ISSN: 0975-833X

Availableonlineathttp://www.journalcra.com

International Journal of Current Research
Vol. 13, Issue, 07, pp.18264-18291, July, 2021

DOI: https://doi.org/10.24941/ijcr.41371.07.2021

INTERNATIONAL JOURNAL OFCURRENTRESEARCH

RESEARCH ARTICLE

ADOLESCENT PCOS GIRLS PRESENTING WITH MENORRHAGIA

***Rahul Anand, Valsa Diana, G. and Sujatha. P**

Department of Obstetrics and Gynecology, Rajiv Gandhi Government Women and Child Hospital, Pondicherry, India

ARTICLEINFO

Article History:
Received 25th April, 2021
Received in revised form
19th May, 2021
Accepted 24th June, 2021
Published online 30th July, 2021

Key Words:
Puberty Menorrhagia

ABSTRACT

PCOS is an ovarian disorder characterised by hyperandrogenism, ovulatory dysfunction and polycystic ovaries. Clinically, the ovulatory dysfunction often presents as oligo/amenorrhoea, although menorrhagia is not uncommon.PCOS can present as heavy menstrual bleeding in adolescent girls because of the associated endometrial thickening caused by unopposed anovulatory hyper-oestrogenism

***Citation: Rahul Anand, Valsa Diana, G. and Sujatha. P.* 2021.** "Adolescent pcos girls presenting with menorrhagia", *International Journal of Current Research*, 13, (07), 18264-18291.

INTRODUCTION

Puberty is a period of transition between childhood and adult life, in which relevant physical and mental changes occur. This transitional stage is also called as adolescence (1–4). Puberty menorrhagia is defined as excessive bleeding occurring between menarche and 19 years of age. This heavy menstrual bleeding in adolescent girls is quite common and it may take 5 to 8 years before menstrual cycle normality is established (5,6). Although puberty menorrhagia is often attributed to physiological immaturity of the Hypothalamo-pituitary-ovarian (HPO) axis, there are many other pathological causes associated with it.(7,8)
The causes for heavy menstrual bleeding in adolescent girls are:

- Hormonal
  - Immaturity of the HPO axis
  - Polycystic Ovarian Syndrome (PCOS)
  - Oestrogen breakthrough
  - Exogenous hormones – Oral contraceptive pills (OCP)
- Coagulation disorders
  - Von Willebrand Disease
  - Thrombocytopenia
  - Leukaemia
  - Bernard-Soulier Syndrome
  - Glanzmannthrombasthenia
  - Coagulopathies -Hepatic failure, warfarin therapy
- Trauma
- Systemic diseases
  - Hypothyroidism
  - Genital tuberculosis

Corresponding author:** ***Valsa Diana Jose,
Department of Obstetrics and Gynecology, Rajiv Gandhi Government Women and Child Hospital, Pondicherry, India.

- Dysfunctional uterine bleeding (DUB)
- Leiomyoma
- Malignancy
- Polyp
- Adenomyosis

PCOS is an ovarian disorder characterised by hyperandrogenism, ovulatory dysfunction and polycystic ovaries. Clinically, the ovulatory dysfunction often presents as oligo/amenorrhoea, although menorrhagia is not uncommon (9–11). PCOS can present as heavy menstrual bleeding in adolescent girls because of the associated endometrial thickening caused by unopposed anovulatory hyper-oestrogenism.(12,13). Diagnosis of PCOS has been traditionally done according to the Rotterdam consensus-2003 (14,15)which requires two out of the three following criteria to be met.

- Clinical/biochemical evidence of anovulation
- Clinical/biochemical evidence of hyper-androgenism
- Polycystic ovaries on ultrasonogram

The diagnosis of PCOS in adolescent girls poses multiple challenges because the Rotterdam's criteria was formulated for adult women and it has many pitfalls when applied to adolescent girls (16–18). When the Rotterdam criteria is used in adolescent girls, it leads to over-diagnosis and unwarranted labelling of otherwise healthy young girls as having PCOS because the changes in PCOS closely mimic the normal physiological changes in adolescent girls (19). The menstrual irregularities associated with PCOS are often attributed to the immaturity of the HPO axis (17). The clinical evidence of hyper-androgenism is difficult to ascertain in adolescent girls as the all the four criteria are potentially confounded by normal pubertal changes. Acne is a common finding in adolescent girls and so is hirsutism. Seborrhoea, in isolation, cannot be used as marker of clinical hyper-androgenism and lastly, androgenic alopecia is extremely rare in adolescence (20–22).

The biochemical evidence of hyper-androgenismis also difficult to ascertain as the adult cut-off values used to establish androgen excess cannot be used in adolescent girls because the values of circulating androgens are higher in healthy adolescent girls when compared to adult females (23–25). Polycystic ovaries on ultrasonogram requires a revised criteria to suit the adolescent population as even in healthy normal girls, physiologically the ovaries can appear enlarged in the post-pubertal years. The virginal status of many adolescent girls precludes the use of transvaginalultrasonogram which is much more sensitive than the trans-abdominal one (26–28). Addition of other radiological parameters like the Stromal thickness, Central stromal Brightness, Stromal/Area (S/A) ratio, uterine and intra-ovarian doppler indices increase the accuracy of the ultrasonogram in diagnosing PCOS (29). The modified Ped-C consensus- 2015 aids to diagnose PCOS in adolescent girls with much higher accuracy and draws a much clearer line of distinction between the normal pubertal changes and the pathological features found in PCOS (30–32). PCOS, as a cause of menorrhagia, in adolescent girls is often overlooked and missed at the time of presentation because of pitfalls in the older criteria and the fact that it is more often associated with oligo/amenorrhoea than menorrhagia (33–35). Accurate diagnosis of PCOS in the girls with puberty menorrhagia will help in devising the treatment protocol and also provide the healthcare personnel an opportunity to give advice on lifestyle modification to optimise the reproductive health and avoid potential long-term metabolic complications (36). This study is conducted with the aim of estimating the proportion of polycystic ovarian syndrome in adolescent girls presenting with heavy menstrual bleeding.

AIM AND OBJECTIVES

AIM

To estimate the proportion of PCOS in adolescent girls presenting with menorrhagia

OBJECTIVES

- To describe the demographic characteristics of puberty menorrhagia
- To objectively verify menorrhagia using the ModifiedPhilip's Screening tool
- To estimate the proportion of PCOS in verified menorrhagia in adolescent girls using the modifies Ped-C consensus

REVIEW OF LITERATURE

QUANTIFICATION OF MENORRHGAIA:

Menorrhagia is defined as excessive vaginal bleeding, which lasts for more than seven days in duration or more than 80 millilitres (ml) (37–39). The NICE clinical guideline 44 states that heavy menstrual bleeding is defined as excessive menstrual blood loss which interferes with an woman's physical, emotional, social and/or material quality of life (40). Quantification of menorrhagia is a challenge because a significant proportion of the women who complain of excessive bleeding don't have menorrhagia. The gold standard method of quantification of menorrhagia is estimation of menstrual blood loss by the alkaline haematin method (41). The various methods used to objectively assess menorrhagia include

- Counting the number of days of menstruation

- Weighing the sanitary pads
- Counting the number of sanitary products used
- Haemoglobin level
- Chemical analysis of blood content of used sanitary products
- Menses cup
- Menstrual pictogram
- Questionnaires like the modified Philip screening tool

Complaint of menorrhagia (CM) is all women presenting with a symptom of menorrhagia. More than one-third of the women with CM do not actually have menorrhagia. Verified menorrhagia (VM) is objective confirmation of the CM by any of the above methods. Refuted menorrhagia (RM) is women presenting with CM but not objectively found to have menorrhagia.(42–46)

MODIFIED PHILIP'S SCREENING TOOL

The methods to quantify menorrhagia are either too cumbersome, like the estimation of blood content by the alkaline haematin method or too tedious and prospective like the menstrual pictogram. An ideal way to assess VM would be a method that can be done in a single setting in the OPD basis. The use of the modified Philip's screening tool (a questionnaire) and the presence of anaemia gives a reliable and convenient method of VM.(47,48) It involves the following questions and even if the respondent answers as yes to a single question then she is said to have verified menorrhagia (VM).

- Duration of >7days
- Need to change tampons/pad every 2nd hourly (Q2H)
- Waking at night to change tampons/pads
- Feeling of flooding/gushing
- History of treatment of anaemia
- Limitation of routine activities

HAEMOGLOBIN LEVEL: The presence of anaemia is also a method used to verify menorrhagia. The cut-off for anaemia is taken as <12g/dl according to ICMR 2003 guideline (49–51).

