Original Article

Evaluation of the Association of Endometrial Thickness, Insulin Resistance, and Menstrual Patterns in Adolescent Females with Polycystic Ovarian Syndrome

Anna Y. Lynn[1], Nadia Solomon[2], Mark Zamani[3], Erin Rowe[2], David B. Seifer[1], Alla Vash-Margita[1,*]

[1] Department of Obstetrics, Gynecology, & Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut
[2] Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, Connecticut
[3] Department of Statistics, Florida State University, Tallahassee, Florida

A B S T R A C T

Study Objective: To evaluate endometrial stripe (EMS) thickness and its association with menstrual pattern and insulin resistance in adolescent females with or at risk for polycystic ovarian syndrome (PCOS)
Methods: This was a retrospective case-control study of adolescent females ranging between 12 and 21 years old evaluated in the Adolescent Gynecology & Endocrinology Clinic (AGEC) at a tertiary children's hospital between 2017 and 2021. Transabdominal pelvic ultrasound (US) was obtained for evaluation of PCOS or acute pelvic pain. Unadjusted comparisons were performed between imaging measurements in the PCOS and control (girls without PCOS with acute pelvic pain) groups, as well as analysis of the PCOS group adjusted for age, body mass index, race, and biochemical values. This study was approved by the Institutional Review Board.
Results: In our study, 54 subjects met the inclusion criteria for the PCOS group and 42 for the control group. EMS thickness was thinner in the PCOS group than in the control (0.55 ± 0.31 cm vs 0.70 ± 0.23 cm; $P < .001$). There was no difference in EMS thickness in the PCOS group when stratified by intermenstrual interval, insulin resistance, and other biochemical factors.
Conclusion: Our findings support recommendations by the 2018 International Guidelines to avoid use of US for the establishment of PCOS diagnosis in adolescents. These results highlight the unique pathophysiology of adolescent PCOS in contrast to PCOS in adult women. Further large-scale prospective studies are needed to understand the role of EMS thickness as a prognostic marker in adolescent PCOS.
Key Words: Polycystic ovarian syndrome, PCOS, Endometrium thickness, Insulin resistance, Pelvic ultrasonography, Menstrual cycle, Adolescents, Endometrial hyperplasia

Introduction

Polycystic ovarian syndrome (PCOS) is a highly prevalent, multifactorial endocrinopathy that is associated with many comorbidities, including cardiovascular disease, depressive disorders, and metabolic syndromes.[1-4] PCOS affects approximately 1 in 10 adult women and is well characterized as one of the most common gynecological endocrinopathies and a frequent cause of infertility.[5,6] The prevalence and comorbidities of PCOS are similar in adolescent girls; however, diagnosis of adolescent PCOS is difficult because many of the clinical signs and symptoms of PCOS can overlap with features of normal pubertal development.[7,8] Recent clinical guidelines have recommended that adolescent girls can be diagnosed as having or at risk for PCOS by using the following criteria: presence of oligomenorrhea and evidence of clinical or biochemical hyperandrogenism.[8] Until 8 years have passed from menarche, adolescents considered at risk for PCOS should be followed clinically for management of bothersome signs and symptoms accordingly.[9] These guidelines recommend against the use of ultrasound (US) imaging in diagnosis of adolescent PCOS because polycystic ovarian morphology, which consists of large ovarian volume and peripherally distributed follicles in the absence of a dominant follicle, may be difficult to distinguish from normal multi-follicular ovaries of early adolescence.[9-11] However, after 8 years of menstrual age, adult diagnostic criteria apply, including US imaging. Therefore, some clinical cases would include adolescent patients with early menarche who have reached 8 years of menstrual life and thus would be diagnosed using adult PCOS criteria. These differences in signs and symptoms highlight the need to better understand adolescent PCOS as a unique pathophysiological entity and manage it accordingly. Appropriate diagnosis and management of PCOS in adolescents is crucial as this disease and its associated comorbidities can have longstanding effects on the overall health of adolescents up to and throughout their adult life.

