Impact of the difference in diagnostic criteria for adolescent polycystic ovary syndrome excluding polycystic ovarian morphology

（多嚢胞性卵巣形態を除いた思春期多嚢胞性卵巣症候群の診断基準の違いによる影響）

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Running Title: Adolescent PCOS diagnosis

Abstract

Aim: To exclude polycystic ovarian morphology (PCOM) from the diagnostic criteria for adolescent polycystic ovary syndrome (PCOS) has been proposed. We analyzed the profiles of adolescent women with suspected PCOS using the Japan Society of Obstetrics and Gynecology (JSOG) diagnostic criteria and Rotterdam criteria, excluding PCOM.

Methods: Thirteen-to twenty-one-year-old women diagnosed with suspected PCOS according to the JSOG criteria were included in this study. The patients were again diagnosed with PCOS using the Rotterdam criteria. Patient profiles, such as hormone levels, and body mass index (BMI), were compared between the two groups. Correlations between BMI and testosterone and BMI and time to diagnosis were also analyzed.

Results: Twenty-nine patients were diagnosed with adolescent PCOS according to the JSOG criteria, and 11 patients were diagnosed according to the Rotterdam criteria after exclusion of the PCOM criteria. Serum testosterone levels were significantly higher in adolescents with PCOS diagnosed using the Rotterdam criteria than in those diagnosed using the JSOG criteria ($p < 0.001$). The obese group shows significantly higher testosterone levels and a longer time from menarche to PCOS diagnosis. A positive correlation was observed between BMI and testosterone levels ($r = 0.318$, $p = 0.014$).

Conclusion: Although adolescents with PCOS diagnosed using the Rotterdam criteria exhibit higher testosterone levels, a typical characteristic of PCOS, the JSOG criteria may be useful for the early diagnosis of adolescent PCOS, including suspected cases. The differences between the two may reflect the natural history of PCOS in terms of its reproductive and metabolic phenotypes.

Key Words: adolescent, JSOG criteria, polycystic ovarian morphology, polycystic ovary syndrome, Rotterdam criteria

Introduction

Polycystic ovary syndrome (PCOS) is characterized by ovulatory dysfunction, hyperandrogenemia, and polycystic ovarian morphology (PCOM), with a prevalence of 8–13% [1] in women and 3.4–19.6% in adolescent girls [2]. Insulin resistance is also a major factor in the pathogenesis of PCOS, and the prevalence of metabolic diseases, including type 2 diabetes, is higher in PCOS-affected women than in unaffected women [3]. These effects continue until after menopause, making PCOS a disease that affects not only reproductive phenotypes but also metabolic phenotypes throughout life.

As amenorrhea and infertility due to ovulation disorders are also important symptoms, PCOS is often diagnosed in adulthood [4]. However, it has been widely accepted that PCOS symptoms are already partially present during adolescence. The probability of transition to adult PCOS has been demonstrated to be higher in women who develop suspected PCOS during adolescence compared to those who are not affected [5, 6]. In other words, they are at high risk of developing metabolic diseases. Therefore, diagnosis and treatment at an early stage of life may be beneficial from the perspective of preventing lifelong health risks [7-9].

Although several different diagnostic criteria for PCOS have been advocated, the Rotterdam criteria are mostly used, in which PCOS is diagnosed by fulfilling two of the three criteria: oligo/anovulation, clinical and/or biochemical hyperandrogenism, and PCOM. In Japan, the criteria of the Japan Society of Obstetrics and Gynecology (JSOG) have also been used [10], taking into consideration the sensitivity and specificity of the diagnosis of PCOS in Japanese women, who often show specific phenotypes, while remaining consistent with the Rotterdam criteria [11]. However, in adolescent PCOS, the cause of amenorrhea/oligomenorrhea must be differentiated from immaturity of the hypothalamic-pituitary-ovarian system. Moreover, it has been another problem that PCOM is often observed in healthy adolescents. Therefore, the diagnosis of adolescent PCOS has become a matter of debate under the exclusion of PCOM from the diagnostic criteria [12].

