Review Article

A narrative review: polycystic ovary syndrome (PCOS) and type 1 diabetes (T1D)

Angelina Bernier[1], Janine Fung[2], Berrin Ergun-Longmire[2]

[1]Department of Pediatrics, University of Florida, Gainesville, FL, USA; [2]Department of Pediatric & Adolescent Medicine, Homer Stryker M.D. School of Medicine, Western Michigan University, Kalamazoo, MI, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final Approval of manuscript: All authors.

Correspondence to: Angelina Bernier, MD. Associate Professor, Department of Pediatrics, University of Florida, 1699 SW 16th Ave. Bldg A, Gainesville, FL 32608, USA. Email: angelina@ufl.edu.

Background and Objective: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, characterized by hyperandrogenism, ovulatory dysfunction, and sonographic evidence of polycystic ovaries. In adolescents, diagnostic features do not always consistently apply but long-term consequences are not any less significant. Treatment of PCOS is symptom-specific, with combined oral contraceptive pills (COCPs) the first-line in alleviating hyperandrogenic symptoms such as acne, hirsutism, and alopecia. However, starting COCPs early in the treatment course does not address the important contributing mechanistic feature of hyperinsulinemia. Insulin therapy in females with type 1 diabetes (T1D) is an overlooked iatrogenic cause of PCOS in adolescents. Despite the relatively high prevalence of PCOS in T1D, there is no established recommendation for screening nor consideration for treatment approaches which improve insulin sensitivity and decrease insulin requirements thereby targeting the underlying mechanism for menstrual irregularity. This review aims to highlight the prevalence of PCOS in T1D, elaborate on the unique pathophysiology and explore the use of lifestyle interventions and insulin sensitizers in contrast to COCPs as first-line therapy.

Methods: We gathered data from the published articles ranging from prospective studies, meta-analyses, retrospective studies, and reviews. We focused on the articles published in English between January 1, 2000, and December 31, 2021. Only a few articles published prior to 2000 were included for historical perspective.

Key Content and Findings: PCOS is a common comorbidity of insulin therapy in T1D, therefore, screening should be included in current guidelines for management. The insulin sensitizer metformin and anti-obesity agents, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), may be favorable treatment alternatives for PCOS in T1D.

Conclusions: Our recognition of early predisposing factors to PCOS and the high frequency of PCOS in the TID population warrants further investigation into the therapeutic targets of improving insulin sensitivity and decreasing insulin requirements. Treatments like metformin which decrease insulin requirements and improve peripheral organ sensitivity may prove more effective than COCPs in the approach to irregular menses in adolescent females with T1D.

Keywords: Type 1 diabetes (T1D); polycystic ovary syndrome (PCOS); obesity; insulin; antidiabetic agents 50

Received: 18 January 2022; Accepted: 24 May 2022; Published online: 06 June 2022.

doi: 10.21037/pm-22-3

View this article at: https://dx.doi.org/10.21037/pm-22-3

Introduction

Adolescent polycystic ovary syndrome (PCOS) has garnered more attention in the past decade with its first inclusion in the Endocrine Society PCOS Guidelines in 2013 (1). There are three defining criteria for PCOS. Early classification and diagnosis introduced by the National Institutes of Health (NIH) in 1990 defined PCOS as including features of: hyperandrogenism and/or hyperandrogenemia, oligo-ovulation, and exclusion of known disorders. In 2003, the Rotterdam criteria further developed the characterization of PCOS to meet 2 out of the 3 following criteria: anovulation or oligo-ovulation causing menstrual irregularities, ultrasound findings revealing polycystic ovaries, and clinically and/or biochemical hyperandrogenism. The definition was restricted to include the sentinel feature of androgen excess in the 2006 criteria posed by the Androgen Excess Society (AES) and PCOS Society in addition to either irregular menses or polycystic ovary (PCO) morphology (*Table 1*). Of these three, the definition of PCOS in adolescents most similarly corresponds to the criteria set forth by the original NIH guidelines including oligomenorrhea and evidence of hyperandrogenism while excluding PCO morphology as a required feature. However, each of these defining features present less clearly in the adolescent population. Oligomenorrhea is not unusual immediately post-menarche so further specifications are useful to describe criteria in time including: (I) a gap in menses of more than 3 months, (II) a pattern of menses initially regular which becomes irregular, or (III) a lack of menarche by 15 years of age or more than 3 years post-thelarche (2).