One of the major concerns in PCOS is that the chronic anovulatory state and unopposed exposure to estrogen lead to an increased risk for endometrial hyperplasia and endometrial cancer. PCOS has been shown to lead to a 2- to 6-fold increase in the risk of endometrial cancer in

The authors have no disclosures or conflicts of interest.
Study Undertaken: New Haven, CT.
Results Presented: North American Pediatric & Adolescent Gynecology 36th Annual Clinical Research Meeting, April 2022. Chicago, IL.
* Address correspondence to: Alla Vash-Margita, 310 Cedar Street, FMB329F, New Haven, CT 06510; Phone (203) 785-4010.
E-mail address: Alla.vash-margita@yale.edu (Alla Vash-Margita).

1083-3188/$ – see front matter
https://doi.org/10.1016/j.jpag.2022.11.005

adult women.[9] Interestingly, studies of endometrial hyperplasia in adult women have shown that increased endometrial stripe (EMS) thickness is associated independently with both PCOS and insulin resistance.[12-16] This suggests that PCOS and insulin resistance, which are known to be closely associated, may induce a positive feedback cycle of molecular interactions that contribute to endometrial hyperplasia.[1,17] However, limited data have been reported on these factors together in adolescent girls, and little is known about the endometrial morphology in adolescents with PCOS.[11] Similar to adults, in adolescence, PCOS is associated closely with insulin resistance and metabolic syndrome.[18,19] Endometrial cancer has low prevalence in adolescent and young adult women but may have serious reproductive outcomes, so it is important to understand the risk factors that adolescents with PCOS face to optimize screening and management guidelines.[20] This study evaluated EMS thickness and its association with menstrual pattern and insulin resistance in adolescent PCOS.

Methods

Study Population

This retrospective case-control study was approved by the Yale Institutional Review Board (Protocol #2000024068) to include patients evaluated at the Adolescent Gynecology & Endocrinology Clinic (AGEC) and Yale New Haven Children's Hospital between 2017 and 2021. We conducted a chart review of adolescent females between the ages of 12 and 21 years who were referred to the AGEC for the evaluation of PCOS due to amenorrhea, oligomenorrhea, hirsutism, acne, and/or elevated androgens. Presence of acne was determined on the basis of clinical provider documentation of significant inflammatory facial or body acne. Presence of hirsutism was determined on the basis of clinical provider documentation of moderate to severe hirsutism that would meet a Ferriman-Gallwey score greater than 8. Due to heterogeneity of medical record entries, there was no formal record of Ferriman-Gallwey score; however, clinical impression was determined on the basis of provider expertise. Inclusion criteria for the group in which subjects had or were at risk for PCOS, on the basis of the updated guidelines at the time of study initiation in 2017, were meeting at least 2 of the Rotterdam criteria (oligo- or amenorrhea, biochemical or clinical hyperandrogenism) and being 2 or more years post-menarche.[1] Exclusion criteria for the PCOS group were the presence of ovarian cysts greater than 3 cm in size and use of hormonal therapy (such as combined oral contraceptive pills) for more than 3 months before evaluation. For our control group, we queried the medical records of adolescent girls between the ages of 12 and 21 years who underwent pelvic US as part of a diagnostic workup in the emergency department for pelvic or abdominal pain. The inclusion criterion for the control group was being 2 or more years post-menarche. Exclusion criteria for the control group included the use of hormonal therapy treatment for more than 3 months before imaging; any history or signs of thyroid disease, pituitary disease, adrenal disease, metabolic syndrome, hyperandrogenism, abnormal uterine bleeding; or evidence of irregular menstrual cycles.

Data Collection

For all subjects in the PCOS and control groups, demographic variables including age, race, and ethnicity were extracted from the medical records. Additionally, transabdominal US measurements of EMS thickness and the right and left ovaries were collected for all subjects. For subjects in the PCOS group, clinical variables were collected from medical records, including body mass index (BMI), age at menarche, amenorrhea/oligomenorrhea, date of the first day of the last menstrual period (LMP), and presence of acne or hirsutism. Additionally, for subjects in the PCOS group, biochemical laboratory values within 1 year of evaluation were collected, including 25-hydroxyvitamin D (vitamin D), anti-Mullerian hormone (AMH), total testosterone, hemoglobin A1c (HbA1c), insulin, triglycerides, and low-density lipoprotein (LDL).

