DOI: https://doi.org/10.53350/pjmhs221641079

ORIGINAL ARTICLE

Evaluating Underlying Endocrine Abnormalities in Adolescents with Menstrual Disorders Presenting at a Tertiary Care Hospital

MARIA ALI[1], TAHIRA YASMEEN[2], ZEHRA NAQVI[3], RABIA FAROOQI[4], SAADIA KHAN[5], BAKHTAWAR[6]
[1]*Post Graduate Resident, Gynae & Obs Department, Liaquat National Hospital, Karachi*
[2]*Assistant Professor, Gynae & Obs Department, Liaquat National Hospital, Karachi*
[3]*Professor, Gynae & Obs Department, Liaquat National Hospital, Karachi*
[4,6]*Senior Registrar, Gynae & Obs Department, Liaquat National Hospital, Karachi*
[5]*Registrar, Gynae & Obs Department, Liaquat National Hospital, Karachi*
Corresponding author: Maria Ali, Email: alidrmaria.24@gmail.com

ABSTRACT

Introduction: Adolescence is a significant period between childhood and adulthood when physical and psychological changes occur along with menstruation. The onset of puberty is governed by genetic, endocrinal, neuronal, socioeconomic, and environmental factors. Endocrine abnormalities in adolescents are not uncommon and can lead to menstrual disorders. This study's objective is to identify the prevalence of underlying endocrine abnormalities and their association with menstrual disorders among adolescents at a tertiary care hospital in Pakistan.

Material and Methods: We conducted a cross-sectional study of adolescent girls presenting with menstrual disorders at the Department of Obstetrics and Gynecology at Liaquat National Hospital, Karachi, Pakistan, from January 1, 2020, to January 1, 2021. We collected a detailed history from each patient. All physical examinations were performed in the presence of a female nurse, and we carefully maintained patient privacy. The physical examinations consisted of recording the patient's height, weight, body mass index (BMI), and thyroid examination. We also noted the patient's hirsutism score and the presence or absence of secondary sexual characteristics. All the patients received a hormonal evaluation in which we measured their thyroid-stimulating hormone levels, and follicle-stimulating hormone (on day two of their menstrual cycle and random FSH was measured for amenorrhea patients), prolactin, and free androgen index.

Results: The study included 143 adolescent girls aged 10 to 19 with menstrual disorders such as primary amenorrhea, secondary amenorrhea, frequent menstrual bleeding, infrequent menstrual bleeding, shortened menstrual bleeding, heavy menstrual bleeding, and intermenstrual bleeding. The mean menarcheal age of the patient population was 12.1 ± 0.4 years, and the mean BMI was 25.27 ± 5.02 kg/m^2. One hundred twenty-four patients (86.7%) reported polycystic ovarian syndrome (PCOS). Most PCOS patients had infrequent menstrual bleeding (85.5%), 46% had biochemical signs of hyperandrogenism, and 18.5% of PCOS patients showed clinical signs of hyperandrogenism. The most common menstrual problems reported by the patients were infrequent menstrual bleeding (74.1%), followed by shortened menstrual bleeding (61.5%), and heavy menstrual bleeding (9.8%). Thyroid dysfunction was present in the form of hypothyroidism (67.4%) and hyperthyroidism (32.6%). Over half of the hypothyroid patients (58.1%) presented with infrequent menstrual bleeding,41.9% presented with shortened menstrual bleeding and 41.9% with heavy menstrual bleeding .Infrequent menstrual bleeding (73.3%) and shortened menstrual bleeding (66.7%) were the most common menstrual problems in hyperthyroid patients. We found a significant association between thyroid disorder and infrequent menstrual bleeding (p=0.037), heavy menstrual bleeding (p<.001), and shortened menstrual bleeding (p=0.051). Heavy menstrual bleeding was also significantly related to hyperprolactinemia (p=0.036).