The diagnosis of adolescent PCOS based on the two criteria, excluding PCOM in the Rotterdam criteria, can consequently be limited compared with adult PCOS. The JSOG criteria allow the substitution of hyperandrogenemia with an increase in serum luteinizing hormone (LH) levels, and require the three main features of oligo/anovulation, biochemical hyperandrogenism or LH

upregulation, and PCOM. Therefore, when PCOM is excluded from the diagnosis of adolescent PCOS, it is less difficult to diagnose adolescent PCOS.

In the current study, we analyzed how excluding PCOM from the diagnostic criteria affects the PCOS population and the characteristics diagnosed using the JSOG and Rotterdam criteria.

Materials and Methods

This was a retrospective study. Patients aged 13–21 years who visited the outpatient clinic of the Department of Obstetrics and Gynecology, Gunma University Hospital between January 2013 and December 2022 were included in the study. The diagnosis of PCOS was made using the criteria of JSOG (Table 1)[10], 1) amenorrhea or oligomenorrhea; 2) PCOM; 3) high blood testosterone or high basal LH (≥ 7 mIU/mL) with normal basal follicle-stimulating hormone (FSH). PCOS was diagnosed when three criteria were met, and suspected PCOS was defined as meeting two criteria, excluding PCOM. Patients who experienced menarche within two years were excluded from the study. Those with other diseases such as metabolic and inflammatory diseases were also excluded from the study. The recruited women were reclassified according to the Rotterdam criteria.

Patient characteristics including age at first diagnosis, age at menarche, body mass index (BMI) and laboratory data were retrieved retrospectively, and compared between BMI stratification (< 25 and ≥ 25), or between diagnostic criteria (Rotterdam and JSOG). We used Student's *t*-test to compare the patient characteristics and variables between BMI < 25 and ≥ 25, or between Rotterdam and JSOG. The Mann–Whitney *U* test was applied instead of the Student's *t*-test when the variables did not pass the normality test. The correlation between BMI and hyperandrogenemia or the time from menarche to diagnosis was evaluated using Spearman's correlation coefficient. This study was approved by the ethics committee of the Gunma University Graduate School of Medicine. A p-value of ≤ 0.05 was considered to be statistically significant.

Results

We recruited 30 patients, 16 with PCOS and 14 with suspected PCOS, based on the JSOG criteria. Figure 1 shows the distribution of adolescent PCOS according to the JSOG and Rotterdam criteria,

with each diagnostic category created as an aggregated group and evaluated using a Venn diagram. Although LH/FSH levels are not included in the Rotterdam criteria, the number of PCOS cases increased to 23 in the Rotterdam criteria, and PCOS can be diagnosed if two of the three criteria are met. Gray areas indicate adolescent patients with PCOS after the exclusion of PCOM as a diagnostic criterion. Twenty-nine patients were diagnosed with adolescent PCOS according to the JSOG criteria and 11 patients were diagnosed according to the Rotterdam criteria. One case and 11 cases were not diagnosed with PCOS with only two items, PCOM and menstrual abnormalities, according to the JSOG and Rotterdam criteria, respectively. The exclusion of PCOM from the diagnosis of adolescent PCOS results in a decrease in the number of PCOS cases diagnosed according to the Rotterdam criteria.

We compared the characteristics of adolescent patients with PCOS according to the JSOG and Rotterdam criteria (Table 2). Serum testosterone levels were significantly higher in adolescents with PCOS diagnosed using the Rotterdam criteria than in those diagnosed using the JSOG criteria ($p < 0.001$).

We then compared the patient characteristics between the two groups stratified by BMI. Table 3 shows that the overweight/obese group had significantly higher testosterone levels than the other groups ($p = 0.019$). We also found a significant increase in the time from menarche to diagnosis in the obese group ($p = 0.029$). The overweight/obese group tended to have earlier onset of menarche; however, the difference was not statistically significant.

A positive correlation was observed between BMI and testosterone levels (Fig. 2A, r = 0.318, $p = 0.014$). It was also demonstrated that the time from menarche to diagnosis is significantly longer in the overweight/obese group (Fig. 2B, r = 0.278, $p = 0.031$).