Laboratory Assays

Quantification of vitamin D (25(OH)D) was obtained via liquid chromatography-tandem mass spectrometry (reference range 5.2-3.11 ng/mL; intra-assay coefficients of variance [CoV] 3.9%-6.9%; inter-assay CoV 7.2%) or immunoassay (reference range 4-150 ng/mL; intra-assay CoV 2.3%-5.4%; inter-assay CoV 7.8%-10.6%) (DiaSorin; Saluggia, Italy). Regardless of quantification method, patients were considered to be vitamin D insufficient if they exhibited levels lower than 30 ng/dL.[21] AMH was quantified via chemiluminescent immunoassay (reference range 0.08-24 ng/mL; intra-assay CoV 1.8%-2.3%; inter-assay CoV 0.9%-4.4%) (Beckman-Coulter; Brea, CA) and was considered elevated if levels were above 4.0 ng/mL.[22] Total testosterone was quantified using competitive chemiluminescent immunoassay and considered elevated if above 40 ng/dL. HbA1c was quantified using the boronate affinity method (reference range 4.0%-5.6%) and was considered elevated if above 5.7%. Insulin was quantified by fasting insulin immunoassay and considered elevated if above 25 uIU/mL. Triglycerides were quantified by spectrophotometry and were considered elevated if above 150 mg/dL. LDL, quantified as part of an enzymatic assay lipid panel, was calculated using the Martin-Hopkins calculation and was considered elevated if above 100 mg/dL.

US Interpretation

Transabdominal US of the pelvis was obtained as part of the patients' clinical evaluation. All available 2D images were re-interpreted by a single university-affiliated pediatric radiologist who re-measured EMS thickness and ovarian volume (0.5 × length × width × height) and assessed for peripheral distribution of follicles. The radiologist was not blinded to PCOS vs control groups. The endometrial thickness was measured as previously established at the widest distance between the endometrium and myometrium junction of one side to the opposing side on

a sagittal view of the uterus using a 5-MHz curved-array transabdominal transducer.[11,23,24]

Statistical Analyses

Descriptive statistics and comparisons of demographic characteristics, clinical characteristics, ultrasonographic measurements, and laboratory values between the PCOS and control groups were performed using the Wilcoxon rank sum test. In patients with PCOS, dichotomous categories for race, ethnicity, BMI, time elapsed between imaging and the first day of LMP (long intermenstrual interval defined as time since the first day of LMP longer than 90 days before imaging), vitamin D, AMH, total testosterone, hemoglobin A1b, insulin, triglycerides, and LDL were made. Comparison of these respective categories with EMS thickness was done using the Wilcoxon rank sum test. Kruskal-Wallis ANOVA with Bonferroni correction was used to perform multiple comparisons of EMS thickness between the PCOS and control groups stratified by insulin resistance (defined as HbA1c greater than or equal to 5.7%). Differences were considered significant with $\alpha \leq 0.05$. All statistical analyses were performed using R Studio 1.2.1335 (Boston, MA).

Results

Study Population

Between the years 2017 and 2020, 149 female patients presented to the AGEC for evaluation of PCOS. Of these patients, 32 did not undergo US imaging and were excluded. On evaluation, 20 patients were found to meet only 1 of the Rotterdam criteria, and 7 patients had ovarian cysts, resulting in their exclusion. Of the remaining 90 patients, 21 were excluded due to use of hormonal therapy longer than 3 months, and 15 were excluded due to a menstrual age less than 2 years. Of note, there were only 2 patients on hormonal treatment, for 1 and 2 months, respectively, in the control group. Of the subjects included in our dataset, 7 were 8 or more years post-menarchal. From the 66 patient medical records that were queried for the control group, 5 patients were excluded due to abnormal uterine bleeding. Of the remaining 61 patients, 10 were excluded due to use of hormonal therapy longer than 3 months, and 9 were excluded due to a menstrual age less than 2 years. Subsequently, the PCOS group had 54 patients and the control group had 42 patients (Fig. 1). Patient demographic characteristics were compared between the PCOS and control groups (Table 1). The PCOS group was younger (15.7 years old vs 17.1 years old; $P = .005$) and had a higher BMI (31.7 kg/m^{2}vs 24.3 kg/m^2; $P < .0001$) than the control group. There was no difference in race or ethnicity between the 2 groups. As expected, the PCOS-associated signs of oligomenorrhea, acne, and hirsutism were present only in patients with PCOS. None of the subjects had clinical concern of endometrial hyperplasia or cancer; therefore, endometrial sampling was not performed. This is in line with the low incidence of endometrial cancer in adolescents that is reported in the National Institutes of Health Surveillance, Epidemiology, and End Results (SEER) Program.