Conclusions: Our study showed that endocrine abnormalities in thyroid dysfunction, PCOS, hyperprolactinemia, and hyperandrogenism could cause various menstrual problems in adolescent girls. Hence, underlying endocrine abnormalities need to be investigated and treated to improve adolescents' physical and mental well-being.

INTRODUCTION

Adolescence is a significant transition period from childhood to adulthood when young people go through physical and psychological changes, including menstruation. Adolescence is often a source of anxiety for young female patients and their families [1,2]. A study conducted on 800 adolescent girls in Egypt concluded that menstrual disorders interfered with their academic and social lives [3]. Various mood disorders and the rise in suicidal behavior are triggered by the onset of puberty in girls in mid-adolescence (i.e., those aged 15 to 18) [4].

The onset of puberty is governed by genetic, endocrinal, neuronal, socioeconomic, and environmental factors. The reactivation of the hypothalamic gonadotropin-releasing hormone-secreting system and the KISS1 gene have been shown to play a vital role in pubertal onset and reproduction. Girls with increased body mass index (BMI)in an upper socioeconomic status who eat well-balanced high-energy-adjusted diets experience early menarche. However, intense exercise delays menarche. Black girls experience menarche earlier than white girls [5].

Endocrine abnormalities in adolescents are not uncommon and can lead to menstrual disorders. These endocrine abnormalities include thyroid disorders, hyperprolactinemia, hyperandrogenism, and disturbed follicle-stimulating hormone (FSH)-to-luteinizing hormone (LH) ratio associated with polycystic ovarian syndrome (PCOS) [1,6].

The hypothalamic-pituitary-thyroid axis has a significant role in regulating the menstrual cycle. Women are more prone to develop thyroid disorders than men, and thyroid disorders such as hypothyroidism, hyperthyroidism, thyroiditis, euthyroid, and thyroid tumors contribute to menstrual problems. Hypothyroid women more commonly experience oligomenorrhea and menorrhagia, and hyperthyroid women mainly present with hypomenorrhea [7,8]. However, data on thyroid dysfunctions leading to menstrual disorders in adolescence is scarce [1].

The association between hyperprolactinemia and menstrual disorders is not rare. Hyperprolactinemia is related to ovulatory dysfunction in women, with an overall prevalence of 9% to 17%, leading to menstrual irregularities. The prevalence ranges from 5.5% in patients with secondary amenorrhea to 2.6% in patients with abnormal uterine bleeding [9].

Hyperandrogenism has been found in 50% of adolescent girls [1]. PCOS is an endocrinopathological disorder associated with hyperandrogenism and anovulation. Adolescents with PCOS may present with signs and symptoms like acne, oligomenorrhea, obesity, hirsutism, hyperinsulinemia, and dyslipidemia [10]. PCOS diagnosis is significant in adolescence since it is related to a greater risk of future development of type 2 diabetes, infertility, cardiovascular diseases, and metabolic syndrome [11]. Signs and symptoms of PCOS overlap normal pubertal development; therefore, caution should be taken for diagnosing PCOS in adolescent girls [12].The study's objective is to identify the

prevalence of underlying endocrine abnormalities and their association with menstrual disorders among adolescents at a tertiary care hospital in Pakistan.

MATERIALS AND METHODS

We conducted a cross sectional study of adolescent girls presenting with menstrual disorders at the Department of Obstetrics and Gynecology at Liaquat National Hospital, Karachi, Pakistan, from January 1, 2020, to January 1, 2021. We included adolescent girls aged 10 to 19 with menstrual disorders such as primary amenorrhea, secondary amenorrhea, frequent menstrual bleeding, infrequent menstrual bleeding, shortened menstrual bleeding, heavy menstrual bleeding, and intermenstrual bleeding.

According to FIGO (The International Federation of Gynecology and Obstetrics) 2011,AUB (abnormal uterine bleeding) is the overarching term used to describe any deviation from normal menstrual cycle pattern [13]. AUB includes the following menstrual disorders:

Primary amenorrhea: It is the absence of menstruation by 14 years of age without secondary sexual characteristics or no menarche by 16 years of age with secondary sexual characteristics.