Prevalence

While the prevalence in adolescence is 1–3%, PCOS is recognized as the most common endocrine disorder in women of reproductive age with an overall prevalence of 10–15% (3). The recognition of PCOS risk in childhood, followed the keen observation of identifiable risk factors over the lifespan, from maternal hereditary risk, to in-utero metabolic priming, and development of premature pubarche (4). Despite progress in literature and guidelines to bring awareness to this relatively common condition, women frequently report dissatisfaction with delayed diagnosis experiences and anxiety related to limited education on prevention of complications and inadequate treatment of symptoms (5).

Mechanisms

PCOS results from a complex of factors which affect various levels of the hypothalamic-pituitary-ovarian axis. Prominent pathologic mechanisms include hypothalamic features which increase gonadotropin-releasing hormone (GnRH) pulse frequency, abnormal ovarian or adrenal steroidogenesis, and a combination of effects from insulin resistance and hyperinsulinemia (6). Hyperinsulinemia conveys metabolic risk with tissue-selective effects associated with diabetes, cardiovascular disease, and hyperandrogenism. In the ovary, insulin has a direct effect on theca cells to amplify androgen production from luteinizing hormone (LH) stimulation, which is often responsible for the clinical symptoms of hyperandrogenism. As such insulin has garnered recognition as a co-gonadotropin. This co-gonadotropin effect was further elucidated when Wu *et al.* (7) demonstrated that sequential disruption in theca cell insulin receptor genes maintained fertility in mice who experience diet-induced obesity whereas, fertility was decreased when the insulin receptor was left intact.

In addition to conditions of insulin resistance with endogenous hyperinsulinemia, exogenous sources of hyperinsulinism as seen in type 1 diabetes (T1D) are similarly able to stimulate receptors in the ovary which promote PCO morphology and androgen production.

This review will further highlight the prevalence of PCOS in T1D, encourage early screening and explore the use of insulin sensitizers in contrast to combined oral contraceptive pills (COCPs) as first-line therapy. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-22-3/rc).

Methods

We gathered data from the published articles ranging from prospective studies, meta-analyses, retrospective studies, and reviews. We focused on the articles published in English and between January 1, 2000 and December 31, 2021. Only a few articles published prior to 2000 were included for historical perspective. Articles ranged from studies, meta-analyses, retrospective studies, and reviews. Search terms included but were not limited to a combination of the following words: “T1DM”, “T2DM”, “PCOS”, “obesity”, “insulin”, “antidiabetic agents”, “metformin”, “GLP-1”, “fertility”, and “androgens”. There were no affiliations or conflicts of interest with the authors of the articles used.

Table 1 Criteria for PCOS diagnosis after exclusion or other causes of androgen excess or related disorders

Year	Organization	Criteria
1990	NIH	Presence of clinical and/or biochemical hyperandrogenism
		Oligo/amenorrhea anovulation
2003	ESHRE/ASRM Rotterdam criteria	Meet 2 out of the 3 following criteria
		Presence of clinical and/or biochemical hyperandrogenism
		Oligo/amenorrhea anovulation
		Polycystic ovarian morphology on ultrasound
2006	AES	Androgen excess
		Oligomenorrhea or polycystic ovarian morphology on ultrasound

PCOS, polycystic ovary syndrome; NIH, National Institutes of Health; ESHRE, European Society of Human Reproduction and Embryology; ASRM, American Society for Reproductive Medicine; AES, Androgen Excess Society.

Table 2 The search strategy summary

Items	Specification
Date of search	December 31, 2021
Databases and other sources searched	PubMed, Google Scholar, Science Direct
Search terms used	"T1DM", "T2DM", "PCOS", "obesity", "insulin", "antidiabetic agents", "metformin", "GLP-1", "fertility", and "androgens"
Timeframe	January 1, 2000, and December 31, 2021
Inclusion criteria	Clinical trial
	Meta-analysis
	Randomized controlled trial
	Review
	Systematic review
	Language: English
Selection process	All authors equally conducted the selection, reviewed and agreed with the selected article

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; PCOS, polycystic ovary syndrome; GLP-1, glucagon-like peptide-1.

A total of 366 articles were identified as relevant to our review. Of those, 34 articles were selected based on their relevance to the aim of this review (*Table 2*).