Table 1
Demographic and Clinical Characteristics of the Participants*

	PCOS ($n = 54$)	Control ($n = 42$)	P value
Age at evaluation (years)	**15.7 ± 2.0**	**17.1 ± 2.2**	**.005**
BMI (kg/m^2)	**31.7 ± 7.5**	**24.3 ± 5.5**	**< .0001**
Race			
White	23 (43%)	22 (52%)	NS
Black	8 (15%)	8 (19%)	NS
Asian	2 (4%)	0 (0%)	NS
Other/Unknown	21 (39%)	12 (29%)	NS
Ethnicity			
Latina	18 (33%)	12 (29%)	NS
Not Latina	31 (57%)	28 (67%)	NS
Unknown	5 (9%)	2 (5%)	NS
Oligomenorrhea	50 (90%)	–	
Acne	28 (52%)	–	
Hirsutism	31 (57%)	–	

BMI, body mass index; NS, no statistically significant difference; PCOS, polycystic ovarian syndrome.
*Values given as mean ± standard deviation or number (percent).

Table 2
Patient Ultrasonographic and Biochemical Characteristics for the Polycystic Ovarian Syndrome (PCOS) and Control Cohorts with Notable Difference in Endometrial Thickness*

	PCOS ($n = 54$)	Control ($n = 42$)	P value
Endometrial thickness (cm)	**0.55 ± 0.31**	**0.70 ± 0.23**	**< .001**
Right ovarian volume (cm^3)	8.75 ± 4.89	7.59 ± 4.49	.28
Left ovarian volume (cm^3)	8.35 ± 4.89	7.81 ± 4.68	.35
Follicle distribution			
Assessed	53 (98%)	40 (95%)	
Peripheral	15 (28%)	0 (0%)	
Non-peripheral	34 (64%)	39 (98%)	
Indeterminant	4 (8%)	1 (2%)	
Vitamin D (ng/mL)			
Reported	38 (70%)		
Laboratory value	20.5 ± 8.9		
AMH (ng/mL)			
Reported	39 (72%)		
Laboratory value	8.2 ± 3.7		
Total testosterone (ng/dL)			
Reported	53 (98%)		
Laboratory value	55.7 ± 23.2		
Hemoglobin A1c (%)			
Reported	43 (80%)		
Laboratory value	5.5 ± 0.7		
Insulin (uIU/L)			
Reported	33 (61%)		
Laboratory value	27.5 ± 18.1		
Triglycerides (mg/dL)			
Reported	44 (81%)		
Laboratory value	106.1 ± 55.3		
LDL (mg/dL)			
Reported	44 (81%)		
Laboratory value	96.9 ± 27.7		

AMH, anti-Mullerian hormone; LDL, low-density lipoprotein.
*Values given as mean ± standard deviation or number (percent).

Comparison Analyses

EMS thickness and ovarian volumes were compared between the PCOS and control groups. The PCOS group was found to have a thinner mean EMS (0.55 ± 0.31 cm vs 0.70 ± 0.23; $P < .001$) (Table 2). No differences were found in right or left mean ovarian volumes between groups. Peripheral follicle distribution could be assessed in 53 of