Secondary amenorrhea: Cessation of menstruation for more than 3 cycles or more than 6 months once they had begun.

Frequent menstrual bleeding: More than four episodes in a 90-day period.

Infrequent menstrual bleeding: One or two episodes in a 90-day period.

Shortened menstrual bleeding: Menstrual bleeding of no longer than two days in duration and is also usually light in volume.

Heavy menstrual bleeding: Excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life.

Intermenstrual bleeding: Vaginal bleeding at any time duringthe menstrual cycle, other than during normal menstruation.

All the patients were subjected to three main investigative/diagnostic protocols which are as follows:

Primary and secondary amenorrhea patients were assessed according to the evaluation criteria of the American society for reproductive medicine,2008 [14].

All the other patients were evaluated according to the practice bulletin of the American College of Obstetricians and Gynecologists (ACOG) on the "Diagnosis of Abnormal Uterine Bleeding in Reproductive -Aged Women", number-128, July 2012 [15]. ACOG had adopted the classification system,of abnormal uterine bleeding introduced by FIGO in 2011,known by the acronym PALM-COEIN.

PALM-Structural Causes	COEIN-Non-Structural Causes
P-Polyp	C-Coagulopathy
A-Adenomyosis	O-Ovulatory dysfunction
L-Leiomyoma	E-Endometrial
M-Malignancy & Hyperplasia	I-Iatrogenic
	N-Not yet classified

PCOS patients were diagnosed according to the Rotterdam 2003 criteria, by the presence of any two of it's three features [16]

The study excluded girls older than 19 years, girls aged 10 to 19 years with other medical disorders (such as inherited or acquired bleeding disorders), girls on hormonal pills (as they may alter menstrual cycle and cause intermenstrual bleeding) girls receiving chemotherapy, girls with primary amenorrhea due to Mullerian duct anomalies, and girls with hypogonadotropic hypogonadism.

Data Collection: The hospital's ethical review committee approved the study (Approval No. 0463-2019-LNH-ERC). All participants provided informed consent. We took detailed histories from all patients, and all physical examinations were performed in the presence of a female nurse. The patient's privacy was always maintained. The physical examination included measuring the patient's height, weight, and BMI. We also performed a thyroid examination and noted the patient's hirsutism score and the presence or absence of secondary sexual characteristics. All the patients received hormonal evaluations in which we assessed their thyroid-stimulating hormone level, FSH (on day two of their menstrual cycle and random FSH was measured for amenorrhea patients), prolactin, and free androgen index. Coagulation profiles (e.g., international normalized ratio, activated partial thromboplastin clotting time, platelet count, and Von Willebrand factor tests) were assessed when any inherited or acquired bleeding disorders were suspected.

Analytical methods that were used to process parametric components of hormones were IFCC (The International Federation of Clinical Chemistry and Laboratory Medicine) and instrument was, Roche cobas e 411 iECL analyzer.

Hormones	Normal Values
TSH	0.27-4.2 uIU/ml
FSH	1.2-16.8 mIU/ml
Prolactin	<23 ng/ml
FAI	0.297-5.62 %

Statistical analysis: We used IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp.) to analyze the data. Frequency and percentage were computed for qualitative variables. We calculated the mean ± standard deviation for quantitative variables. We used the chi-squared and Fisher's exact tests to determine the association, and $p<0.05$ was considered significant.

RESULTS

One hundred forty-three adolescent girls were enrolled in the study. The mean menarcheal age of the study population was 12.1 ± 0.4 years, and the mean BMI was 25.27 ± 5.02 kg/m^2. Table 1 presents the mean hormonal profile of the study population. Most patients (n=124; 86.7%) reported PCOS, and 85.5% had infrequent menstrual bleeding. Biochemical signs of hyperandrogenism were present in 46% of patients, and 18.5% showed clinical signs of hyperandrogenism (Table 2).

