REVIEW ARTICLE
https://doi.org/10.5653/cerm.2020.04329
pISSN 2233-8233 · eISSN 2233-8241
Clin Exp Reprod Med 2021;48(3):194-197

CERM

Update on polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a common disorder in reproductive-age women. In 2018, an international evidence-based guideline announced recommendations spanning a wide range of issues on the assessment and management of PCOS. From the 166 recommendations, the present study reviews those that are of particular clinical relevance for daily practice and introduces other relevant studies that have been published since the global guideline. The 2018 guideline increased the antral follicle count cutoff for the diagnosis of PCOS from 12 to 20 when using a high-frequency probe. Hirsutism was defined as having a score of ≥4–6 based on a lower percentile of 85%–90% or cluster analysis, which was lower than the traditionally used 95th percentile-based cutoff. The diagnosis of PCOS in adolescents is challenging, and irregular menstruation was defined carefully according to years from menarche. The use of ultrasonography for the diagnosis of PCOS was restricted to those 8 years after menarche. As medication for non-fertility indications, combined oral contraceptives are the first-line drug. Metformin, in addition to lifestyle modifications, should be considered for adult patients with a body mass index ≥25 kg/m^2 for the management of weight and metabolic outcomes. An aromatase inhibitor is the recommended first-line medication for ovulation induction, a subsequent individual patient data meta-analysis also reported the same conclusion. Whether the new global guideline will be fully adopted by many specialists and change clinical practice is open to question. Further studies are needed to better understand and manage PCOS patients well.

Keywords: Hirsutism; Hyperandrogenism; Infertility; Ovulation induction; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age, and is characterized by chronic anovulation and hyperandrogenism (HA). Although the pathophysiology of PCOS remains unclear, insulin resistance (IR) is one of the core etiologies of this syndrome; thus, PCOS is also recognized as a metabolic disorder.

There have been several guidelines in the field of PCOS, and in July 2018, an international evidence-based guideline for the assessment and management of PCOS announced recommendations spanning a wide range of issues on PCOS [1]. The guideline focuses on diagnosis, management, and fertility treatment for women with PCOS, and provides 166 recommendations and practice points. However, whether this new global PCOS guideline will be fully adopted by many specialists and change clinical practice is open to question.

Although the 2018 global guideline deals with all-inclusive aspects of PCOS, it is thought that some recommendations are substantially more important than others for clinicians who care for PCOS patients. In addition, a considerable number of studies have been conducted since the 2018 guideline. From this point of view, the present study reviews clinically relevant findings in the 2018 global guideline and subsequent studies, and discusses how these studies will affect our daily clinical practice.

Diagnosis

PCOS is usually diagnosed based on the Rotterdam criteria [2], according to which a diagnosis of PCOS is made if a woman meets two of the following three criteria: (1) oligo-and/or anovulation, (2) HA (clinical and/or biochemical), and (3) polycystic ovary morphology (PCOM) on ultrasonography (either 12 or more follicles measuring 2–9 mm in diameter and/or an increased ovarian volume >10 cm^3). Irreg-

Received: December 16, 2020 · Revised: April 16, 2021 · Accepted: May 12, 2021
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ular menstruation (IM) is defined as < 21 days or > 35 days or < 8 cycles per year. Clinical HA includes hirsutism, acne, or alopecia. Biochemical HA typically refers to an elevated serum testosterone level.

One of the notable recommendations in the 2018 international evidence-based guideline was the revision of the ultrasound criteria for the diagnosis of PCOM. Since the Rotterdam criteria, substantial improvements have been made in ultrasound resolution. A high-resolution probe facilitates the detection of more antral follicles, and when using transvaginal transducers including 8 MHz, the guideline development group recommended that the antral follicle count (AFC) threshold for PCOM should be ≥ 20 in adult women. Other recommended protocols such as the follicle size (2–9 mm) for the AFC, the ovarian volume criterion (> 10 cm^3), and ensuring the absence of corpus luteum, cysts, or dominant follicles (> 10 mm) have not changed.