- Mild anaemia – 10 to 11.9g/dl
- Moderate anaemia – 7 to 9.9g/dl
- Severe Anaemia - <7g/dl

CASUES OF PUBERTY MENORRHAGIA

IMMATURITY OF THE HPO AXIS: The physiological immaturity of the HPO axis is the commonest cause of puberty menorrhagia and requires only reassurance, symptomatic relief and correction of anaemia, if present.It may take two years or more for the complete maturation of the HPO axis. During the initial years of menarche, there is immature timing of the Luteinising Hormone (LH) pulse and elevated basal levels of LH which results in anovulatory cycles (52). In these cycles, Follicle Stimulating Hormone (FSH) and LH are sufficient enough to stimulate the development of follicles and secretion of oestrogen but inadequate to cause follicular maturation and ovulation. The resulting unopposed levels of increased oestrogen causes endometrial proliferation that outgrows its blood supply leading to menorrhagia (53). Until recently, the demarcation between the changes in menstrual pattern caused by the physiological immaturity of the HPO axis and the other pathological causes has not been clearly made (54). On studying the maturational mechanisms and implications of adolescent ovulation, the following cut-offs have been proposed to define the abnormal uterine bleeding in adolescent girlswhich warrants detailed evaluation to identify the aetiology.(55,56)

- Primary amenorrhoea
  - Lack of menarche by 15 years
  - Lack of menarche by 3 years after thelarche
- Secondary amenorrhoea
  - Over 90 days without a period, after initially menstruating
- Oligomenorrhoea
  - Post-menarcheal year 1 – average cycle length >90 days
  - Post-menarcheal year 2 – average cycle length >60 days
  - Post-menarcheal year 3 to 5 – average cycle length >45 days
  - Post-menarcheal year ≥6 years – average cycle length >38 to 40 days
- Menorrhagia
  - Post-menarcheal year 1 – average cycle length <19 days
  - Post-menarcheal year ≥2 – average cycle length <21 days
  - Excessive bleeding >7 days
  - Soaks >1 pad/tampon every 1-2 hours

BLEEDING DISORDERS: Although quite rare in the Indian context, bleeding disorders should be screened as a part of the baseline investigations in a case of puberty menorrhagia as heavy menstrual bleeding is often the first symptom in most of these disorders.(57–60). Von-Willebrand disease, Bernard-Soulier syndrome, thrombocytopenia and leukaemia are a few of the frequently encountered bleeding disorders which present as menorrhagia and are screened by the platelet count, peripheral smear and the coagulation profile (61–63).

THYROID DYSFUNCTION: Both hypothyroidism and hyperthyroidism are implicated in the aetiology of puberty menorrhagia, although chronic untreated hypothyroidism causes oligo/amenorrhoea. Hypothyroidism is more commonly encountered in the clinical setting. All girls presenting with menorrhagia should be offered a thyroid function test because it is one of the easily treatable causes of menorrhagia (64–70).

HYPER-PROLACTINEMIA: Elevated levels of prolactin, most commonly caused by a pituitary macro/micro-adenoma disturbs the secretion of gonadotrophin releasing hormone and eventually causes hypogonadism. This actually leads to oligo/amenorrhoea but in the interim period till the hypogonadism sets in, hyper-prolactinemia can present as menorrhagia. If associated with other symptoms and there is a strong clinical suspicion, serum levels of prolactin should be estimated because, like thyroid dysfunction, hyper-prolactinemia is also a treatable cause of menorrhagia (71–75).

LEIOMYOMA: Leiomyomata are extremely rare in adolescence,unlike in the reproductive age group, where they are a common cause for menorrhagia. Very few cases of leiomyomatahave been reported in literature as causes for puberty menorrhagia.(76–79)

GENITAL TUBERCULOSIS: Genital tuberculosis is also more frequently associated with oligo/amenorrhoea because of the substantial weight loss, cachexia and systemic inflammatory response. However, in ovulatory cycles associated with a tubo-ovarian mass and tuberculoussalpingitis, there may be heavy menstrual bleeding. In the absence of constitutional symptoms and a history of contact with an open case of tuberculosis and a high index of suspicion,investigations specific for genital tuberculosis are seldom done (80–82).

PCOS : PCOS is a disorder of ovarian function and is an important cause for menorrhagia, although it is more often associated with oligo/amenorrhoea. The primary pathology in PCOS is still poorly understood, but it is clearly established that in PCOS there exists unopposed hyper-oestrogenemia which causes the endometrium to outgrow its vascularity and is subsequently shed, causing menorrhagia (83) PCOS is one of the most common endocrine disorders in women but it does not have a universally accepted definition. There are many criteria which have been proposed over the years to define and diagnose PCOS.

STEIN LEVENTHAL SYNDROME (1935)(84,85)

- Amenorrhoea
- Hirsutism
- Enlarged ovaries

NATIONAL INSTITUTE OF HEALTH (NIH) CONSENSUS (1990)(86,87)

- Clinical/biochemical evidence of hyper-androgenism
- Oligo/anovulation

ROTTERDAM CONSENSUS (2003)(88)

- Any two of the three criteria
- Clinical/biochemical evidence of hyper-androgenism
- Oligo/anovulation
- Polycystic ovaries on ultrasonogram

ANDROGEN EXCESS-POLYCYSTIC OVARIAN SYNDROME (AE-PCOS) SOCIETY (2009)(89–91)

- Presence of clinical/biochemical evidence of hyper-androgenism (mandatory)
- With eitherOligo/anovulation
- And /or Polycystic ovaries on ultrasonogram

All these criteria were formulated based on adult women and cannot be applied to adolescent PCOS because of significant overlap in the diagnostic criteria and the normal physiological changes that take place in adolescence. In order to diagnose adolescent PCOS, a criteria which takes into consideration the changes that take place in healthy post-pubertal girls is needed.(92–94)

PED-C CONSENSUS (2015)(31,32)

- Unexplained combination of atleast any two of the following

- Abnormal uterine bleeding pattern
  - Abnormal for age or gynaecologic age
  - Persistent symptoms for 1-2 years
- Evidence of hyper-androgenism
  - Persistent testosterone elevation in a reliable reference laboratory is the best evidence
  - Moderate-severe hirsutism is a clinical evidence of hyper-androgenism
  - Moderate to severe inflammatory acne vulgaris
- Polycystic ovaries on ultrasonogram
  - Ovarian volume >12 ml
  - >12 follicles, 2-9mm diameter, peripherally placed

CLINICAL HYPER-ANDROGENISM

HIRSUTISM

Hirsutism is defined as abnormal, excessive, male-pattern, coarse hair growth in post-pubertal women. Hirsutism of any grade is taken as clinical evidence of hyper-androgenism in adult women. But in adolescent girls, mild hirsutism is an innocuous finding. Grading of hirsutism is done in adolescent girls by the Modified FerrimanGallwey (MFG) scoring. (95–97)

- MFG >8 – mild hirsutism
- MFG >16 – moderate hirsutism
- MFG >24 – severe hirsutism

Moderate and severe hirsutism is taken as clinical evidence of hyper-androgenism in adolescent girls as one of the diagnostic criteria of PCOS.(98)

ACNE: Acne is a dermatologic condition due by inflammation of the pilo-sebaceous unit, characterised by comedones, caused by the bacillus Propionibacterium acnes. Acne is classified into three grades by the Indian Acne Alliance (IAA) (2009) (99–101)

Table 1. IAA Classification of Acne Vulgaris in Adolescent girls

Grade	Type	Comedones	Papules	Nodules	Scarring
Mild	Comedonal	<30	<10	0	Nil
Moderate	Papular	Any number	>10	<3	±
Severe	Nodular cystic	Any number	Any number	>3	+

Only moderate and severe acne is taken as clinical evidence of hyper-androgenism in adolescent girls as a diagnostic criteria of PCOS (102)

SEBORRHOEA: It is a chronic inflammatory condition characterised by accumulation of scales of oily and greasy skin. It is one of the common cutaneous manifestations of PCOS and is used as an indicator to test for hyper-androgenism and is more of a diagnostic aid rather than a strict criteria (103–105)

ANDROGENIC ALOPECIA (AGA): Androgenic Alopecia is a non-scarring, progressive miniaturisation of the hair follicle with a usually characteristic pattern distribution, in genetically predisposed men and women. Early onset of AGA can be the presenting sign of an underlying endocrine disorder. It is seen as a diffuse, progressive thinning of the hair at the crown akin to the male pattern baldness and it significant in adolescent girls and is taken as a clinical evidence of hyper-androgenism. However, it is relatively infrequent even in biochemically proven cases of hyper-androgenism in the Indian population (106–111).