Discussion

One of the problems in the management of adolescent PCOS is the delay in the initial diagnosis [13]. Menstrual abnormalities are often recognized by the family because of immaturity, which delays the first medical contact with affected girls. Furthermore, in the diagnosis of adolescent PCOS, PCOM not derived from PCOS is another problem that makes the differential diagnosis of PCOS difficult. A previous study evaluated PCOM using ultrasound at 2, 3, and 4 years after menarche and reported that

up to 40%, 35%, and 33.3% of patients, respectively, had PCOM [14]. Therefore, international guidelines recommend that pelvic ultrasound should not be performed until 8 years after menarche [15]. In other words, adolescent PCOS is diagnosed when two conditions are met: oligo/anovulation and clinical and/or biochemical hyperandrogenism, corresponding to the two Rotterdam criteria, excluding PCOM [16]. This is consistent with the diagnostic criteria for adolescent PCOS [12, 17, 18].

The pathogenesis of PCOS involves an increase in androgen secretion in the ovary, followed by an additional effect on gonadotropin secretion from the pituitary gland, which leads to anovulation [19]. Excess androgen also interacts with insulin sensitivity and secretion; hypersecretion of LH and hyperinsulinemia further enhance androgen production by ovarian theca cells [20], and hyperinsulinemia suppresses the secretion of sex hormone-binding globulin from the liver, leading to further hyperandrogenemia, including hirsutism [21].

Racial differences exist in hyperandrogenemia and its clinical manifestation, for example, hypertrichosis, is rare in Japanese patients with PCOS. Therefore, unlike the Rotterdam criteria, the JSOG criteria for the diagnosis of PCOS in adults include high basal LH and normal basal FSH as substitutes for high blood testosterone levels. In the present study, we adapted the JSOG criteria, excluding PCOM to our patients based on a foreign example of excluding PCOM from the Rotterdam criteria. When we created the Venn diagram using the JSOG diagnostic criteria, 29 of the 30 patients had hyperandrogenemia or LH/FSH >1 and menstrual abnormalities, and these patients accounted for over 90% of the suspected cases. However, if we applied the Rotterdam criteria to create the Venn diagram, the diagnostic criterion of LH/FSH >1 would be eliminated so that only cases with hyperandrogenemia or menstrual abnormalities would be classified as adolescent PCOS. Therefore, 11 of the 30 cases were classified as adolescent PCOS, accounting for 37% of the suspected cases.

When comparing the two groups from JSOG and Rotterdam, there was a significant difference in serum testosterone levels. Furthermore, we found a tendency for more obese cases of adolescent PCOS diagnosed using the Rotterdam criteria, although no statistical significance was found. These two observations are reasonably supported by the fact that there is a significant correlation between testosterone levels and BMI in this study. Adolescent PCOS diagnosed using the Rotterdam criteria includes higher BMI and higher testosterone levels, which are typical characteristics of PCOS.

By contrast, the JSOG criteria, excluding PCOM, can be used to identify cases of suspected PCOS. However, widely diagnosed PCOS may require differentiation from other hypothalamic ovulatory disorders. In our study, hypothalamic ovulation disorders, especially those associated with weight loss, were excluded based on the LH and FSH levels. Phylactou et al. referred to good differentiation PCOS from functional hypothalamic amenorrhea using several serum markers such as LH and testosterone in their review article [22]. However, they also demonstrated that PCOS and functional hypothalamic amenorrhea were mixed and not in extreme proportions at BMI less than 25. Especially during the recovery period from functional hypothalamic amenorrhea, LH is elevated, making diagnosis more difficult in Japanese patients with PCOS, in whom elevated androgen levels and obesity are not very prevalent [23].

It has recently been demonstrated that glucose intolerance in obese and nonobese adolescent PCOS occurs with equal frequency [24]. Nonobese girls with intolerance to glucose, despite their marked difference in body size from obese girls, have been reported to have similar means in insulin 2 h postprandial, as well as in high-density lipoprotein, C-reactive protein, and testosterone levels as obese girls [24]. These factors may be useful for the differential diagnosis of hypothalamic ovulation disorders. In addition, the rate of glucose intolerance among young Japanese women has been reported to be 13.3% in lean young women, which is much higher than 1.8% in standard weight women [25]. The high rate among young lean Japanese women is similar to that among obese women in the United States. Taken together, the possible presence of PCOS-like menstrual abnormalities with a background of insulin resistance among young lean women suggests that it is increasingly difficult to differentiate PCOS from hypothalamic amenorrhea.