Table 1: Patient characteristics and hormonal profiles

Characteristics	Mean ± SD
Age (years)	17.6 ± 1.2
Age of Menarche (years)	12.11 ± 0.46
Height (cm)	162.91 ± 5.57
Weight (kg)	65.13 ± 13.99
Body Mass Index (kg/m^2)	25.27 ± 5.02
Hirsutism Score	12.00 ± 9.07
Tanner Scale of Secondary Sexual Characteristics	4.00 ± 0.00
TSH	3.21 ± 2.85
Serum FSH	6.85 ± 2.43
Free Androgen Index (%)	21.59 ± 32.50
Prolactin	23.03 ± 14.80

Abbreviations: SD, standard deviation; TSH, thyroid-stimulating hormone

Table 2: PCOS with infrequent menstrual bleeding and hyperandrogenism

PCOS	Prevalence, n (%)
Present	124 (86.7)
Absent	19 (13.3)
With infrequent menstrual bleeding	106 (85.5)
With Biochemical Signs of Hyperandrogenism	57 (46)
With Clinical Signs of Hyperandrogenism	23 (18.5)

Abbreviation: PCOS, polycystic ovarian syndrome.

Table 3: Prevalence and type of menstrual concerns

Menstrual Concerns	Prevalence, n (%)
Primary Amenorrhea	4(2.8)
Secondary Amenorrhea	10(7.0)
Frequent menstrual bleeding	2(1.4)
Infrequent menstrual bleeding	106(74.1)
Shortened menstrual bleeding	88(61.5)
Heavy menstrual bleeding	14(9.8)
Intermenstrual Bleeding	3(2.1)

The most common menstrual problems reported were infrequent menstrual bleeding (74.1%), followed by shortened menstrual bleeding (61.5%) and heavy menstrual bleeding (9.8%; Table 3).

Thyroid dysfunction was present in the form of hypothyroidism (67.4%) and hyperthyroidism (32.6%). Most hypothyroid patients presented with infrequent menstrual bleeding (58.1%), along with shortened menstrual bleeding (41.9%) and heavy menstrual bleeding (41.9%). Infrequent menstrual bleeding (73.3%) and shortened menstrual bleeding (66.7%) were the most common menstrual problems of hyperthyroid patients (Table 4). We found a significant association between thyroid disorder and infrequent menstrual bleeding (p=0.037), heavy menstrual bleeding (p=0.000), and shortened menstrual bleeding (p=0.051). Heavy menstrual bleeding was also significantly related to hyperprolactinemia (p=0.036; Table 5).

Table 4: Prevalence of various menstrual concerns with hypothyroidism and hyperthyroidism

Menstrual Problems	Hypothyroid (n=31), n (%)	Hyperthyroid (n=15), n (%)
Primary Amenorrhea	4 (12.9)	0 (0)
Secondary Amenorrhea	8 (25.8)	2 (13.3)
Frequent menstrual bleeding	1 (3.2)	1 (6.7)
Infrequent menstrual bleeding	18 (58.1)	11 (73.3)
Shortened menstrual bleeding	13 (41.9)	10 (66.7)
Heavy menstrual bleeding	13 (41.9)	0 (0)
Intermenstrual Bleeding	0 (0)	0 (0)

Table 5: Association of underlying endocrine abnormalities with various menstrual concerns