BIOCHMEICAL HYPER-ANDROGENISM: Biochemical hyper-androgenism is defined as an elevation in the serum levels of one or more androgens, that is, total testosterone (TT), free testosterone (FT), Dehydro-epi-androsterone sulphate (DHEAS) and androstenedione (ADD) (112). Clinical hyper-androgenism is a poor predictor of biochemical hyper-androgenism. There is no consensus on which androgens should be measured, when and how often they should be measured, normal androgen level cut-offs in adolescent girls and which analytical techniques should be used (113,114). The commercial assays perform well in the male range but poorly in the female range. More-often than not, clinical laboratories report normal ranges that are so broad that women with true biochemical hyper-androgenism and/or severe clinical hyper-androgenism are included and are thus undiagnosed.(115) Thus, it is recommended to measure free testosterone, in a single sample, on a morning of day 1-5 of the menstrual cycle, following at least three months furlough hormonal therapies and to develop age related reference values, from a group of women with regular cycles, no hirsutism or PCOS and work with the local laboratories to optimise normative ranges for the health region (116,117)

CLINICAL ANOVULATION: In adolescent girls, clinical evidence of anovulation is taken as oligo/amenorrhoea or heavy menstrual bleeding (32)

BOCHEMICAL EVIDENCE OF ANOVULATION: Routine testing of the hormonal assays to establish biochemical anovulation is seldom needed because unlike hyper-androgenism, clinically anovulation correlates exceedingly well with the hormonal panel.(118–122)

Table 2. Hormonal panel to diagnose anovulation in PCOS

Hormone	Upper limit- Serum level	Unit of measurement	Timing of sampling
FSH	10-25	mIU/ml	Day 3
LH	10-20	mIU/ml	Day 3
LH/FSH Ratio	2:1	-	Day 3
Oestradiol	60-90	pg/ml	Day 3
Progesterone	10-30	nmol/L	Day 21/ mid-luteal phase

OVARIAN IMAGING IN PCOS: Two-dimensional pelvic ultrasonogram is the gold standard imaging modality to diagnose PCOS. It is done in the mid-follicular phase. Even one ovary fulfilling the criteria is enough to diagnose PCOS.If there is evidence of corpus luteum or dominant follicle then the scan should be repeated in the next cycle (123).

OVARIAN VOLUME: Ovarian volume is calculated with the simplified formula for an ellipsoid (0.5 X length X width X thickness). There is a physiological enlargement of the ovaries in adolescence and hence the adult cut-off of 10ml is unsuitable for post-pubertal girls. The cut-off of 12ml ensures minimal false positive rates (124–126). The presence of a dominant follicle or a corpus luteum may increase the ovarian volume by >12ml.A dominant follicle is defined as a follicle whose longitudinal, transverse and anteroposterior diameters average more than 10mm. such a finding should prompt a repeat ultrasonogram in the next cycle for a more accurate assessment of ovarian volume.(127,128)

CENTRAL STROMAL BRIGHTNESS: Central stromal brightness is due to stromal hypertrophy and is caused by the prolonged, unopposed, excessive oestrogen in PCOS. The normal echogenicity of the stroma is simil ar to that of the myometrium and if it is hyper-intense than the myometrium, then it is indicative of stromal thickening (129,130)

STROMAL THICKNESS: Ovarian stromal hypertrophy measured as increased stromal thickness is a frequent and specific feature of hyper-androgenism. It correlates well with ovarian androgenic dysfunction. Ironically, it is not always associated with elevated LH levels (131).

POLYCYSTIC OVARIES (PCO) VERSUS MULTI-FOLLICULAR OVARIES (MFO): MFO mimics PCO and must be carefully differentiated from PCO as the fundamental patho-physiology is completely different for both the conditions (131,132)

Table 3. Polycystic Ovaries (PCO) versus Multi-Follicular Ovaries (MFO)

Parameter	**PCO**	**MFO**
Ovarian volume	>12 ml	<12 ml
Number of follicles	>12	≤6
Diameter of cysts	2-9 mm	4-10 mm
Ovarian Stroma	Hypertrophied	Normal
Hirsutism	Present/absent	Absent
Serum LH	Increased	Normal
Serum FSH	Increased	Decreased
Uterine size	Normal/enlarged	Small
BMI	Obese	Underweight
Response to gonadotrophin	40%	80%
Morphology in ovulatory cycles	Does not revert to normal	Reverts to normal

STROMAL/AREA (S/A) RATIO: An S/A ratio of more than 0.3 is indicative of stromal hypertrophy and directly correlates with hyper-androgenism. The ovarian stromal area is evaluated by outlining with the calliper, the peripheral profile of the stroma which is identified by the central hyper-echoic area. It has the distinct advantage of a very low inter-observer variation. It is easily reproducible and highly reliable and should be a part of the general routine diagnostic approach to PCOS (133).

UTERINE ARTERY DOPPLER: Colour Doppler studies have shown that the blood flow in uterine arteries is reduced because of the higher resistance index in cases of PCOS. The increase in the resistance correlates with obesity, insulin resistance and hyper-androgenism. (134–137)

INTRA-OVARIAN DOPPLER: The blood flow pattern of an organ directly reflects its morphology and functioning. In PCOS, intra-ovarian blood flow is mostly limited to the thickened hyper-echoic stroma. It is found that the ovarian blood flow is increased as evident by the decrease in the resistance index of the intra-ovarian blood flow. This is associated to the angiogenic effect of the unopposed oestrogen seen in PCOS (138–140).

LATERALITY OF PCOS: Even one ovary fulfilling the criteria is enough to diagnose PCOS. Unilateral PCOS amounts to nearly one-third of the total PCOS which is diagnosed. However, there is no difference in the long-term reproductive and metabolic health of girls with unilateral and bilateral PCOS (141).

ENDOMETRIAL THICKNESS: Uterine artery and sub-endometrial blood flow are impaired in PCOS. The unopposed oestrogen causes thickening of the fragile endometrium which outgrows its vascularity as it is not kept in check by the cyclical production of progesterone from the ovary that normally follows ovulation. The endometrium is considerably thicker in girls with PCOS as compared to healthy controls. This is significant because a thickened endometrium is associated with future risk of endometrial hyperplasia and endometrial carcinoma (142–145).

ANTHROPOMETRIC INDICATORS

BODY WEIGHT is the simplest method of assessment of cardio-metabolic risk, but it must be standardised to the study population and is rarely used as an independent anthropometric indicator to predict adverse cardio-metabolic outcomes in adolescent girls (146,147)

BODY MASS INDEX is the next anthropometric indicator which is commonly used for assessment of cardio-metabolic risk in PCOS. However, it has a lower negative predictive value than the other indices. Moreover, the standards of BMI used in adults cannot be extrapolated to the adolescent population (148,149)

In adolescent girls the cut-off for BMI to be followed is:

- <18.5 kg/m^2 –Underweight
- 19 to 22.5 kg/m^2 - Normal
- 23 to 26.5kg/m^2 – Overweight
- >27 – Obese

WAIST CIRCUMFERENCE (WC) is increased in girls with PCOS and is a marker for the risk of developing metabolic syndrome in the future. Even in the non-obese PCOS girls, there is increased deposition of excessive visceral adipose tissue around the abdomen. A waist circumference of 80cm is taken as the cut-off (150–152).

WAIST TO HIP RATIO (WHR) is a better indicator of the risk of metabolic syndrome and values of >0.85 is considered as a definitive risk in cases of PCOS (153–156).

WAIST TO HEIGHT RATIO (WHtR) is another novel anthropometric indicator and predicts the cardio-metabolic risk in cases of PCOS. The normal values are usually <0.8 but according to the NIH, a cut-off of >1 is indicative of a higher than normal risk of developing heart disease.(157–159).

VISCERAL ADIPOSITY INDEX (VAI) is an empirical, mathematical model that is gender-specific and is based on anthropometric measurements like BMI, waist circumference and biochemical proportions of the lipid profile. (160–162)

VAI = (Waist circumference/ {36.58 + [1.86*BMI]}) * (TG/0.81) * (1.52/HDL)

A cut-off of 1.675 makes it possible to differentiate metabolically unhealthy PCOS (MU-PCOS) from the metabolically healthy PCOS (MH-PCOS). It is a simple and effective method for the evaluation of cardio-metabolic risk and can be used in everyday medical practice and in population studies (163,164)

BIOCHEMICAL PARAMETERS TO PREDICT THE CARDIO-METABOLIC RISK: There are many biochemical investigations that are useful in predicting the future cardio-metabolic risk in adolescent girls with PCOS such as renal function tests, liver function tests, fasting lipid profile and 75grams glucose tolerance test (165).

SOCIO-ECONOMIC CLASS (SEC): SEC is stratified based on the Modified Kuppuswamy Classification 2019 and it has been showed that low SEC is associated with PCOS. (166–169)

Table 4. Parameters scored in Modified Kuppuswamy SEC 2019

Education of the head of the family	Score	Occupation of the head of the family	Score	Total per capita income per month in rupees	Score
Professional degree	7	Legislators, senior officials & managers	10	>78,063	12
Graduate	6	Professionals	9	39,033 to 78,062	10
Intermediate/Diploma	5	Technicians &Associate professionals	8	29,200 to 39,032	6
High school	4	Clerks	7	19,516 to 29,199	4
Middle school	3	Skilled, shop & market workers	6	11,708 to 19,515	3
Primary school	2	Skilled agricultural & fishery workers	5	3,908 to 11,707	2
Illiterate	1	Craft & related trade workers	4	≤3907	1
		Plant & machine operators & assemblers	3		
		Elementary occupation	2		
		Unemployed	1		

Table 5. SEC and the Modified Kuppuswamy classification 2019

SEC No.	Score	SEC
I	26 – 29	Upper
II	16 – 25	Upper middle
III	11 – 15	Lower middle
IV	5 – 10	Upper lower
V	<5	Lower

INCIDENCE OF PCOS IN PUBERTY MENORRHAGIA IN LITERATURE: There are many studies done across the globe, to establish the cause of puberty menorrhagia and it has been shown that adolescent PCOS is one of the important causes.

