REVIEW ARTICLE
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Polycystic ovary syndrome in adolescents with obesity

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SUMMARY

INTRODUCTION: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age with the prevalence from 5% to 15%, and the prevalence of PCOS in adolescents with obesity seems even higher. The weight status is significantly associated with the quality of life in adolescents with PCOS.

OBJECTIVE: This review aims to summarize the latest findings of pathogenesis, diagnosis, comorbidity, and management in PCOS adolescents with obesity.

METHODS: This is a narrative review of articles published in PubMed from June 2013 to June 2020 Data were searched using the key words of "polycystic ovary syndrome" AND "adolescent" AND "obesity."

RESULTS: Pubertal obesity, particularly central obesity, could have a negative impact on the pathophysiology of PCOS. In adolescents with obesity, a review of medical history and a long-term follow-up for PCOS symptoms are essential to avoid misdiagnosis. There is a link between obesity and comorbidities of PCOS in adolescents. Holistic treatment and concern for related comorbidities should ideally begin as early as possible in obese adolescents once the diagnosis of PCOS is confirmed.

CONCLUSION: Adolescents with PCOS and obesity need more attention from physicians and researchers, and the effective interventions in the early stage are critical to improve their life quality.

KEYWORDS: Polycystic ovary syndrome. Adolescent. Obesity.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age with the prevalence from 5% to 15%, and the primary cause of anovulatory female infertility.[1-2] It was reported that many manifestations and biomarkers of PCOS changed with the advancing age, involving androgen concentrations, fat distribution, and menstrual irregularity.[3]

Obesity, especially visceral obesity, is common among adolescences and adults with PCOS.[4] A recent study indicating that the prevalence of PCOS among overweight or obese pubertal patients seemed to be higher than in adult patients,[5] and its prevalence seemed to be associated with the state of obesity in adolescent girls.[6] In addition, it was shown that weight status was closely associated with the relationship between PCOS and health-related quality of life in those girls with PCOS,[7] and the

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risk factors related to metabolic syndrome were also found in obese adolescents with PCOS.[8-9]

Treatments of PCOS include not only improvement of menstrual cycles and hirsutism but also reducing risk factors of metabolic syndrome and cardiovascular events, such as insulin resistance, dyslipidemia, and obesity.[10] Considering the impact of obesity on adolescents, the early-stage interventions should play an important role in this population. Therefore, the aim of this article was to conduct a narrative review of PCOS in obese adolescents, including the pathogenesis, diagnosis, comorbidity, and management. This review might also contribute to improving the quality of life in obese girls with PCOS.

METHODS

In this narrative review, we searched the PubMed database using the following key words: "polycystic ovary syndrome" AND "obesity" AND "adolescent." The inclusion criteria for selection were as follows: articles in the English language and articles published during the period of 7 years (June 2013—June 2020), with studies related to obese adolescents with PCOS. We excluded studies that did not specify which populations were probably involved, either adults or nonobese people.

RESULTS

First, we found 455 studies related to this subject, of which 30 were included for this review after further exclusion. Then we summarized the results and divided them into four aspects, including pathogenesis, diagnosis, comorbidity, and management in PCOS adolescent with obesity.

Pathogenesis

Adolescent PCOS was the outcome of a mismatch between energy saving and obesogenic environment.[6] The hypothesis of adipose tissue expandability speculated that hyperinsulinemic androgen excess in PCOS was usually caused by depletion of the capacity to expand subcutaneous adipose tissue in a metabolically safe way. If prenatal weight gain was less than postnatal weight gain, more fat would be stored in central tissues than in subcutaneous adipose, which induced central obesity.[11] However, young girls might increase the speed of their growth and/or maturation to avoid such central obesity.[12] At adolescence and adulthood, this homeostatic mechanism could be out of balance and PCOS might ensue.[13] It was reported that high body mass index (BMI) during childhood was associated with menstrual irregularity, and weight gain during adolescence to adulthood was also related to PCOS.[14-15] In addition, omentin-1, an adipokine secreted essentially by visceral adipose tissue, was negatively correlated with free testosterone level in obese girls with PCOS as compared with obese girls without PCOS, suggesting that virilization of adipose tissue might have a role in the pathogenesis of PCOS *via* alternating adipokine profile.[16] In addition, S100A4, a marker of subcutaneous adipose tissue dysfunction, might become a circulating marker of hepato-visceral fat excess in adolescents with PCOS.[17]