The AFC threshold change for PCOM is relevant because ultrasound criterion is the most commonly used parameter for the diagnosis of PCOS [3,4], which was observed in 96.5% of a sample of Korean PCOS patients [4]. Furthermore, among subgroups based on the Rotterdam criteria, the IM and PCOM phenotype and the HA and PCOM phenotype essentially require the presence of PCOM, and 38.0% of Korean PCOS patients were categorized as having an IM and PCOM phenotype [4]. In large Chinese studies, 36.5% and 52.2% of PCOS patients had the IM and PCOM phenotype, respectively [5,6]. As shown by those findings, the IM and PCOM phenotype constitutes a major subgroup in East Asian patients; thus, the AFC threshold change might have particular significance in these populations. Therefore, we investigated the impact of the AFC cutoff change in Korean women with PCOS [7]. In that study, about one-fifth of the total adult patients were excluded from the diagnosis of PCOS using the new AFC cutoff. However, the excluded subjects had worse metabolic profiles (body mass index [BMI] and diabetes status, and the prevalence of IR and metabolic syndrome) and were more androgenized than controls, and were indistinguishable from the remaining patients. Our study suggests that a substantial proportion of PCOS patients might be labeled as "not having PCOS" according to the new AFC cutoff, although these women visited a clinic for IM or hyperandrogenic symptoms. The impact of the AFC cutoff change needs to be consistently evaluated, especially in diverse ethnicities.

The major diagnostic tool for clinical HA is hirsutism. The modified Ferriman-Gallwey (mFG) score is widely used for the diagnosis of hirsutism, and the international evidence-based guideline defines hirsutism as an mFG score of ≥ 4–6 based on a lower percentile of 85%–90% or cluster analysis. Traditionally, using the 95th percentile of the population, a score of 6–8 represented hirsutism in women [8,9]. However, the guideline development group considered that the 95th percentile is not appropriate for defining hirsutism. In our Korean study, which defined a cutoff score of 6, 50.0% of women had a score of 0, 83.2% had a score of ≤ 3, and 89.9% had a score of ≤ 5 [9]. Thus, it is reasonable to suppose that a cutoff score of 4–6, which was equivalent to the lower percentile range of 85%–90% in our study, can also be used for Korean women.

Alopecia can be used as a marker of clinical HA in adult women. Since the publication of the international evidence-based guideline, the Androgen Excess and PCOS Society reported that the relationship between hair loss and HA in women is neither clear nor consistent, and the term "female pattern hair loss" (FPHL) should be used instead of the previously used terms, alopecia or androgenetic alopecia [10]. They stated that isolated FPHL should not be regarded as a sign of HA when androgen levels are normal, but in all women with FPHL, assessment of potential excess androgen level is mandatory.

The diagnosis of PCOS in adolescents is always challenging. As in a previous guideline [11], the international evidence-based guideline also recommends that the diagnosis of PCOS in adolescents be made based on both the presence of HA and persistent oligomenorrhea. Ultrasound criteria should not be used for the diagnosis of PCOS in adolescent girls (more specifically, within 8 years after menarche). Adolescent girls who have HA or persistent oligomenorrhea, but do not meet the diagnostic criteria, can be labeled as being at "increased risk," and reassessment is advised at or before full maturity.

Management

Screening for diabetes is important for the management of PCOS. The prevalence of type 2 diabetes in women with PCOS is significantly increased regardless of age (odds ratio, 2.87; 95% confidence interval, 1.44–5.72) compared to women without PCOS, and this relationship is independent of, yet exacerbated by, obesity [12]. The prevalence of type 2 diabetes in young Korean women with PCOS (mean age, 24.7 ± 5.8 years) was 3.0% (27/899) in our recent study [13], whereas that of the young population (15,050 women aged 20–29 years) in the Korean National Health Insurance Database was 0.3% [14]. Moreover, the incidence rate of type 2 diabetes was 9.3 per 1,000 person-years in women with PCOS, which was significantly higher ($p < 0.0001$) than that of the overall population of women aged 20–29 years (0.9 per 1,000 person-years).

The optimal screening protocol for women with PCOS remains controversial, but baseline glycemic status should be assessed in all patients. Measurements of fasting glucose, hemoglobin A1c, and the 75-g oral glucose tolerance test (OGTT) can be used [15]. Although the 75-g OGTT is relatively inconvenient, it is recommended for high-risk women with PCOS (including a BMI > 23 kg/m^2 in Asians, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes, hypertension, or high-

risk ethnicity). South Asian women with PCOS showed an increased degree of hirsutism, early onset of symptoms, severe IR, and metabolic risks compared with Caucasians [16], and thus they can be considered a high-risk ethnicity.