Table 6. Proportion of PCOS in Puberty Menorrhagia in other studies

Study	Proportion of PCOS causing Puberty menorrhagia (%)	Sample size
Shantisri et al. (77)	20.8%	48
Shika Joshi et al. (170)	14%	50
SujathaDeo et al. (74)	9.8%	51
SaimaGillani et al. (171)	8.6%	26
SayaniDouli et al. (172)	6.15%	65
Joydeb Chowdhury et al. (173)	3.07%	65
PrakritiGoswami et al. (174)	0%	25
Khosla et al. (6)	0%	18
ArchanaD.Rathod et al. (175)	0%	17

LACUNAE IN EXISTING LITERATURE

- Criteria used to diagnose PCOS causing puberty menorrhagia has not been mentioned in most of the studies.
- In the studies which do mention the specific methodology, adult criteria wereused to diagnose adolescent PCOS in Puberty menorrhagia.
- Concerns of the diagnostic conundrum in diagnosing adolescent PCOS has not been addressed in any of the studies.
- Wide variation has been observed in the incidence of PCOS among existing studies due to lack of uniform diagnostic criteria.
- Studies analysing the South Indian population of adolescent girls, with heavy menstrual bleeding and the proportion of PCOS in them, have been sparse.

MATERIALS AND METHODS

STUDY AREA: Outpatient and In-patient department of Obstetrics and Gynaecology in RGGWCH – PUDUCHERRY.

STUDY POPULATION: Adolescent girls (Post-pubertal to 19 years) presenting with menorrhagia to the OPD/IP fulfilling the inclusion criteria were included in the study after obtaining informed, written and valid consent.

STUDY DESIGN: Longitudinal- prospective study.

STUDY PERIOD: January 2018 – May 2019.

SAMPLE SIZE:90

SAMPLE SIZE CALCULATION:

Table 7. Sample size calculation

Population Size	65
Anticipated frequency	10
Confidence limits	5.0
Design effect	1.0
Calculated sample size	90

Calculated using openEpi software with the data from the reference study by SayaniDouli et al (172)

INCLUSION CRITERIA

- Adolescent girls with heavy menstrual bleeding
- Post pubertal to 19 years

EXCLUSION CRITERIA

- >20 years
- Known cases of bleeding diathesis and endocrinopathies
- Not willing for follow up or not available throughout the study period

METHODOLOGY

- The adolescent girls presenting with heavy menstrual bleeding fulfilling the inclusion criteria were selected after obtaining informed, written and valid consent.
- Detailed history was obtained including the presenting complaints, date of the last menstrual period, age of menarche, duration and amount of flow, regularity of the cycles and any other associated complaints.
- Specific History of acne, excessive hair growth, male pattern of hair loss, excessive weight gain was obtained.
- Based on the modified Philip's Screening tool and the presence of anaemia, the complaint of menorrhagia was verified.
- Anthropometric indicators and vital signs were measured and the general physical examination, examination of the abdomen, per vaginal examination in married/sexually active adolescent girls was done.
- The following investigations were sent:
- Complete haemogram
- Free T3, free T4, TSH
- 75 grams OGTT
- Fasting lipid profile
- Renal function tests
- Liver function tests
- Ultrasonogramof the abdomen and pelvis - TAS
- Polycystic ovarian syndrome was diagnosed using the Ped-C consensus
- Any 2 of the 3 criteria
- Oligo/anovulation (clinical or biochemical evidence)
- Hyper-androgenism (clinical or biochemical evidence)
- Polycystic ovaries on imaging

OPERATIONAL DEFINITIONS

- Clinical evidence of anovulation
  - Oligomenorrhoea
  - Amenorrhea
  - Excessive Abnormal uterine bleeding
- Clinical evidence of hyper-androgenism
  - Moderate to severe acne
- Quantified according to the IAA consensus (2009)
- Moderate acne - >10 papules, <3 nodules
- Severe acne – any number of papules, >3 nodules/cysts
  - Moderate to severe Hirsutism
- Modified FerrimanGallwey scoring system was be used
- MFG>16 - Moderate hirsutism
- MFG >24 – Severe hirsutism
  - Male pattern hair loss
- Androgenic alopecia
- Polycystic ovaries on imaging
  - Two-dimensionalultrasonogram of the abdomen and pelvis was usedas the imaging modality
  - Trans-abdominal route
  - Done in the mid follicular phase
  - One or both ovaries demonstrate 12 or more follicles
  - Measuring 2-9mm diameter
  - Ovarian volume of more than 12ml
  - Peripheral distribution of follicles
  - Central stromal brightness
  - Stromal/Total area ratio > 0.3
  - Only one ovary meeting the criteria was consideredenough to establish the presence of polycystic ovaries
  - If there was evidence of corpus luteum or dominant follicle then the scan was repeated in the next cycle
  - Endometrial thickness
  - Uterine and intra-ovarian doppler

OPERATIONAL DEFINITIONS

Table 8. Reference values for the tests performed in the present study

PARAMETER	BIOCHEMICAL TEST	NORMAL VALUE	UNIT OF MEASUREMENT
Blood pressure(176,177)		≤120/80	mmHg
Coagulation profile(178)	Prothrombin time	<13.5	Seconds
	Activated partial thromboplastin time	<40	Seconds
	International normalised ratio	<1.3	
Renal function tests (179)	Blood urea	<20	mg/dl
	Serum creatinine	<1.3	mg/dl
Liver function tests(165)	Serum bilirubin	<1	mg/dl
	Alanine transaminase	<40	U/L
	Aspartate transaminase	<56	U/L
Fasting lipid profile(180)	Total cholesterol	<170	mg/dl
	HDL	>45	mg/dl
	LDL	<110	mg/dl
	Triglycerides	<90	mg/dl
75 grams oral Glucose(180) tolerance test	Fasting blood sugar	<95	mg/dl
	1 hour	<180	mg/dl
	2 hours	<140	mg/dl
Thyroid function tests (181)	Thyroid stimulating hormone (TSH)	<5	µIU/ml
	Free T3	<480	pg/dl
	Free T4	<1.53	ng/dl

METHOD OF STATISTICAL ANALYSIS

- Data was entered in Microsoft excel data sheet
- Analysed in SPSS software 2019
- Presented in the form of descriptive and inferential statistics
- Descriptive statistics were expressed in the form of appropriate frequencies, percentages, measures of central tendencies and dispersion.

RESULTS

AGE DISTRIBUTION OF THE STUDY POPULATION

The mean age of the study population was 14.95 years.

Table 9. Age distribution of study population (n=90)

AGE (years)	FREQUENCY	PERCENTAGE
13	26	28.89%
14	18	20.00%
15	15	16.67%
16	10	11.11%
17	7	7.78%
18	14	15.56%

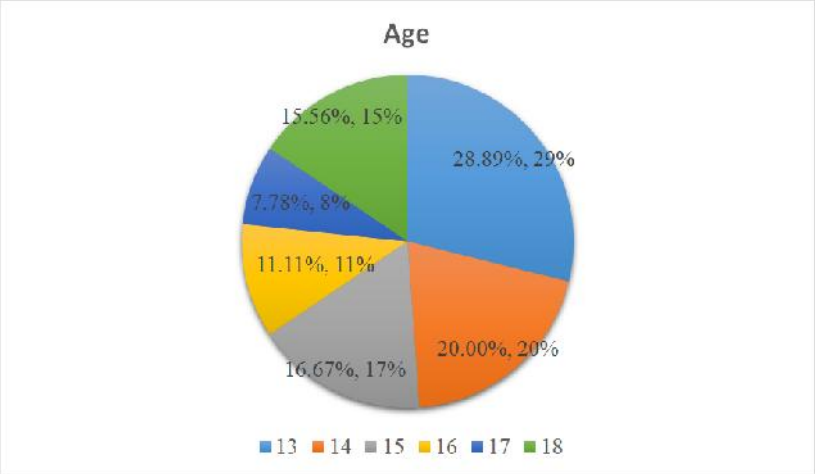

Figure 1 - Age distribution of the study population (n=90

VERIFIED MENORRHAGIA USING THE MODIFIED PHILIP'S SCREENING TOOL AND THE PRESENCE OF ANAEMIA

Based on the modified Philip's Screening tool and the presence of anaemia, 100% (n=90) of the study population with complaint of menorrhagia was objectively found to have verified menorrhagia.

There was no case of refuted menorrhagia in the study population.