Pubertal obesity was one of the adverse factors underlying the pathophysiology of PCOS in adolescents. First, considering the role of mitochondrial dysfunction and systemic inflammation played in the pathogenesis of PCOS in adult patients, it was investigated that manifestations of oxidative stress and systemic inflammation also performed in overweight adolescents with PCOS, but less obvious in PCOS adolescents with normal weight due to the homeostasis control system and adaptive compensative mechanism of antioxidant defense in adolescence.[18] In addition, obesity could exacerbate the insulin-resistant (IR) and hyperinsulinemia to aggravate hyperandrogenism indirectly,[19] and peripubertal obesity was a potential factor of hyperandrogenism, which was especially prominent in early puberty.[20] It was found that obese adolescents with PCOS had significantly lower sex hormone-binding globulin (SHBG) and significantly higher free testosterone levels as compared with normal-weight girls with PCOS.[21] Furthermore, the free testosterone levels were significantly higher in obese adolescents with PCOS than those without PCOS.[21]

In summary, pubertal obesity, including central obesity, is associated with PCOS, which reminds physicians to perceive the appearance of PCOS. Early interventions need to put on PCOS adolescents with increased BMI to restrict weight as obesity could have a negatively multifactor impact on the pathophysiology of PCOS in the pubertal time.

Diagnosis

The diagnosis of PCOS in adolescents was challenging, because of the overlap of the normal puberty with manifestations of PCOS, such as menstrual irregularity, acne, and hirsutism, and now mainly determined by the coexisting of menstrual irregularity and hyperandrogenism according to different published guidelines.[22]

Obesity in puberty might be an important marker for the diagnosis of PCOS in the early stage. A prospective study indicated that early adiposity rebound, the second rise in BMI following a nadir occurring before 5 years old, was correlative with the diagnosis of PCOS. It was crucial for adolescents with adiposity rebound and continuous obesity to screen for PCOS manifestations, such as persistently menstrual irregularities and hirsutism.[23] In addition, adolescents "at risk" of PCOS are those who only have a single condition of PCOS

diagnostic criteria, that is, irregular menstrual cycles or clinical hyperandrogenism. These adolescents needed reassessment in menstrual cycle irregularity at 3-year post-menarche and polycystic ovarian morphology at 8 years post menarche, which was particularly important for those with persisting PCOS features and significant weight gain.[24] In addition, the cutoff of hirsutism score with Ferriman–Gallwey index was associated with ethnic background, and the diagnosis of hirsutism might create psychological pressure for women, and even more for adolescents. Thus, accurate cutoff of diagnostic criteria of hyperandrogenism needs more studies to verify in order to avoid overdiagnosis.[25]

The serum level of anti-Müllerian hormone (AMH) is correlated to the antral follicular count or the excessive number of follicles per ovary.[26] The serum AMH levels in adolescents and adults with PCOS were mostly higher than in those without PCOS, but they were not recommended for PCOS diagnosis due to insufficient studies and inaccurate standard for different populations.[24] Considering the difficulties of performing vaginal ultrasound in obese adolescent girls and distinguishing PCOS-related hyperandrogenic manifestations from obesity-related alterations, a study reported that the AMH of 6.26 ng/mL seemed to be an optimal cutoff value in obese girls for predicting PCOS; addition of SHBG and total testosterone to AMH increased the predictive power to 93.4% for diagnosing PCOS.[27]

In conclusion, a review of medical history and a long-term follow-up of symptoms related to PCOS were important for adolescents with obesity to avoid misdiagnosis. In addition, obese adolescents, especially "at risk" of PCOS, with high serum levels of AMH need more attention to detect the alterations of manifestations associated with PCOS.