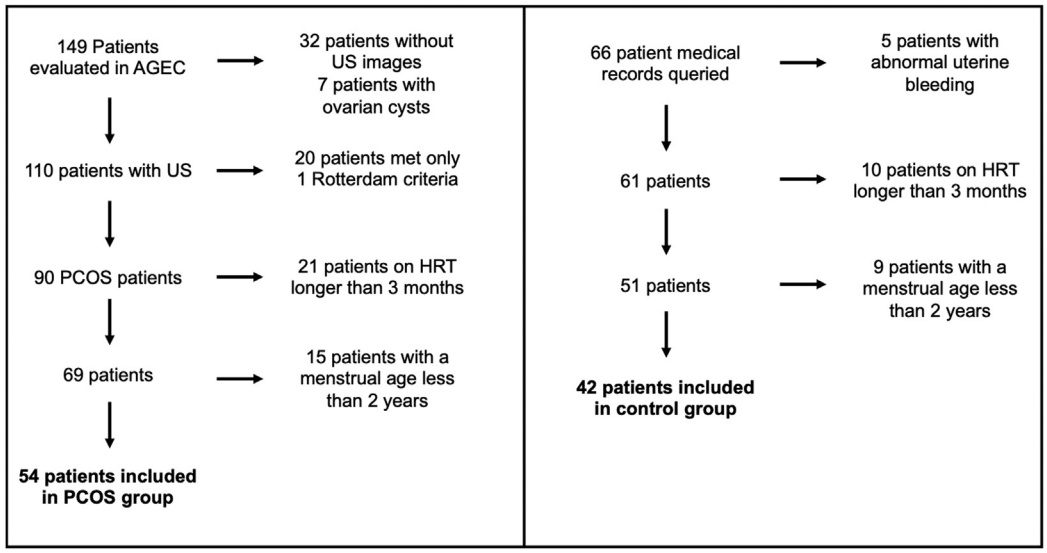

Fig. 1. Flowchart demonstrating subject selection according to inclusion and exclusion criteria for both polycystic ovarian syndrome (PCOS) and control groups.

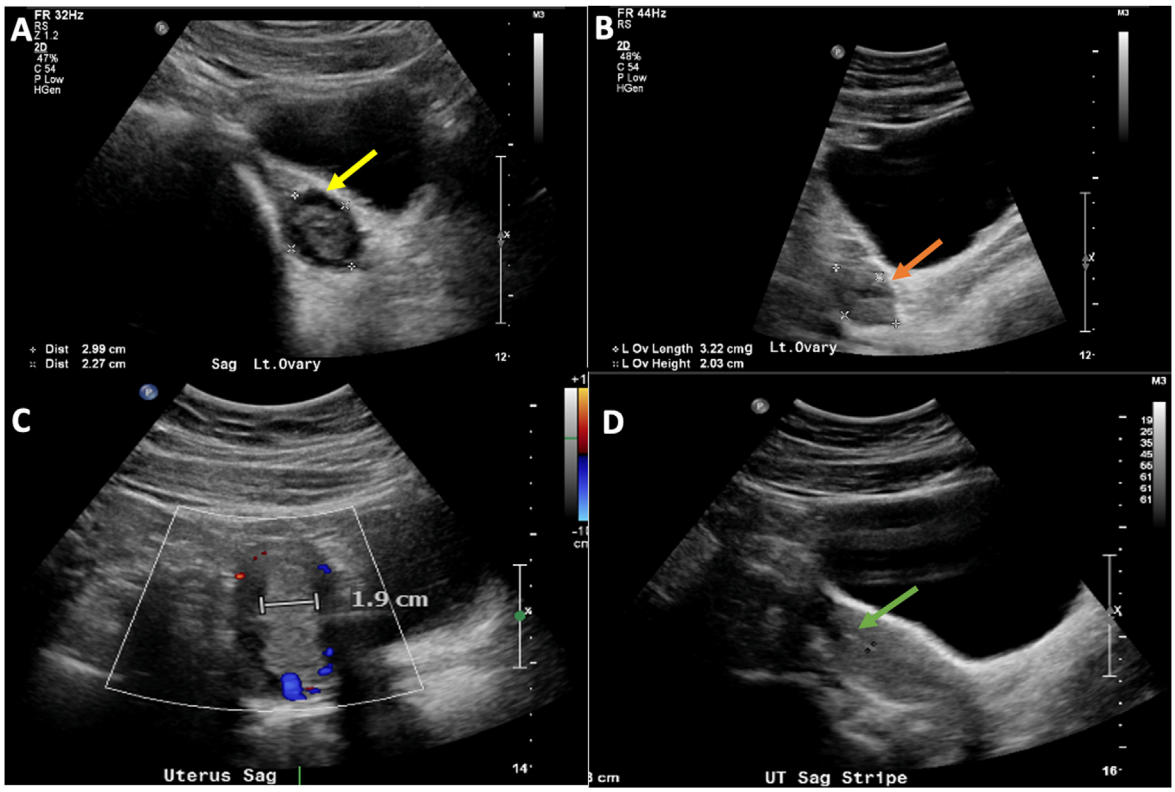

Fig. 2. Representative transabdominal ultrasound (TAUS) images of the pelvis in the sagittal plane highlighting morphological characteristics recorded in study subjects. (A) An ovary with central hyperechoic stroma and multiple peripheral follicles (yellow arrows) found in a 16-year-old girl at risk for polycystic ovarian syndrome (PCOS); (B) an ovary that is normal in size, position, and parenchymal echotexture, and permeated by normal-appearing follicles (orange arrows) in a 17-year-old girl at risk for PCOS; (C) a thickened endometrial stripe measuring up to 1.9 cm in a 14-year-old girl at risk for PCOS; and (D) an endometrial stripe within normal limits with no evidence of endometrial thickening (green arrow) in a 14-year-old girl at risk for PCOS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