Table 10. Modified Philip's Screening tool and Verified Menorrhagia (n=90)

Modified Philip's Screening tool Question	Yes n (%)	No n (%)
Cycle length >7 days	90 (100%)	0 (0%)
Flooding/Gushing	74 (82.22%)	16 (17.78%)
Pad/tampon change Q2H	51 (56.67%)	39 (43.33%)
Waking at night	41 (45.56%)	49 (54.44%)
H/o treatment for anaemia	61 (67.78%)	29 (32.22%)
Limitation of Routine activity	69 (76.67%)	21 (22.33%)

Anaemia (Haemoglobin <12g/dl) was prevalent in 100% (n=90) of the study population.

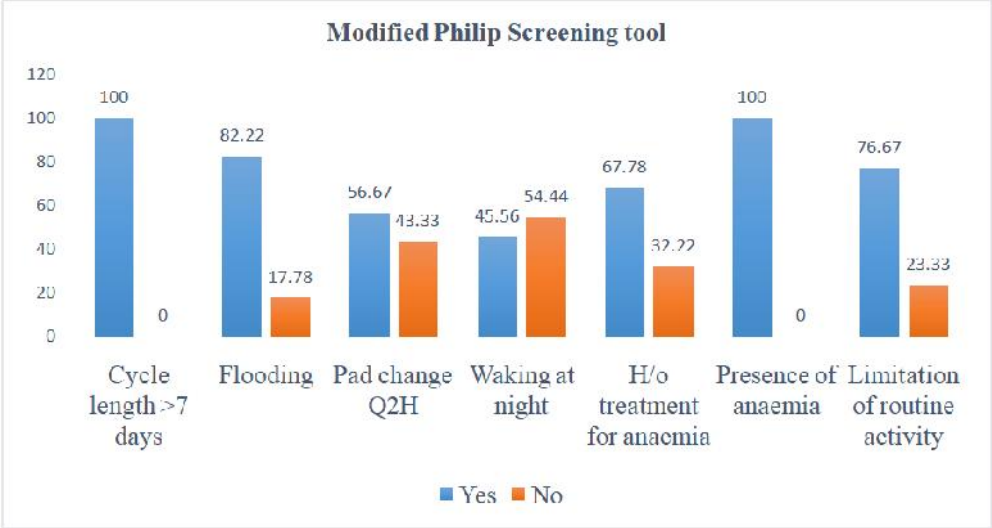

Figure 2. Modified Philip Screening tool and Verified Menorrhagia (n=90)

CLINICAL EVIDENCE OF HYPER-ANDROGENISM IN THE STUDY POPULATION

There was no clinical evidence of hyper-androgenism in the study population. (n=90)

Table 11 - Clinical Hyper-androgenism in the study population (n=90)

CLINICAL HYPER-ANDROGENISM	FREQUENCY
Moderate/severe Acne	0
Seborrhoea	0
Alopecia	0
Hirsutism – MFG>16	0

DISTRIBUTION OF ANTHROPOMETRIC INDICES IN THE STUDY POPULATION

It was observed that 100% (n=90) of the study population had normal anthropometric indicators and did not have any higher risk of cardio-metabolic complications irrespective of the presence or absence of PCOS.

Table 12. Distribution of Anthropometric Indices in the study population (N=90)

Anthropometric index	Normal n (%)	Abnormal n (%)
BMI <23 kg/m^2	90 (100%)	0 (0%)
Waist circumference <80cm	90 (100%)	0 (0%)
WHR<0.85	90 (100%)	0 (0%)
WHtR<1	90 (100%)	0 (0%)
VAI<1.675	90 (100%)	0 (0%)

DISTRIBUTION OF METABOLIC PARAMETERS IN THE STUDY POPULATION (N=90)

It was observed that 100% (n=90) of the study population had normal metabolic parameters and did not have any higher risk of cardio-metabolic complications irrespective of the presence or absence of PCOS. It was also observed that 100% (n=90) of the study population was euthyroid.

Table 13. Distribution of metabolic parameters in the study population (n=90)

Parameter	Normal n (%)	Abnormal n (%)
Blood pressure	90 (100%)	0 (0%)
Coagulation profile	90 (100%)	0 (0%)
Blood urea	90 (100%)	0 (0%)
Serum creatinine	90 (100%)	0 (0%)
Serum bilirubin	90 (100%)	0 (0%)
Liver enzymes	90 (100%)	0 (0%)
75 grams Glucose tolerance test	90 (100%)	0 (0%)
Fasting lipid profile	90 (100%)	0 (0%)
Thyroid function test	90 (100%)	0 (0%)

PROPORTION OF PCOS IN PUBERTY MENORRHAGIA USING THE MODIFIED PED-C CONSENSUS

The proportion of PCOS in adolescent girls presenting with heavy menstrual bleeding was 12.22% (n=11)

Table 14. Proportion of PCOS in Puberty Menorrhagia using the Modified Ped-C consensus

Criteria	Yes n (%)	No n (%)
Clinical anovulation	90 (100%)	0(0%)
Clinical hyper-androgenism	0 (0%)	90 (100%)
Polycystic ovaries in ultrasonogram	11 (12.22%)	79 (87.78%)
PCOS in Puberty menorrhagia	11 (12.22%)	79 (87.78%)

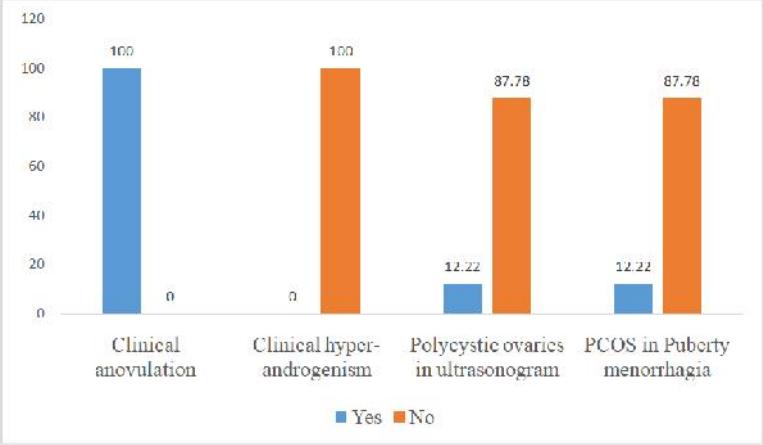

Figure 3 - Proportion of PCOS in Puberty Menorrhagia using the Modified Ped-C consensus

AGE DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean age of girls with menorrhagia and diagnosed to have PCOS was 17.18 years.The mean age of girls with menorrhagia but without PCOS was 14.65 years.The difference was statistically significant (p- 0.0198).

Table 15. Age distribution in PCOS versus Non-PCOS Menorrhagia

Age (years)	PCOS n (%)	Non-PCOS n (%)
12	0 (0%)	0 (0%)
13	26 (33%)	0 (0%)
14	18 (23%)	0 (0%)
15	13 (16%)	2 (18%)
16	10 (13%)	0 (0%)
17	4 (5%)	3 (27%)
18	8 (10%)	6 (55%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.0198

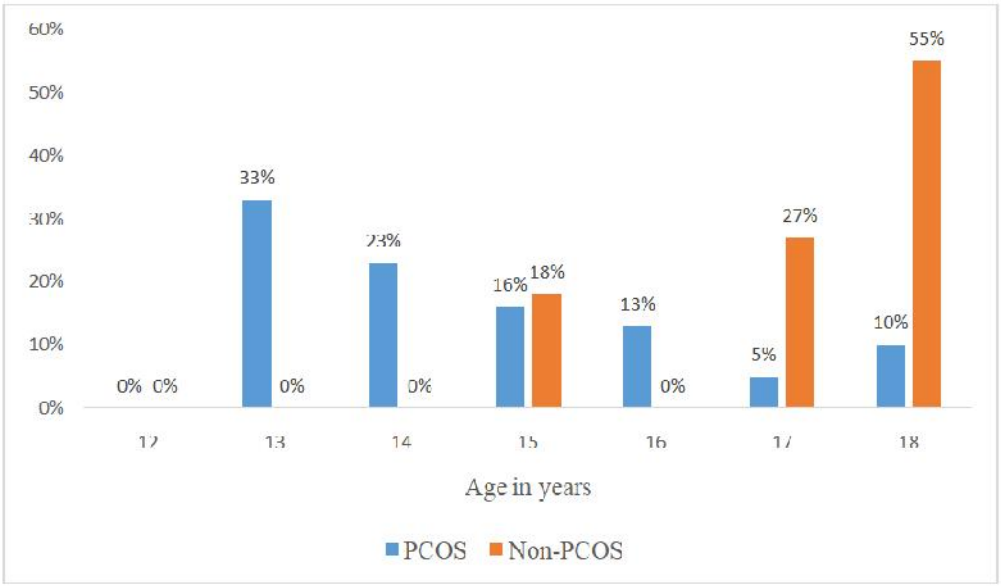

Figure 4. Age distribution in PCOS versus Non-PCOS Menorrhagia

SOCIO-ECONOMIC CLASS IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean socio-economic class of both the PCOS and the Non-PCOS menorrhagia was Lower middle class (III).There was no statistically significant difference (p – 0.087)