Menstrual abnormalities	Hormonal Abnormalities								
	Thyroid Disorder			Hyperandrogenism			Hyperprolactinemia		
	Yes, n (%)	No, n (%)	P-value	Yes, n (%)	No, n (%)	P-value	Yes, n (%)	No, n (%)	P-value
Primary Amenorrhea	4 (100)	0 (0)	0.010	2 (50)	2 (50)	0.598	1 (25)	3 (75)	0.620
Secondary Amenorrhea	10 (100)	0 (0)	0.000	4 (40)	6 (60)	0.729	2 (20)	8 (80)	0.097
Frequent menstrual bleeding	2 (100)	0 (0)	0.102	0 (0)	2 (100)	0.497	0 (0)	2 (100)	1.000
Infrequent menstrual bleeding	29 (27.4)	77 (72.6)	0.037	51 (48.1)	55 (51.9)	0.534	39 (36.8)	67 (63.2)	0.106
Shortened menstrual bleeding	23 (26.1)	65 (73.9)	0.051	48 (54.5)	40 (45.5)	0.139	33 (37.5)	55 (62.5)	0.148
Heavy menstrual bleeding	13 (92.9)	1 (7.1)	<.001	5 (35.7)	9 (64.3)	0.272	1 (7.1)	13 (92.9)	0.036
Intermenstrual Bleeding	0 (0)	3 (100)	0.551	3 (100)	0 (0)	0.12	1 (33.3)	2 (66.7)	1.000

Chi-square/fisher exact test was applied.

DISCUSSION

Menstrual problems are common among adolescent females due to the immaturity of the hypothalamic-pituitary-ovarian axis. Although various menstrual problems and irregularities are physiological, they can represent underlying endocrine abnormalities. Therefore, evaluation of the cause is important [1,7]. In European countries, the age of menarche has changed from 16 to younger than 14 years old in the last 150 years [17]. In our study, the mean age of menarche was 12.1 ± 0.4 years, which was younger than the average age at menarche of 15.8 ± 1.0 years reported by Zegeye et al. [18], but quite similar to the 12.5 ± 1.0 years mean menarcheal age reported by Amu et al. in their more recent study [2]. The declining menarcheal age is attributed to better socioeconomic status, nutritional status and healthcare [18]. The difference in the results reported by Zegeye et al. and our research is probably due to the fact that our study population had better socioeconomic status.

Infrequent menstrual bleeding (74%), shortened menstrual bleeding (61.5%), and heavy menstrual bleeding (9.8%) were the three most common menstrual problems reported in our study. Aryani et al. also reported oligomenorrhea (infrequent menstrual bleeding) (24.5%) as the most common menstrual abnormality in Indonesian adolescent girls [19]. However, Anikwe et al. found a lower prevalence of oligomenorrhea (infrequent menstrual bleeding) and menorrhagia (heavy menstrual bleeding), 8.5% and 6.25%, respectively, in secondary school students in Abakaliki, Southeast Nigeria [20]. Hyperprolactinemia was found in 36.8% of patients with oligomenorrhea (infrequent menstrual bleeding) and 37.5% of patients with hypomenorrhea (shortened menstrual bleeding) in our study. However, Lee et al. found a high prevalence of hyperprolactinemia (5.5%) in patients with secondary amenorrhea [9]. Investigation of oligomenorrhea is crucial since it may indicate an underlying prevalence of PCOS, as discovered by Van Hooff et al. [21].

Irregular menstrual cycles are typical in the initial post-pubertal years. Data suggest cycles usually range from 21 to 45 days among adolescents, and wide variation from this range might imply pathological causes like hyperandrogenism and PCOS [22]. PCOS in adolescent girls is challenging to diagnose since the pathological criteria used for the diagnosis in adults could be normal physiological pubertal changes in adolescents [12]. The prevalence of polycystic ovarian syndrome was 86.7% in our study population, which was much higher than the 9.13% prevalence reported by Nidhi R et al. [23].The difference in the prevalence can be attributed to various genetic and environmental factors that are involved in the development of PCOS. We found menstrual irregularity in the form of infrequent menstrual bleeding (85.5%) as the most common presenting concern of PCOS patients. Maslyanskaya et al. also discovered that menstrual cycle abnormalities were among the most common problems in adolescents with PCOS [24].The prevalence of clinical hyperandrogenism (18.5%) in PCOS patients in our research was lower when compared to the 30% prevalence reported by Rajiwade et al. [1]. Hickey et al. also found a lower prevalence of clinical hyperandrogenism (8.2%) in adolescent PCOS patients than in our study [25].