Recently, it has been proposed that the pathogenesis of PCOS is a combination of inborn factors due to in utero exposure and acquired factors such as weight gain [26]. According to this concept, in utero exposure is strongly related to reproductive function, and the characteristic pathophysiology of PCOS is formed when metabolic function is affected by hyperandrogenism. In the current study, the time to diagnosis and testosterone levels were significantly lower and LH tended to be higher, although not significantly, in the normal-weight group than in the overweight/obese group. In the comparison according to the diagnostic criteria, the time to diagnosis was shorter in the JSOG group, although this

difference was not statistically significant. Overall, the inclusion of high LH levels in the diagnosis of PCOS suggests that adolescent PCOS due to reproductive function-centric influences may be diagnosed earlier, that is, before the metabolic phenotype becomes more pronounced.

Several clinical studies have reported that serum anti-Müllerian hormone (AMH) levels can replace PCOM. However, it has been difficult to set a cross-generational cutoff throughout the reproductive years because of the age-dependent decline in AMH [27]. Although transvaginal ultrasound has established its position as an indispensable examination in gynecology, it is sometimes difficult to adapt it to adolescent females. A previous systematic review limited to young women, including mainly adolescents, showed a favorable summary receiver operating characteristic curve and indicated that a possible cut-off value of AMH is approximately 6–7.25 ng/mL in this age group [28]. The serum AMH level is a useful replacement test for PCOM in adolescent patients with PCOS. The expansion of cases selected by excluding PCOM in the diagnosis of adolescent PCOS may allow a more appropriate population to be selected using AMH as an alternative criterion and/or an auxiliary diagnosis.

In the present study, we examined the distribution of adolescent PCOS using two different diagnostic criteria, the JSOG and Rotterdam criteria, which are used for adult PCOS, excluding PCOM. We found that the characteristics of the selected patients varied depending on the presence or absence of LH/FSH > 1, which was included only in the JSOG criteria. These results suggest that the JSOG criteria may be useful for the early diagnosis of adolescent PCOS, including suspected cases. However, further longitudinal studies are needed to elucidate the transition to adult PCOS and its relationship with PCOS pathophysiology.

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Disclosures

The authors declare that they have no conflicts of interest.

Data availability statement

The data supporting the findings of the study are available at the following link: https://docs.google.com/spreadsheets/d/1AJQSLDnpUR-4Ap1xIdUMf1Lr9fKDk8dh24a7eZpc3Ko/edit#gid=0.

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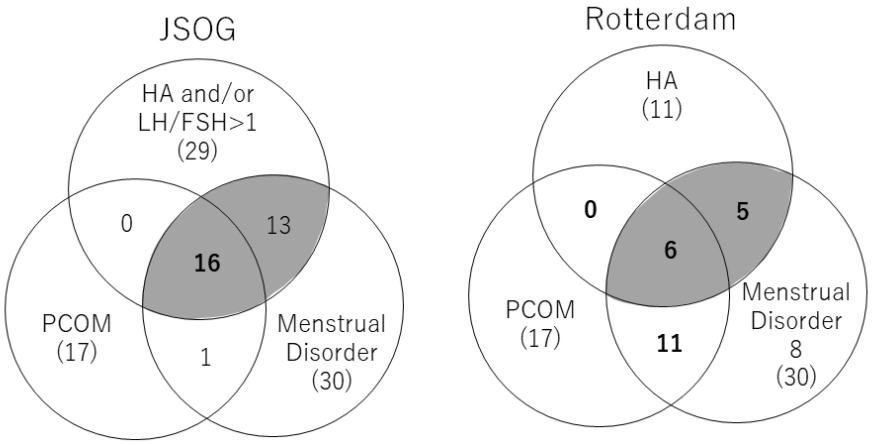

Figure 1. A. Venn diagram showing the distribution of each diagnostic criterion in the Japan Society of Obstetrics and Gynecology (JSOG) criteria. Polycystic ovary syndrome (PCOS) is diagnosed when all three criteria are met. B. Venn diagram showing the distribution of each diagnostic criterion in the Rotterdam criteria. PCOS is diagnosed when any two of the three criteria are met. The numbers corresponding to PCOS diagnosis are shown in bold. When PCOM is excluded, each gray portion could be diagnosed as PCOS. The numbers in parentheses represent the total number of each criterion.