Table 16. Socio-Economic Class in PCOS versus Non-PCOS Menorrhagia

Socio-economic Class	PCOS n (%)	Non-PCOS n (%)
Upper (I)	0 (0%)	0 (0%)
Upper Middle (II)	6 (8%)	0 (0%)
Lower Middle (III)	52 (65%)	5 (45%)
Upper Lower (IV)	18 (23%)	6 (55%)
Lower (V)	3 (4%)	0 (0%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.087

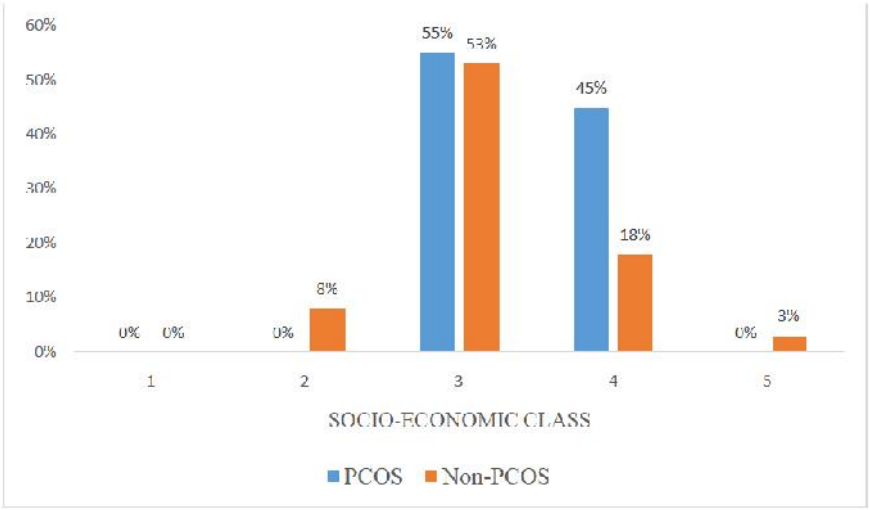

Figure 5. Socio-Economic Class in PCOS versus Non-PCOS Menorrhagia

AGE OF MENARCHE AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA: The mean age of menarche for girls with menorrhagia, diagnosed to have PCOS was 11.3 years.The mean age of menarche for girls with menorrhagia but without PCOS was 12.54 years.The difference was statistically significant (p – 0.026)

Table 17. Age of Menarche and its Distribution in PCOS versus Non-PCOS Menorrhagia

Age of menarche (years)	PCOS n (%)	Non-PCOS n (%)
11	6 (55%)	11 (14%)
12	4 (36%)	29 (37%)
13	1 (9%)	39 (49%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.026

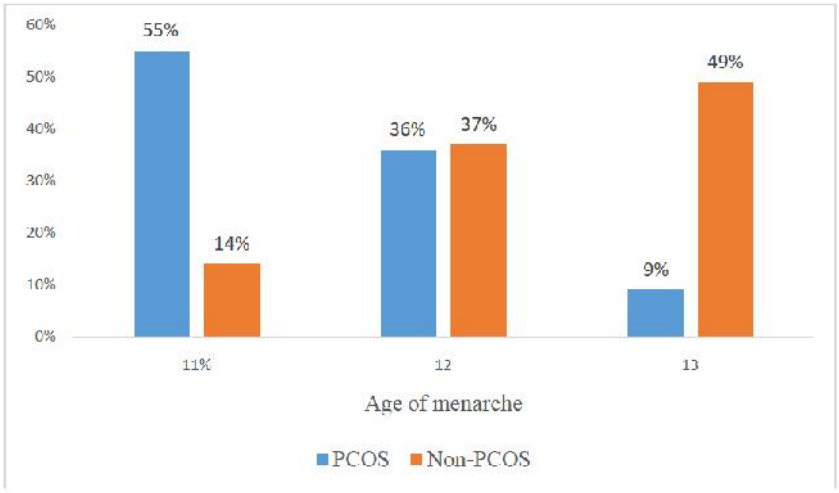

Figure 6. Age of Menarche and its Distribution in PCOS versus Non-PCOS Menorrhagia

FREQUENCY OF MENSTRUAL CYCLES AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean frequency of menstrual cycles in girls with menorrhagia, diagnosed to have PCOS was 34.09 days.The mean frequency of menstrual cycles in girls with menorrhagia but without PCOS was46.54 days.The difference was significant statistically (p – 0.043)

Table 18. Frequency of Menstrual cycles and its distribution in PCOS versus Non-PCOS Menorrhagia

Frequency of Menstrual cycles (days)	PCOS n (%)	Non-PCOS n (%)
30	8 (73%)	20 (25%)
45	3 (27%)	37 (47%)
60	0 (0%)	19 (24%)
90	0 (0%)	3 (4%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.043

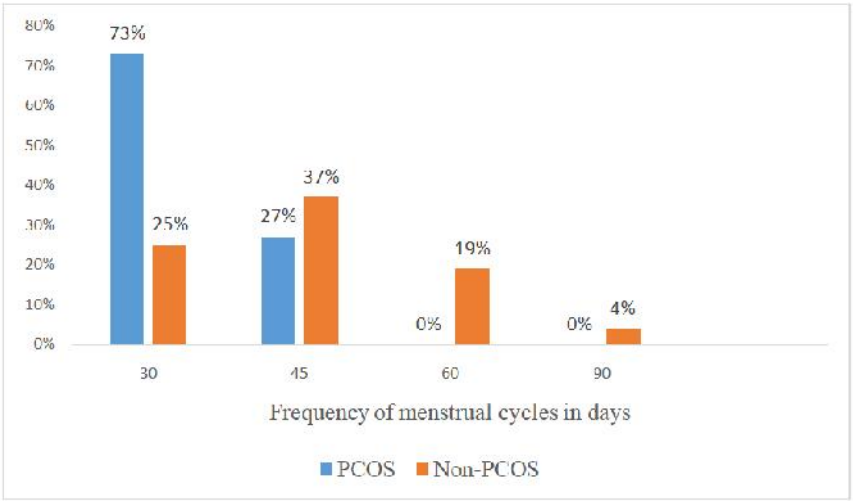

Figure 7. Frequency of Menstrual cycles and its distribution in PCOS versus Non-PCOS Menorrhagia

DURATION SINCE MENARCHE AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean duration since menarche to the time of presentation with menorrhagia, in girls with PCOS was 5.2 years.The mean duration since menarche to the time of presentation with menorrhagia in girls without PCOS was 2.47 years.The difference was statistically significant (p – 0.014)

Table 19. Duration since Menarche and its distribution in PCOS versus Non-PCOS Menorrhagia

Duration since menarche (In years)	PCOS n (%)	Non-PCOS n (%)
0.25	0(0%)	7 (9%)
0.5	0 (0%)	3 (4%)
1	0 (0%)	15 (19%)
2	0 (0%)	22 (28%)
3	0 (0%)	13 (16%)
4	3 (27%)	5 (6%)
5	5 (46%)	10 (13%)
6	3 (27%)	4 (5%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.014

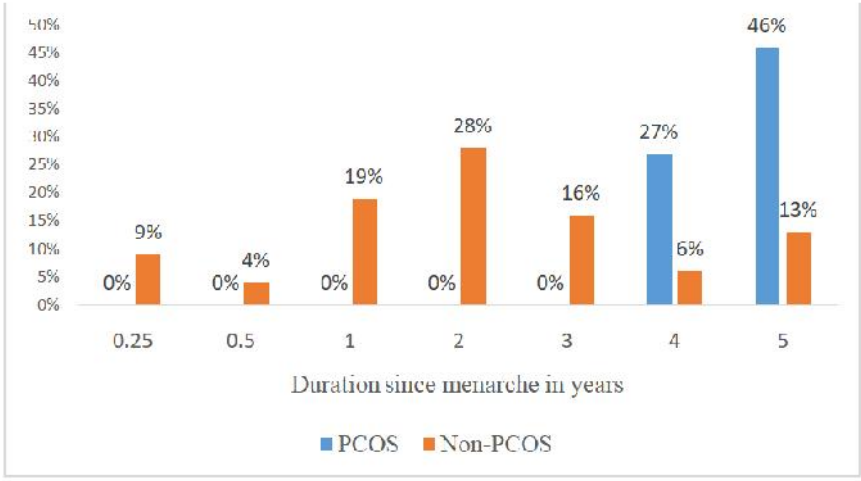

Figure 8. Duration since Menarche and its distribution in PCOS versus Non-PCOS Menorrhagia

DURATION OF MENORRHAGIA AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS ADOLESCENT GIRLS

The mean duration of menorrhagia at the time of presentation in girls diagnosed to have PCOS was 8.27 months.The mean duration of menorrhagia at the time of presentation in girls without PCOS was 3.81 months.The difference was statistically significant (p – 0.031)

Table 20. Duration of Menorrhagia and its distribution in PCOS versus Non-PCOS adolescent girls

