prevent recurrence. Assisted reproductive techniques (ART) were recommended to the patients who wanted to conceive.

Wang et al. [5] found that oncologic outcomes were adversely affected by PCOS, irrespective of which regimen was applied as fertility-sparing treatment. Women with PCOS exhibited lower 16-week CR rate, longer treatment duration to CR, and shorter recurrence interval than women without PCOS. Interestingly, PCOS and overweight were independently associated with a lower 16-week CR rate, after adjusting for potential confounders, including insulin resistance and HA. These findings suggested that endometrial characteristics differed in women with and without PCOS. A recent comprehensive literature review reported aberrant endometrial function in patients with PCOS, including dysregulated expression and function of sex hormone receptors and steroidogenic enzymes, increased insulin resistance, chronic low-grade inflammation, and altered angiogenesis [7]. Alterations in endometrial function may be due to prenatally programmed inherent abnormalities in the endometrium, with these abnormalities exacerbated by postnatal systemic hormonal and metabolic insults in PCOS [7]. Future studies comparing oncologic outcomes in patients with the four subtypes of PCOS (HA+OD+PCOM, HA+OD, HA+PCOM, and OD+PCOM) may clarify the potential mechanisms that promote carcinogenesis in the endometrium of women with PCOS and provide personalized approaches to the treatment of patients with each subtype.

In evaluating reproductive outcomes, Wang et al. [5] found no differences in pregnancy and livebirth rates between the 29 PCOS and 55 non-PCOS patients who achieved CR and attempted to conceive. To our knowledge, this is the first study reporting pregnancy outcomes in PCOS patients with endometrial cancer receiving fertility-sparing treatment; however, these findings should be interpreted cautiously. In addition to the small sample sizes, the details of treatment promoting conception and the comorbidities that may have caused infertility were unclear, except that 16 of the 29 PCOS and 45 of the 55 non-PCOS patients underwent ART. Fertility-sparing treatments may have adversely affected implantation. Frequent intrauterine operations may result in endometritis, endometrial thinning, and intrauterine adhesion, and high-dose progestin may induce histological and functional changes in the endometrium. A retrospective study comparing 45 pregnant with 53 non-pregnant patients receiving fertility-sparing treatment revealed that pregnancy was significantly associated with disease recurrence; endometrial thickness during ovulation that was negatively associated with the number of dilatation and curettage procedures; and the age of pregnancy permission [8]. A retrospective study comparing outcomes of in vitro fertilization cycles found that the endometrium was thinner and the implantation rate lower in 21 patients with than in 42 patients without endometrial cancer receiving fertility-sparing treatment [9]. The patients with endometrial cancer required more embryos to achieve a live birth, although there were no significant between-group differences in cumulative clinical pregnancy and delivery rates. Because PCOS itself adversely affects oncologic outcomes, including a lower CR rate, a longer treatment duration to CR, and a shorter interval to recurrence interval [5], PCOS may also adversely affect reproductive outcomes. Comparable reproductive outcomes in patients with and without PCOS, shown by Wang et al. [5], may have been due to the PCOS patients being significantly younger and/or the methods used to evaluate therapeutic efficacy. For example, endometrial biopsy under hysteroscopy, the method utilized in the current study, may induce less endometrial damage than dilatation and curettage and/or endometrial biopsy without hysteroscopy. Further prospective studies are needed to determine reproductive outcomes in PCOS patients receiving fertility-sparing treatment.

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Few studies to date have assessed the efficacy of fertility-sparing treatment in PCOS patients with endometrial cancer. Prospective studies are needed to determine the oncologic and reproductive outcomes of fertility-sparing treatment according to PCOS phenotypes, to optimize fertility-sparing treatment regimens and methods of evaluating therapeutic efficacy, and to determine methods that promote conception based on patient background, including age, other comorbid conditions, and history of endometrial cancer treatment.

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