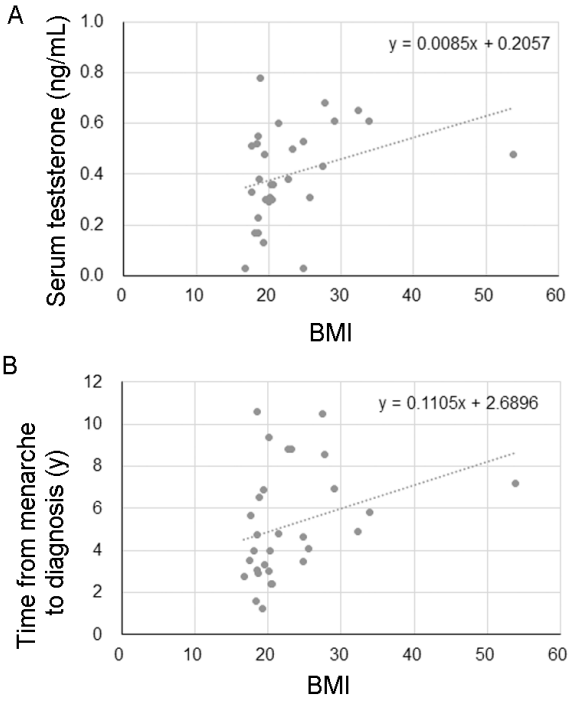

Figure 2. Correlations between body mass index (BMI) and testosterone levels (A, r = 0.318, p =0.014), and BMI and the time from menarche to diagnosis (B, r = 0.278, p = 0.031).

Table 1. Criteria for the diagnosis of polycystic ovary syndrome

JSOG	Rotterdam
Include all of the followings:	Include any two of the following:
Oligo/anovulation	Oligo/anovulation
Polycystic ovaries	Polycystic ovaries
High levels of serum androgens and/or LH (with normal range of FSH)	Clinical and/or biochemical hyperandrogenism

Note. JSOG, Japan Society of Obstetrics and Gynecology; LH, luteinizing hormone; FSH, follicle-stimulating hormone

Table 2. Characteristics of PCOS women diagnosed by JSOG and Rotterdam

Criteria (*n*)	JSOG (29)		Rotterdam (11)		
	median	mean ± SD	median	mean ± SD	P value
Age at menarche (y)	12.0	12.2 ± 1.6	12.0	11.7 ± 1.4	0.294
Age at diagnosis (y)	17.4	17.5 ± 2.0	17.8	17.4 ± 1.8	0.784
Time from menarche to diagnosis (y)	4.8	5.3 ± 2.6	5.7	5.6 ± 2.0	0.720
BMI	20.3	23.1 ± 7.3	23.3	24.2 ± 5.6	0.492
Estradiol (pg/mL)	49.9	50.9 ± 19.3	54.8	57.3 ± 21.6	0.381
LH (mIU/mL)	12.0	11.6 ± 5.0	12.0	12.3 ± 6.2	0.733
LH/FSH	2.0	2.1 ± 1.0	2.2	2.3 ± 0.8	0.419
Testosterone (ng/mL)	0.38	0.40 ± 0.19	0.60	0.59 ± 0.08	< 0.001

Table 3. Comparison between normal weight and overweight/obese in PCOS women

BMI	-24.9		25-		
	median	mean ± SD	median	mean ± SD	P value
n	23		7		
Age at menarche (y)	13.0	12.5 ± 1.5	12.0	11.6 ± 1.3	0.107
Age at diagnosis (y)	16.8	17.2 ± 1.9	18.5	18.4 ± 1.3	0.114
Time from menarche to diagnosis (y)	4.0	4.7 ± 2.6	6.9	6.9 ± 2.0	0.029
BMI	19.4	19.9 ± 2.1	29.1	32.9 ± 8.9	< 0.001
Estradiol (pg/mL)	49.9	48.4 ± 20.2	50.1	54.9 ± 16.6	0.441
LH (mIU/mL)	12.0	12.0 ± 5.2	10.7	9.3 ± 4.3	0.266
LH/FSH	2.0	2.2 ± 1.1	2.0	1.8 ± 0.4	0.564
Testosterone (ng/mL)	0.40	0.40 ± 0.19	0.61	0.53 ± 0.13	0.019