Comorbidity

The presence of obesity seems to be clearly associated with metabolic syndromes and psychological issues in adolescents with PCOS. The prevalence of abnormal glucose metabolism in adolescent patients with PCOS was reported at 17.2%, who were mostly overweight or obese.[8] In obese girls with PCOS, more markers of cardiovascular disease (CVD) risk were found as compared with those without PCOS.[9] Furthermore, it was found that nonalcoholic fatty liver was connected with increasing abdominal adiposity in adolescents with PCOS.[28] The emotional depress partly was also connected with some certain symptoms of PCOS such as obesity and hirsutism in adolescents with PCOS.[29] The depression scores were definitely higher with elevated BMI, which meant potentially important interaction between obesity and depression in adolescents with PCOS.[30]

Increasing clinical and laboratory data emerge as early evidence of metabolic disorders in obese adolescents with PCOS. It was reported that elevated fasting and postprandial plasma triglyceride and apolipoprotein (Apo)B-lipoprotein remnants could provide evidence of early subclinical CVD risk in obese girls with PCOS, which were highly associated with impaired insulin metabolism and hyperandrogenaemia.[31] Moreover, increased pulse wave velocity, vascular cell adhesion molecule-1, and high-sensitivity C-reactive protein might be the earliest subclinical atherosclerosis biomarkers in obese girls with PCOS.[32] The oral glucose tolerance test (OGTT, using a dose of 1.75 g/kg to a maximum of 75 g) was a superior diagnostic test to assess abnormal glucose levels in obese girls with PCOS.[8] In addition, estimate of insulin sensitivity (e-IS), an index without an OGTT derived from waist circumference, fasting triglyceride concentrations, and HbA1c, could predict server IR in girls with PCOS.[33]

In a word, there is also a link between obesity and comorbidities of PCOS in adolescents. Special biomarkers or clinical tests could provide evidences of metabolic disorders in obese adolescents with PCOS, periodical tests for the condition of the liver and emotional counseling are also necessary for those girls.

Management

The long-term management for reproductive, metabolic, and mental health was suggested once a pubertal girl was diagnosed with PCOS.[34] It was reported that both lifestyle interventions and pharmacological strategies for weight management were beneficial to obese women with PCOS.[35] Considering the influence of obesity in PCOS, weight management is important for obese adolescents with PCOS, even for those "at risk" of PCOS.

Lifestyle interventions, with an objective of weight loss, were recommended as a first-line treatment for adolescent PCOS girls with overweight or obesity.[36] Evidences indicated that successful weight loss in obese PCOS girls was associated with improvement in the menstrual cycle, reduction in androgens, and cardiovascular risk factors.[37-39] In order to get rid of the side effects of medicine, lifestyle interventions could also be recommended to the obese girls "at risk" of PCOS. Comprehensive lifestyle interventions, including a balanced diet, exercise, behavioral education and psychotherapy, were significantly achieved weight loss.[39] As we know, women with PCOS had increased appetite and calorie input; therefore, the general management rule of diet was calorie restriction (500–1000 kcal per day) and reduced amount of carbohydrate (not exceeding 200 g or no more than 30% of total energy).[40] It was also shown that low-glycemic load (45% carbohydrate, 35% fat, 20% protein) or low-fat ((55% carbohydrate, 25%

fat, 20% protein)) diet over 6 months were both efficacious for promoting weight loss and reductions in body fat among overweight and obese adolescents with PCOS.[41] Exercise with at least 60 min of moderate-to-vigorous intensity physical activity per day, including those that strengthen muscle and bone, at least three times weekly was recommended for adolescents.[42] However, the optimal exercise dose for promoting weight loss in adolescents with overweight–obesity was still uncertain.[43] In addition, it was found that poor sleep behaviors were associated with metabolic dysfunction and metabolic symptoms among obese adolescents with PCOS, so sleep health should be included in the assessment of adolescents with PCOS and obesity.[44]