There is a paucity of data on thyroid disorders in adolescents with menstrual abnormalities. The available data revealed that the frequency of menstrual abnormalities in adolescents with thyroid disorders was either not different from healthy individuals or not frequently related to menstrual irregularities [1]. Hafiichuck et al. reported a significant association between thyroid dysfunction and hypomenorrhea (shortened menstrual bleeding) ($p<0.05$) and amenorrhea ($p<0.05$) in adolescent girls [26]. We also found secondary amenorrhea ($p<.001$) to be significantly related to thyroid disorders [18]. We reported a high prevalence of infrequent menstrual bleeding (73.3%) and shortened menstrual bleeding (66.7%) in hyperthyroid patients, and hypothyroid patients in our study presented most commonly with infrequent menstrual bleeding (58.1%) along with heavy menstrual bleeding (41.9%) and shortened menstrual bleeding (41.9%). Kakuno et al. conducted a study on women aged 20 to 45 and discovered a high prevalence of hypomenorrhea (shortened menstrual bleeding) (3.7%) and secondary amenorrhea (2.5%) in severe hyperthyroid cases. Overall, menstrual disorders were more common (34.8%) in severe hypothyroid cases than mild to moderate hypothyroidism (10.2%) in their study [8].

The strengths of our study were its novelty, large sample size and being conducted at a tertiary care hospital. It has opened new horizons for future research. However our study was limited as a single-center study, limiting our results' generalizability to other geographic regions. Therefore, similar multicentric studies should be conducted.

CONCLUSIONS

According to our results, endocrine abnormalities in thyroid dysfunction, PCOS, hyperprolactinemia, and hyperandrogenism could cause various menstrual problems in adolescent girls. However, immaturity of the hypothalamic-pituitary-ovarian axis is considered the most common cause of menstrual cycle problems in young girls. Our study emphasizes the need for evaluation of underlying endocrine abnormalities as they may be solely responsible for many menstrual disorders. Furthermore, endocrine abnormalities need to be investigated and treated to improve the physical and mental well-being of adolescents.