PCOS and diabetes

Despite the recommendations for PCOS screening in women with type 2 diabetes (T2D), there is no such recommendation in women with T1D. As a potentially significant iatrogenic etiology, exogenous administration of insulin in T1D is often overlooked as a cause of PCOS in young women.

After the Diabetes Control and Complications Trial (DCCT), the sentinel intensive insulin therapy study in the 90s, the reproductive pathologic features in women with T1D changed. The features shifted from more frequent occurrence of hypogonadism and delayed menarche to oligomenorrhea and hyperandrogenism and the change was attributed to higher peripheral insulin exposure (8).

Normally, 40–80% of endogenous insulin production secreted from the pancreas is extracted by the liver resulting in a much smaller proportion entering the peripheral circulation. In contrast, exogenous insulin administered

subcutaneously, bypasses liver extraction, exposing all peripheral tissue to the full effect of insulin dosing.

The manifestations of PCOS in those with T1D are similar regarding menstrual irregularity but differ in symptoms and concentration of androgen excess. Concentrations of sex hormone-binding globulin are not reduced in patients with T1D as they are in other causes of endogenous hyperinsulinism due to lack of liver exposure to pancreatic insulin production (9). Subsequently levels of free testosterone and external signs of hirsutism are lower and more subtle in this population.

In addition to higher peripheral insulin exposure, insulin resistance is a less familiar but prominent feature of T1D as assessed by hyperinsulinemic euglycemic clamp studies (10). Subsequently, metformin use in adolescents with T1D has been shown to result in a decrease in total insulin requirements (11-13). However, in a study conducted by Amato *et al.* (14), there was no difference in the insulin requirements of women with T1D with or without PCOS. This suggests that exogenous insulin may contribute to the exacerbation of PCOS development in genetically predisposed, adolescent females.

The frequency of PCOS in T1D exceeds any other population ranging from 24% to 40% depending on diagnostic criteria (NIH *vs.* Rotterdam respectively) (15,16). In comparison, the prevalence of PCOS in T2D is 26% (17) and in women with severe obesity [body mass index (BMI) ≥35 kg/m^2] 25% (18) both based on NIH criteria. Despite the significant prevalence, the screening recommendations for comorbidities of diabetes according to American Diabetes Association (ADA) guidelines updated in 2021 did not include screening for PCOS.

Weight gain is a recognized consequence of intensive insulin therapy (19) however, overweight and obesity prevalence in youth with T1D generally remains similar to the general pediatric population. As such these youth are at risk for obesity related comorbidities which include lower high-density lipoprotein (HDL) levels, increased prevalence of hypertension (HTN), and metabolic syndrome (20).

PCOS and obesity

Approximately 40% to 80% of women with PCOS have a BMI that exceeds the 85th percentile. Non-medical management is the first-line therapy for adolescents with PCOS and obesity with focus on dietary changes and exercise to promote weight loss (1). Increases in BMI place women with PCOS at higher risk for metabolic abnormalities, specifically, having a BMI greater than 30 kg/m^2 is the strongest predictor of insulin resistance (21). When lifestyle changes are not sufficient to reduce BMI, therapeutic options that target weight loss have included: metformin, orlistat, glucagon-like peptide-1 receptor agonist (GLP-1 RA), phentermine, and phentermine/topiramate combinations.

A recent comparison of a GLP-1 RA in combination with the sodium-glucose cotransporter-2 inhibitor (SGLT-2) and phentermine/topiramate demonstrated comparable reduction in BMI, however, improvement in insulin sensitivity and secretion were seen with the GLP-1 RA/SGLT-2 combination (22). In pediatrics, only GLP-1 RA and orlistat are approved for weight loss.

Orlistat, a lipase inhibitor, is an option for treatment as one of the few anti-obesity agents approved in adolescents. In a randomized control trial conducted by Kumar and Arora, orlistat showed a significant decrease in weight, improved ovulation rates, and an improved lipid profile after 3 months (23). Despite its potential efficacy, Orlistat is limited by its side effect tolerability.

GLP-1 RAs have been studied in T1D not for their incretin effect, but for their unique ability to address alpha cell dysfunction and suppress inappropriate glucagon secretion which contributes to postprandial hyperglycemia (24). As such, studies in T1D have consistently demonstrated weight loss and decreases in total daily dose with concomitant improvement in glycemia. These agents may serve as adjuvant therapy for those with T1D with higher insulin requirements and obesity.