54 (98%) and 40 of 42 (95%) patients in the PCOS and control groups, respectively (Table 2). Of the PCOS group, 15 of 53 (28%) exhibited peripherally distributed follicles, 34 of 53 (64%) exhibited normal follicular distribution, and 4 of 53 (8%) were indeterminant (Fig. 2). None of the subjects in the control group demonstrated peripherally distributed follicles. In the PCOS group, vitamin D was recorded for 38 of 54 (70%), AMH was recorded for 39 of 54 (72%), HbA1c was recorded for 43 of 54 (80%), total testosterone was recorded for 53 of 54 (98%), insulin was recorded for 33 of 54 (61%), triglycerides were recorded for 44 of 54 (81%), and LDL was recorded for 44 of 54 (81%) (Table 2). The PCOS group showed insufficiency in vitamin D (mean 20.5 ng/mL; standard deviation [SD] 8.9 ng/mL), elevated AMH (mean 8.2 ng/mL; SD 3.7 ng/mL), elevated total testosterone (mean 55.7 ng/dL; SD 23.2 ng/dL), and

Table 3
Analysis of Endometrial Thickness in Polycystic Ovarian Syndrome (PCOS) and Control Cohorts with and without Insulin Resistance (IR)*

PCOS	Endometrial thickness (cm)	Comparison group	Endometrial thickness (cm)	*P* value
With IR^†	0.53 ± 0.37	Control	0.7 ± 0.23	.007
Without IR^	0.57 ± 0.27	Control	0.7 ± 0.23	.03
Long intermenstrual interval‡	0.51 ± 0.23	Short intermenstrual interval	0.58 ± 0.35	.68
PCOS stratification variables				
Age				.29
BMI				.8
Race				.18
Ethnicity				.48
Vitamin D				.81
AMH				.91
Total testosterone				.13
Hemoglobin A1c				.95
Insulin				.63
Triglycerides				.92
LDL				.9

AMH, anti-Mullerian hormone; BMI, body mass index; LDL, low-density lipoprotein.
*Values given as mean ± standard deviation.
†^IR defined as hemoglobin A1c ≥ 5.7%.
‡Long intermenstrual interval = last menstrual period occurred longer than 90 days before ultrasound imaging.

elevated insulin levels (mean 27.5 uIU/L; SD 18.1 uIU/L). HbA1c, triglyceride, and LDL levels were normal for the PCOS group.

Stratified Analyses of EMS

The differences in mean EMS thickness between the PCOS and control groups persisted when stratified by insulin resistance status (Table 3). Subjects in the PCOS group, with or without insulin resistance, were found to have thinner EMS than subjects in the control group (0.53 ± 0.37 cm vs 0.57 ± 0.27 cm vs 0.70 ± 0.23 cm; $P < .01$). Intermenstrual interval, or the time elapsed between LMP and imaging, was reported for 50 of 54 (93%) subjects in the PCOS group. When the subjects in the PCOS group were stratified by intermenstrual interval, no difference was found in the mean EMS thickness between a long or short intermenstrual interval (Table 3). No difference was found between PCOS and control groups in mean EMS thickness when stratified by age, BMI, or race/ethnicity (Table 3). When the PCOS group was stratified by vitamin D, AMH, testosterone, HbA1c, insulin, triglycerides, or LDL, no difference was found in mean EMS thickness (Table 3).