Duration of menorrhagia (in months)	PCOS n (%)	Non-PCOS n (%)
1-3	0 (0%)	48 (60%)
4-6	3 (28%)	29 (37%)
7-9	4 (36%)	2 (3%)
10-12	4 (36%)	0 (0%)
>12	0 (0%)	0 (0%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.031

Table 21. Body Mass Index and its distribution in PCOS versus Non-PCOS Menorrhagia

BMI (kg/m^2)	PCOS n (%)	Non-PCOS n (%)
<18.5	5 (45%)	51 (65%)
19-22.5	6 (55%)	28 (35%)
23-26.5	0 (0%)	0 (0%)
>27	0 (0%)	0 (0%)

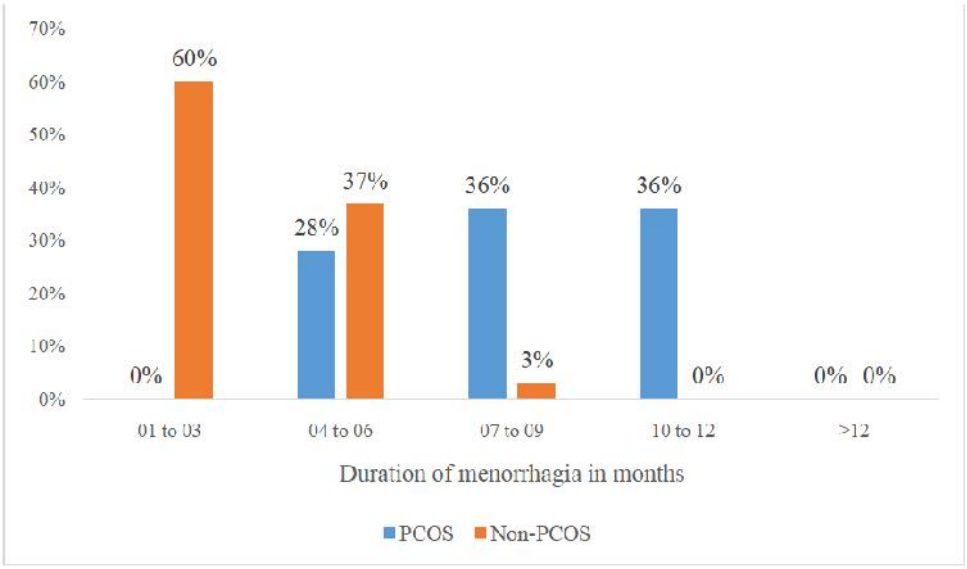

Figure 9 - Duration of Menorrhagia and its distribution in PCOS versus Non-PCOS adolescent girls

BODY MASS INDEX AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean Body mass index of the girls with menorrhagia, who were diagnosed with PCOS was 19.The mean Body Mass Index of the girls with menorrhagia but without PCOS was 17.86. The difference was not of statistical significance (p – 0.13)
Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.13

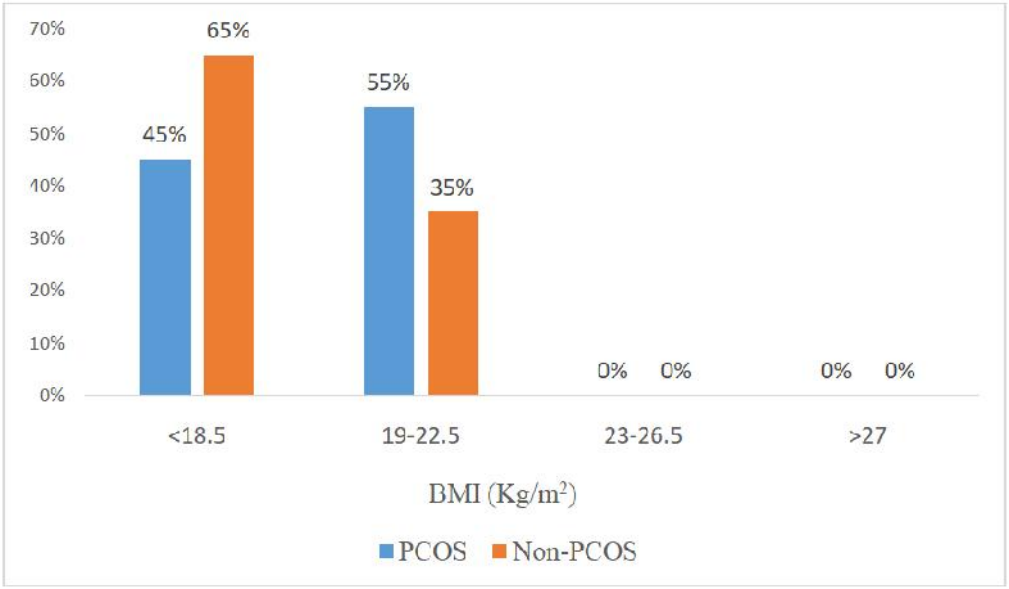

Figure 10. Body Mass Index and its distribution in PCOS versus Non-PCOS Menorrhagia

SEVERITY OF ANAEMIA AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean haemoglobin in girls with menorrhagia, who were diagnosed to have PCOS was 9.53 g/dl. The mean haemoglobin in girls with menorrhagia but without PCOS was 8.72 g/dl.The difference was not statistically significant (p – 0.019)

Table 22. Severity of Anaemia and its distribution in PCOS versus Non-PCOS Menorrhagia

Haemoglobin (g/dl)	Severity	PCOS n (%)	Non-PCOS n (%)
<7	Severe	0 (0%)	17 (22%)
7-9.9	Moderate	7 (64%)	46 (58%)
10-11.9	Mild	4 (36%)	16 (20%)
≥12	Normal	0 (0%)	0 (0%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.019.

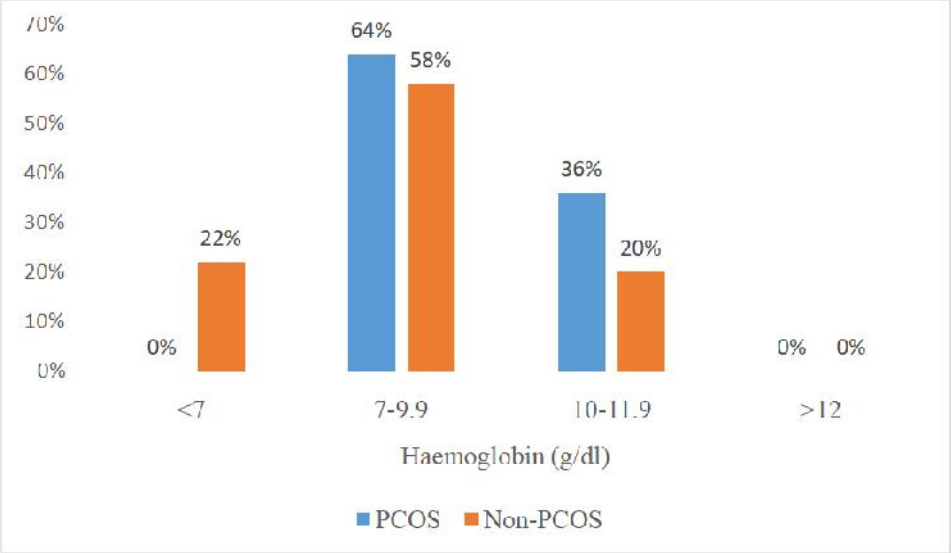

Figure 11. Severity of Anaemia and its distribution in PCOS versus Non-PCOS Menorrhagia

ANTRAL FOLLICULAR COUNT AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA

The mean antral follicular count in the right ovary of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 15.09 and that of the left ovary was 12.73. Thus, the mean AFC in girls PCOS was 13.91.The mean antral follicular count in the right ovary of the girls with menorrhagia but without PCOS (n=79) was 5.63 and that of the left ovary was 5.84. Thus, the mean AFC of girls without PCOS was 5.74.

Table 23. Antral follicular count and its distribution in PCOS versus Non-PCOS Menorrhagia

AFC	PCOS (n=11)	Non-PCOS (n=79)
Right Ovary	15.09	5.63
Left Ovary	12.73	8.84
Mean	13.91	5.74

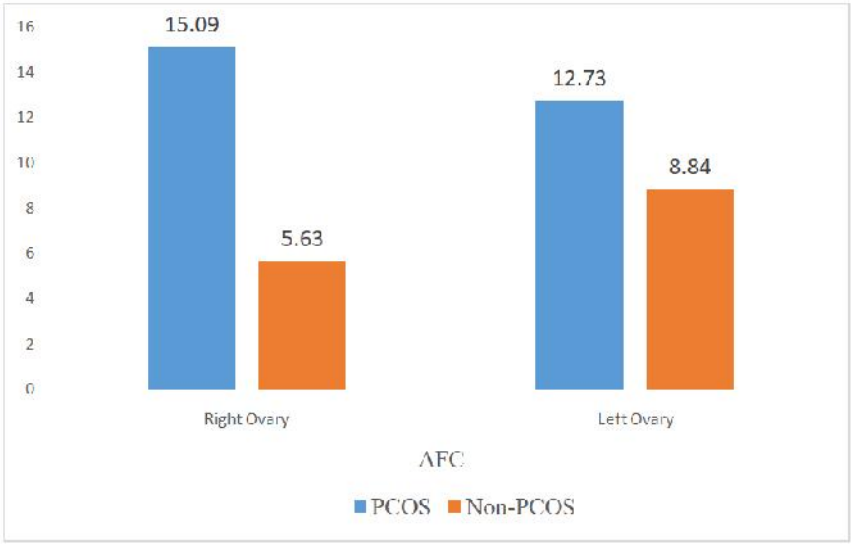

Figure 12- Antral follicular count and its distribution in PCOS versus Non-PCOS Menorrhagia

OVARIAN VOLUME AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA: In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right ovarian volume was 14.62ml and the mean left ovarian volume was 12.03ml. Thus, the mean ovarian volume in girls with PCOS was 13.33ml.In the girls with menorrhagia but without PCOS (n=79), the mean right ovarian volume was 5.83ml and the mean left ovarian volume was 6.31ml. Thus, the mean ovarian volume in girls without PCOS was 6.07ml.