The current state of care

The first-line of treatment for women with PCOS is lifestyle modification to encourage weight loss by means of energy restriction and exercise. Typically, COCPs are recommended to address features of menstrual irregularity, acne and hirsutism, however, this use of COCPs is not supported by strong evidence as the best first-line pharmacologic treatment after lifestyle modification in adolescents. In 2015 the American Association of Clinical Endocrinology made a change to the guidelines for first-line therapy in adolescents from symptom management with COCPs to metformin (25). The following year, results of a systematic review of randomized controlled trials comparing the use of COCPs to metformin in adolescents, revealed that metformin caused significantly greater BMI reduction with improvement in dysglycemia while COCPs

resulted in only modest improvement in cycle frequency and acne scores (26). Additionally, studies have shown that insulin sensitization also induces ovulation in adolescents with PCOS (27). In practice, the choice between first-line agents remains varied among pediatric endocrinologists. Further investigation into the long-term consequences of these dichotomous treatment approaches may better guide future recommendations.

A recent effort to characterize the risk of early mortality associated with menstrual irregularity throughout the life course was carried out by Wang *et al.* (28). The prospective cohort study of more than 70,000 women from the Nurses' Health Study II, revealed that menstrual cycle irregularity was associated with premature mortality (age <70 years). Additionally, those treated with COCPs in adolescence (14–17 years) had an increased risk for premature mortality (28). Whether COCPs were used for the treatment of underlying conditions such as PCOS or contraception alone could not be elaborated. Irrespectively, current practices around menstrual cycle screening, monitoring, and treatment may require closer examination.

Future considerations

Considering the early recognition of features that predispose to PCOS and the known frequency of PCOS in the T1D population, exploration into the use of insulin sensitizing or anti-obesity agents, to decrease insulin requirements and improve peripheral organ sensitivity, may prove to be more effective for the treatment of irregular menses in adolescent females with T1D.

Just as there is currently strong support for screening women with T2D for PCOS, screening women with T1D is warranted based on studies that have consistently shown the increased prevalence of PCOS in this population. The consequence of screening, early detection, and treatment of PCOS symptoms may result in improved metabolic, reproductive, and emotional wellbeing.

Questions which remain unanswered require a multifaceted approach to shed light on insulin requirements, such as optimal dosing or identification of critically susceptible windows of peripubertal exposure which should be targeted to improve insulin sensitivity. Studies are needed to evaluate whether improving insulin sensitivity by some degree of carbohydrate restriction, increased attention to physical activity, or use of an insulin sensitizer, might decrease the risk of developing PCOS in adolescence. Currently, there are conflicting studies regarding whether a link between total insulin requirements in women with T1D and PCOS exists, but this has not yet been studied in adolescence (15). If this link exists, use of insulin sensitizers to decrease the total daily dose by some increment rather that COCPs may result in improved menstrual and fertility outcomes.

Conclusions

PCOS appears to be a common comorbidity seen in adolescent females with T1D. Although our understanding of the pathophysiology of PCOS in T1D remain largely unknown, there is growing evidence that insulin therapy is the most likely etiology. A better understanding and early recognition of predisposing factors leading to PCOS will lead to more effective treatment and the development of evidence-based recommendations for its management.

Key concepts

- PCOS is a common comorbidity of T1D and screening should be included in current guidelines for management.
- Metformin, an insulin sensitizer, can decrease insulin dose requirements which may be a better treatment approach for PCOS in T1D.
- Anti-obesity agents which promote weight loss, such as GLP-1 RAs, may be beneficial for treatment of PCOS in females with obesity and T1D.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Pediatric Medicine*, for the series "Clinical Pearls in Pediatric Endocrinology and Metabolism". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-22-3/rc

Conflicts of Interest: All authors have completed the

ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-22-3/coif). The series "Clinical Pearls in Pediatric Endocrinology and Metabolism" was commissioned by the editorial office without any funding or sponsorship. BEL served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Pediatric Medicine* from October 2020 to September 2022. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pm-22-3
Cite this article as: Bernier A, Fung J, Ergun-Longmire B. A narrative review: polycystic ovary syndrome (PCOS) and type 1 diabetes (T1D). Pediatr Med 2023;6:25.