Discussion

EMS thickness is a commonly used metric in the evaluation of PCOS and in evaluation for endometrial hyperplasia and cancer. Because severe implications and outcomes are associated with endometrial cancer, endometrial hyperplasia is concerning, and it is important that proper screening protocols are developed and followed. In adult women, increased EMS thickness has been associated with PCOS and insulin resistance independently and together.[11] Interestingly, we found that the mean EMS was thinner in adolescent girls with PCOS, regardless of insulin resistance status or intermenstrual interval. The presence of a thinner EMS in adolescents is counterintuitive to what we expected to find on the basis of data seen in adults. This strengthens the evidence that clinicians and researchers should approach adolescent PCOS as a unique pathophysiology and distinct from adult PCOS, and further prospective studies are needed. The finding of ovarian volumes that were no different between PCOS and control groups supports recent recommendations against use of US imaging in diagnosis of adolescent PCOS.[9] In addition, peripheral distribution of follicles may be indicative of PCOS phenotype and of greater diagnostic value than ovarian volume.

As the adolescent reproductive system and hormonal axes are developing through puberty, it is established that normal physiological changes and variations might not be able to be clearly differentiated from those due to PCOS.[10] Because of this, other potential criteria, such as biochemical markers, should be established to aid in the proper diagnosis of adolescent PCOS. Herein, we report that adolescents with PCOS exhibited vitamin D insufficiency and elevated AMH, which is consistent with previous findings and suggests that further investigation into these biomarkers could lead to accumulation of enough evidence to merit inclusion as diagnostic criteria for PCOS.[25] However, AMH and vitamin D levels were not found to correlate with endometrial hyperplasia, indicating that further studies are needed to improve screening criteria and find potential modifiable therapeutic factors for endometrial hyperplasia in adolescent PCOS.

Among adolescents with PCOS, factors that affect EMS thickness are also of interest to help identify patients who could be at higher risk for hyperplasia and may be followed with more frequent endometrial screening. We investigated the association of EMS thickness with age, race, BMI, intermenstrual interval, insulin resistance status, and biochemical markers including vitamin D, AMH, total testosterone, and metabolic parameters. Interestingly, none of the variables that we included in our stratified analysis yielded statistical significance, suggesting that other complex molecular factors may have a dominant role in the pathogenesis of endometrial cancer in adolescents. EMS was consistently thinner in adolescents with PCOS than in controls, regardless of insulin resistance status, and insulin resistance status itself did not significantly affect the EMS thickness. This

finding is also counterintuitive to what has been reported in adult women. During pubertal development, there is a maturation of insulin and metabolic pathways that has complex integration with molecular growth factor activity and hormonal axes.[12] These processes may allow the body to compensate for a wider range of insulin sensitivity with respect to its interaction with ovarian function and therefore result in the lack of induction of endometrial hyperplasia seen in adults. This could imply that endometrial hyperplasia in adolescents is caused by an independent set of molecular factors and pathways specific to this time in pubertal development and raises the need for further investigation.

Another clinically modifiable factor of interest is the amount of time elapsed between menstrual periods and the corresponding effect on EMS thickness. Studies in adult women have shown that an increased intermenstrual interval is associated with a higher risk of endometrial hyperplasia.[26] Our findings are consistent with previous evidence that the length of time that elapses between menstrual periods in adolescents does not significantly affect EMS thickness.[11] Our findings raise a question of the practicality and evidence behind the pragmatic approach recommended by the Teede et al to use combined oral hormonal preparations or progestin therapy in those patients with cycles longer than 90 days.[9] Our findings uncover the need for further studies defining optimal prevention of endometrial hyperplasia and endometrial cancer, as well as delineation of the best clinical practice for induction of scheduled menstrual bleeding in adolescents with PCOS.

To our knowledge, this is the first study to examine these clinical and biochemical variables in association with EMS thickness and PCOS in an adolescent population. Our study limitations include the retrospective nature of the study, data collection within a single institution, and the lack of a full biochemical and clinical dataset in the control group due to the nature of their clinical evaluation for pelvic pain, which included lack of explicit data on menstrual cycles in 14 patients. Future directions of this work could include large-scale prospective studies examining EMS thickness and risk of endometrial hyperplasia or cancer, as well as optimization of the scheduled withdrawal bleeding in relation to cancer prevention in adolescents with PCOS. Such work could identify modifiable factors leading to development of endometrial malignancy throughout the life span. Prospective studies on the role of potential diagnostic biomarkers, such as vitamin D and AMH, could also be instrumental in optimizing diagnostic criteria for adolescent PCOS.