REFERENCES

1. Rajiwade SR, Sagili H, Soundravally R, Subitha L: Endocrine abnormalities in adolescents with menstrual disorders. J Obstet Gynaecol India. 2018, 68:58-64. 10.1007/s13224-017-1035-y
2. Amu EO, Bamidele JO: Prevalence of menstrual disorders among adolescent girls in Osogbo, South Western Nigeria. Int J Adolesc Med Health. 2014, 26:101-106. 10.1515/ijamh-2013-0500.
3. Abdelmoty HI, Youssef MA, Abdallah S, et al.: Menstrual patterns and disorders among secondary school adolescents in Egypt. A cross-sectional survey. BMC Womens Health. 2015, 15:70. 10.1186/s12905-015-0228-8
4. Born L, Shea A, Steiner M: The roots of depression in adolescent girls: is menarche the key?. Curr Psychiatry Rep. 2002, 4:449-460. 10.1007/s11920-002-0073-y
5. Karapanou O, Papadimitriou A: Determinants of menarche. Reprod Biol Endocrinol. 2010, 8:115. 10.1186/1477-7827-8-115
6. Saadia Z: Follicle stimulating hormone (LH: FSH) ratio in polycystic ovary syndrome (PCOS) - obese vs. non- obese women. Med Arch. 2020, 74:289-293. 10.5455/medarh.2020.74.289-293
7. Jacobson MH, Howards PP, Darrow LA, et al.: Thyroid hormones and menstrual cycle function in a longitudinal cohort of premenopausal women. Paediatr Perinat Epidemiol. 2018, 32:225-234. 10.1111/ppe.12462
8. Kakuno Y, Amino N, Kanoh M, et al.: Menstrual disturbances in various thyroid diseases. Endocr J. 2010, 57:1017-1022. 10.1507/endocrj.k10e-216
9. Lee DY, Oh YK, Yoon BK, Choi D: Prevalence of hyperprolactinemia in adolescents and young women with menstruation-related problems. Am J Obstet Gynecol. 2012, 206:213.e1-213.e2135. 10.1016/j.ajog.2011.12.010
10. Pfeifer SM, Kives S: Polycystic ovary syndrome in the adolescent. Obstet Gynecol Clin North Am. 2009, 36:129-152. 10.1016/j.ogc.2008.12.004
11. Buggs C, Rosenfield RL: Polycystic ovary syndrome in adolescence. Endocrinol Metab Clin North Am. 2005, 34:677-x. 10.1016/j.ecl.2005.04.005
12. Peña AS, Witchel SF, Hoeger KM, et al.: Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med. 2020, 18:72. 10.1186/s12916-020-01516-x
13. Fraser IS, Critchley HO, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. InSeminars in reproductive medicine 2011 Sep (Vol. 29, No. 05, pp. 383-390). © Thieme Medical Publishers.
14. Practice Committee of American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril. 2008 Nov;90(5 Suppl):S219-25. doi: 10.1016/j.fertnstert.2008.08.038. PMID: 19007635.
15. Practice Committee of American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril. 2008 Nov;90(5 Suppl):S219-25. doi: 10.1016/j.fertnstert.2008.08.038. PMID: 19007635.
16. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human reproduction. 2004 Jan 1;19(1):41-7.
17. Rigon F, De Sanctis V, Bernasconi S, et al.: Menstrual pattern and menstrual disorders among adolescents: an update of the Italian data. Ital J Pediatr. 2012, 38:38. 10.1186/1824-7288-38-38
18. Zegeye DT, Megabiaw B, Mulu A: Age at menarche and the menstrual pattern of secondary school adolescents in northwest Ethiopia. BMC Womens Health. 2009, 9:29. 10.1186/1472-6874-9-29
19. Aryani I, Rachma UP, Rokhayati E, Moelyo AG: Menstrual cycle patterns of Indonesian adolescents. Paediatrica Indonesiana. 2018, 58:101-5. 10.14238/pi58.3.2018.101-5
20. Anikwe CC, Mamah JE, Okorochukwu BC, Nnadozie UU, Obarezi CH, Ekwedigwe KC: Age at menarche, menstrual characteristics, and its associated morbidities among secondary school students in Abakaliki, southeast Nigeria. Heliyon. 2020, 6:e04018. 10.1016/j.heliyon.2020.e04018
21. van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasing RA, Koppenaal C, Schoemaker J: Polycystic ovaries in adolescents and the relationship with menstrual cycle patterns, luteinizing hormone, androgens, and insulin. Fertil Steril. 2000, 74:49-58. 10.1016/s0015-0282(00)00584-7
22. Adams Hillard PJ: Menstruation in young girls: a clinical perspective. Obstet Gynecol. 2002, 99:655-662. 10.1016/s0029-7844(02)01660-5
23. Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R: Prevalence of polycystic ovarian syndrome in Indian adolescents. J Pediatr Adolesc Gynecol. 2011, 24:223-227. 10.1016/j.jpag.2011.03.002
24. Maslyanskaya S, Talib HJ, Northridge JL, Jacobs AM, Coble C, Coupey SM: Polycystic ovary syndrome: an under-recognized cause of abnormal uterine bleeding in adolescents admitted to a children's hospital. J Pediatr Adolesc Gynecol. 2017, 30:349-355. 10.1016/j.jpag.2016.11.009
25. Hickey M, Doherty DA, Atkinson H, Sloboda DM, Franks S, Norman RJ, Hart R: Clinical, ultrasound and biochemical features of polycystic ovary syndrome in adolescents: implications for diagnosis. Hum Reprod. 2011, 26:1469-1477. 10.1093/humrep/der102
26. Hafiichuk S: Characteristics of puberty period in adolescent girls and major risk factors of menstrual function disorders against the background of endemic goiter. Galician Med J. 2020,27:E202029. 10.21802/gmj.2020.2.9