Meanwhile, the 2018 international evidence-based guideline recommends that an OGTT should be considered for all women with PCOS when they plan pregnancy or seek fertility treatment, given the high risk of gestational diabetes and associated complications in pregnancy. Although many obstetricians will not plan an OGTT purely based on PCOS alone, this recommendation may have a significant impact on future clinical practice. In a USA study, a high prevalence (19%) of gestational diabetes was reported in a cohort of 988 consecutive pregnant women with PCOS [17], which was 2–3 times higher than the prevalence of 6%–8% in the general population [18]. In contrast, a Korean study reported that gestational diabetes frequently developed in obese women, rather than being linked to PCOS itself, and that PCOS without obesity was not a risk factor for gestational diabetes [19]. Thus, the recommendation that advises routine OGTT in all women with PCOS who plan pregnancy or fertility treatment needs to be further evaluated, especially in non-obese women with PCOS.

In terms of pharmacological treatment for non-fertility indications, there is a clear recommendation to consider combined oral contraceptives as a first-line medication, including for adolescents. There is not enough evidence to choose the "best" oral contraceptives, despite the common approach of using the lowest effective estrogen dose (20–30 μg of ethinylestradiol).

There is a wealth of literature on metformin use in PCOS, and the international evidence-based guideline states that metformin, in addition to lifestyle modification, should be considered for adult women with PCOS with a BMI ≥ 25 kg/m^2 for the management of weight and metabolic outcomes. In this guideline, there are no Asian-specific recommendations, such as a BMI ≥ 23 kg/m^2 based on Asian criteria for being overweight [20]. The 2013 Endocrine Society guideline recommends metformin for PCOS patients who have type 2 diabetes or impaired glucose tolerance in whom lifestyle modification fails [11]. It also suggests metformin as a second-line medication for PCOS patients with menstrual irregularity who cannot take or tolerate combined oral contraceptives. The Endocrine Society guideline may be more specific than that of the international evidence-based guideline since the latter vaguely defines the indications as the "management of weight and metabolic outcomes." The specific meaning of metabolic outcomes is not described in detail in the 2018 international guideline.

Inositol is a nutritional supplement that plays a role in insulin signaling, and has also been reported as playing a role in modifying metabolic and biochemical components of PCOS. Menstrual cyclicity and ovulation may also be improved. Although caution is needed due to limited data, the international evidence-based guideline suggests that inositol has only a few side effects and low costs. However, a recent Cochrane review could not make a recommendation on the benefits of inositol for subfertile women with PCOS [21].

In terms of pharmacological treatment for fertility indications, an aromatase inhibitor (letrozole) is the recommended first-line medication for ovulation induction in PCOS patients. However, clomiphene citrate (CC) is still an acceptable choice within this guideline. According to the international guideline, women with PCOS were significantly more likely to ovulate after the use of letrozole than after the use of CC. The likelihood of live birth has also been reported to be 40%–60% higher with letrozole than with CC. Multiple pregnancy rates appear to be lower with letrozole than with CC, but it needs to be further investigated whether this shift in favor of letrozole results in an obvious reduction in multiple pregnancy rates.

After the international evidence-based guideline, the International Ovulation Induction Collaboration group reported the results of an individual participant data meta-analysis [22]. In this meta-analysis, letrozole improved clinical pregnancy and the live birth rate and reduced time-to-pregnancy compared to CC. Thus, it can be considered as the preferred first-line ovulation induction medication for women with PCOS, which is consistent with the recommendation of the international evidence-based guideline. CC with metformin may increase clinical pregnancy and reduce time to pregnancy compared to CC alone. The treatment effects of letrozole are affected by baseline serum total testosterone levels, while those of CC with metformin are influenced by baseline serum insulin levels. These associations between treatment effects and markers of hyperandrogenemia or IR provide the basis for a personalized approach to ovulation induction related to PCOS.

In terms of *in vitro* fertilization, the gonadotropin-releasing hormone (GnRH) antagonist cycle is recognized as superior to the agonist cycle in reducing ovarian hyperstimulation syndrome (OHSS) with similar outcomes, and a GnRH agonist trigger might further eliminate the risk of OHSS. In the GnRH agonist cycle, adjunct metformin reduces the risk of OHSS. *In vitro* maturation has been performed over the years as a tool to eradicate OHSS.

Conclusion

The international evidence-based PCOS guideline summarizes evidence-based key points for all features of PCOS, and might provide an opportunity to appraise the literature about PCOS. Other relevant recommendations or studies have also been reported in the field of PCOS since the publication of the global guideline. However, controversies still exist, and further updates and collaborative studies are needed to better understand and manage women with PCOS.

https://doi.org/10.5653/cerm.2020.04329

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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