Pharmacological treatments of the combined oral contraceptive pill (COCP) and/or metformin were recommended in adolescents clearly diagnosed with PCOS or in adolescents deemed "at risk" of PCOS for the management of symptoms. In obese adolescents with PCOS, COCP combined with metformin could be considered when COCP and lifestyle changes could not achieve desired targets.[24] A study reported that treatment with metformin or oral contraceptives in obese adolescents with PCOS could lead to reduction in androgen levels, weight loss, and increased insulin and sensitivity.[45] In addition, lifestyle interventions combined with oral contraceptives and metformin could reduce central adiposity and total testosterone and increase high-density lipoprotein, but could not enhance overall weight reduction.[46] However, there was no exact recommendation for special types and doses of COCP due to insufficient data in adolescents.[24] Local therapies like photoepilation were recommended as first-line therapies to treat localized hirsutism in adolescents with PCOS.[47] Antiandrogens were advised to consider after the use of the COCP alone with cosmetic therapy for at least 6 months, and antiandrogens should only be used when contraceptive measures are guaranteed in those sexually active adolescents.[24] The use of anti-obesity medications in children and adolescents was not approved.[48] However, it was found early low-dose combination of spironolactone 50 mg/day, pioglitazone 7.5 mg/day, and metformin 850 mg/day (SPIOMET) treatment for PCOS in adolescent girls normalized posttreatment ovulation rates more than oral contraceptive, with normalizing visceral fat and insulinemia but no significant change on body weight. Thus, the intervention on early reduction of hepato-visceral fat in adolescents with PCOS could be an important strategy.[49]

In summary, weight management is crucial for obese adolescents with PCOS. Holistic treatments should ideally begin at early time once obese adolescents get diagnosed with PCOS in case situations get worse in adults, and weight loss is significantly important in obese adolescents with PCOS or in obese girls "at risk" of PCOS. In addition, treatments of PCOS-related symptoms could be considered for obese girls "at risk" of PCOS.

DISCUSSION

Polycystic ovary syndrome is one of the most common endocrine disorders in women of reproductive age, and its manifestations could start at pubertal period and change with advancing age.[1-3] According to our narrative review, pubertal obesity, particularly central obesity, could have an impact on the pathophysiology of PCOS. The diagnosis of PCOS in adolescents with obesity requires a review of medical history and a long-term follow-up of PCOS symptoms to avoid misdiagnosis. There is a link between obesity and comorbidities of PCOS in adolescents. The holistic treatment for obese adolescents with PCOS, involving diet, exercise, emotion, sleep, and concern for comorbidities associated with PCOS should ideally begin at early time once they get diagnosed with PCOS, in case that situation would get worse in adults. This narrative review provides a comprehensive summary of studies about obese adolescents with PCOS in recent years, which might facilitate physicians in clinical practice and arise their awareness to take management in early stage in order to improve long-term health in adults.

However, this review has several limitations. One is that the selection of articles was restricted to one database with one language, which might reduce the number of relevant publications. Another limitation is that the samples involved in most of the included studies were from South America and Europe; this might bias the conclusion about the association between obesity and PCOS toward the above ethnic populations.

CONCLUSIONS

The pubertal obesity is related to the pathogenesis of PCOS. Obese adolescents with PCOS or "at risk" of PCOS need more attention of physicians to undertake holistic management in time to avoid the deteriorating scenario with advancing age. The exact mechanism underlying the relationship between obesity and PCOS in adolescence is still not fully understood; future work is required to explore its etiology. More studies with a large sample size are needed on the diagnosis criteria, comorbidities supervision, and treatments in obese adolescents with PCOS.

AUTHORS' CONTRIBUTIONS

LF: Writing – Review and Editing. **FQ:** Supervision, Writing – Review and Editing. JP: Writing – Review and Editing. **TW:** Writing – Review and Editing. **FW:** Supervision, Writing – Review and Editing.

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