References

1. Ibanez L, Oberfield SE, Witchel S, et al: An International Consortium Update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. Horm Res Paediatr 2017; 88(6).
2. Goodzari MO, Dumesic DA, Chazenbalk G, et al: Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 2011; 7(4).
3. Scicchitano P, Dentamaro I, Carbonara R, et al: Cardiovascular risk in women with PCOS. Int J Endocrinol Metab 2012; 10(4).
4. Hollinrake E, Abreu A, Maifeld M, et al: Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertil Steril 2007; 87(6).
5. Deswal R, Narwal V, Pundir CS: The prevalence of polycystic ovary syndrome: a brief systematic review. J Hum Reprod Sci 2020; 13(4).
6. Hanson B, Johnstone E, Dorais J, et al: Female infertility, infertility-associated diagnoses, and comorbidities: a review. J Assist Reprod Genet 2017; 34(2).
7. Naz MSG, Tehrani FR, Majd HA, et al: The prevalence of polycystic ovary syndrome in adolescents: a systematic review and meta-analysis. Int J Reprod Biomed 2019; 17(8).
8. Roe AH: Dokras A: the diagnosis of polycystic ovary syndrome in adolescents. Rev Obstet Gynecol 2011; 4(2).
9. Teede HJ, Misso ML, Costello MF, et al: Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018; 110(3).
10. Fulghesu AM, Canu E, Casula L, et al: Polycystic ovarian morphology in normocyclic non-hyperandrogenic adolescents. J Pediatr Adolesc Gynecol 2021; 34(5).
11. Shah B, Parnell L, Milla S, et al: Endometrial thickness, uterine, and ovarian ultrasonographic features in adolescents with polycystic ovarian syndrome. J Pediatr Adolesc Gynecol 2010; 23(3).
12. Iatrakis G, Tsionis C, Adonakis G, et al: Polycystic ovarian syndrome, insulin resistance and thickness of the endometrium. Eur J Obstet Gynecol Reprod Biol 2006; 127(2).
13. Shan W, Ning C, Luo X., et al: Hyperinsulinemia is associated with endometrial hyperplasia and disordered proliferative endometrium: a prospective cross-sectional study. Gynecol Oncol 2014; 132(3).
14. Mu N, Zhu Y, Wang H, et al: Insulin resistance: a significant risk factor of endometrial cancer. Gynecol Oncol 2012; 125(3).
15. McCormick BA, Wilburn RD, Thomas MA, et al: Endometrial thickness predicts endometrial hyperplasia in patients with polycystic ovary syndrome. Fertil Steril 2011; 95(8).
16. Park JC, Lim SY, Jang TK, et al: Endometrial histology and predictable clinical factors for endometrial disease in women with polycystic ovary syndrome. Clin Exp Reprod Med 2011; 38(1).
17. Orostica L, Rosas C, Plaza-Parrochia F, et al: Altered steroid metabolism and insulin signaling in PCOS endometria: impact in tissue function. Curr Pharm Des 2016; 22(36).
18. Fazleen NE, Whitttaker M, Mamun: A: Risk of metabolic syndrome in adolescents with polycystic ovarian syndrome: a systematic review and meta-analysis. Diabetes Metab Syndr 2018; 12(6).
19. Fu L, Xie N, Qu J, et al: The association between polycystic ovary syndrome and metabolic syndrome in adolescents: a systematic review and meta-analysis. Reprod Sci 2022. doi:10.1007/s43032-022-00864-8.
20. Rosen MW, Tasset J, Kobernik EK, et al: Risk factors for endometrial cancer or hyperplasia in adolescents and women 25 years old or younger. J Pediatr Adolesc Gynecol 2019; 32(5).
21. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al: Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96(7).
22. Bhide P, Pundir J, Homburg R, et al: Biomarkers of ovarian reserve in childhood and adolescence: a systematic review. Acta Obstet Gynecol Scand 2019; 98(5).
23. Langer JE, Oliver ER, Lev-Toaff AS, et al: Imaging of the female pelvis through the life cycle. RadioGraphics 2012; 32(6).
24. Fleischer AC, Mendelson EB, Böhm-Vélez M, et al: Transvaginal and transabdominal sonography of the endometrium. Semin Ultrasound CT MR 1988; 9(2).
25. Simpson S, Seifer DB, Shabanova V, et al: The association between anti-Mullerian hormone and vitamin 25(OH)D serum levels and polycystic ovarian syndrome in adolescent females. Reprod Biol Endocrinol 2020; 18(1).
26. Cheung AP: Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. Obstet Gynecol 2001; 98(2).