Table 24. Ovarian Volume and its distribution in PCOS versus Non-PCOS menorrhagia

Ovarian Volume	PCOS (n=11)	Non-PCOS (n=79)
Right Ovary (ml)	14.62	5.83
Left Ovary (ml)	12.03	6.31
Mean (ml)	13.33	6.07

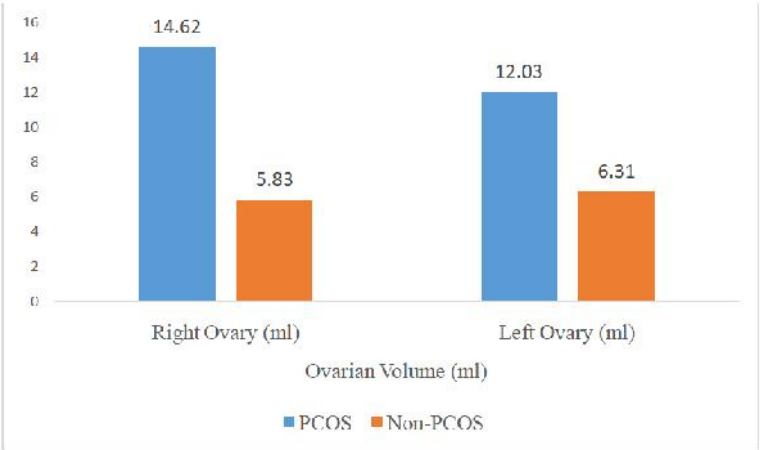

Figure 13. Ovarian Volume and its distribution in PCOS versus Non-PCOS menorrhagia

STROMAL THICKNESS AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA;In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right ovarian stromal thickness was 10.73mm and the mean left ovarian stromal thickness was 9.0mm. Thus, the mean ovarian stromal thickness of girls with PCOS was 9.87mm.In the girls with menorrhagia but without PCOS (n=79), the mean right ovarian stromal thickness was 4.20mm and the mean left ovarian stromal thickness was 4.28mm. Thus, the mean ovarian stromal thickness of girls with PCOS was 4.24mm.

Table 25 - Stromal thickness and its distribution in PCOS versus Non-PCOS menorrhagia

Stromal Thickness	PCOS (n=11)	Non-PCOS (n=79)
Right Ovary (mm)	10.73	4.20
Left Ovary (mm)	9.0	4.28
Mean (mm)	9.87	4.24

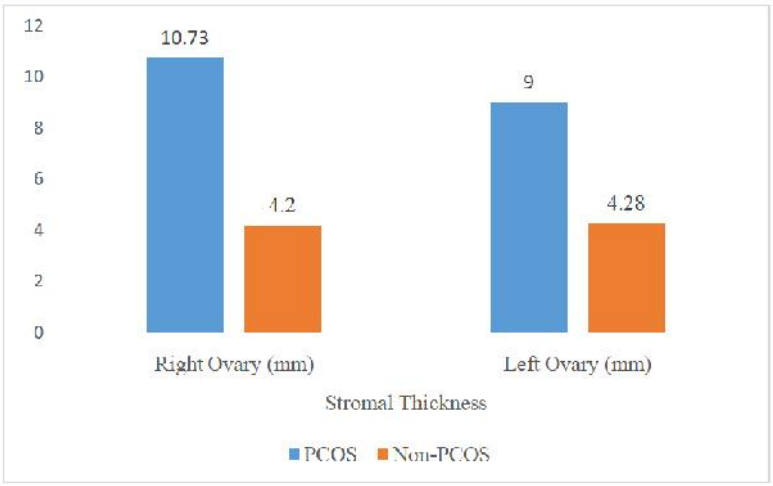

Figure 14. Stromal thickness and its distribution in PCOS versus Non-PCOS menorrhagia

STROMAL/AREA RATIO AND ITS DISTRIBUTION IN PCOS VERSUS NON PCOS MENORRHAGIA: In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right ovarian S/A ratio was 0.44 and the mean left ovarian S/A ratio was 0.36. Thus, the mean ovarian S/A ratio of girls with PCOS was 0.40. In the girls with menorrhagia but without PCOS (n=79), the mean S/A ratio was 0.15 in both the ovaries. Thus, the mean ovarian S/A ratio of girls without PCOS was 0.15.

Table 26. Stromal/Area ratio and its distribution in PCOS versus Non-PCOS menorrhagia

S/A Ratio	PCOS (n=11)	Non-PCOS (n=79)
Right Ovary	0.44	0.15
Left Ovary	0.36	0.15
Mean	0.40	0.15

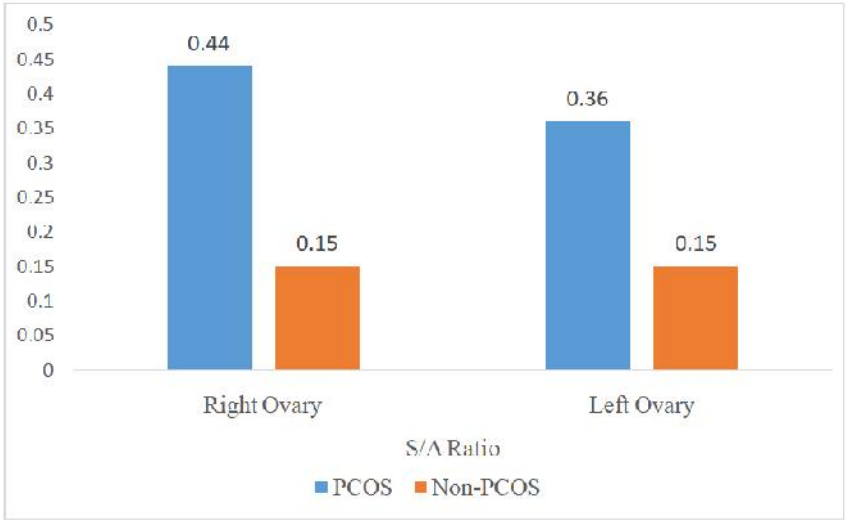

Figure 15. Stromal/Area ratio and its distribution in PCOS versus Non-PCOS menorrhagia

ENDOMETRIAL THICKNESS AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA: The mean endometrial thickness in girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 9mm.The mean endometrial thickness in girls with menorrhagia but without PCOS (n=79) was 6.15mm.The difference was statistically significant (p – 0.025)

Table 27. Endometrial thickness and its distribution in PCOS versus Non-PCOS menorrhagia

Endometrial Thickness (mm)	PCOS n (%)	Non-PCOS n (%)
<5	0 (0%)	20 (25%)
5-10	6 (55%)	54 (69%)
>10	5 (45%)	5 (6%)

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.025

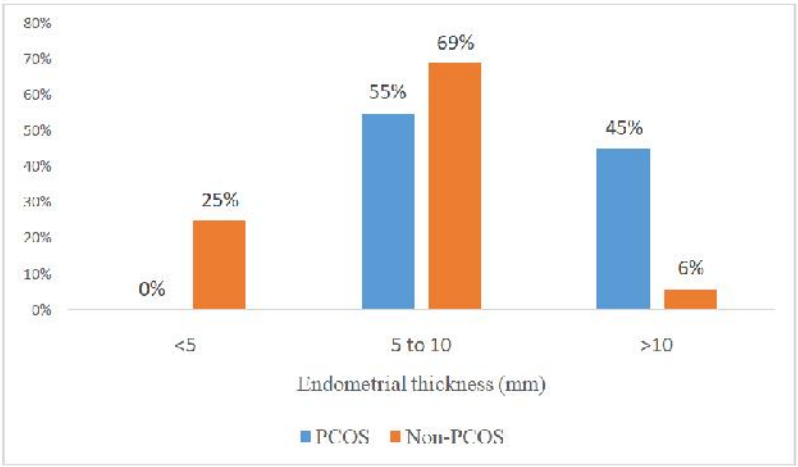

Figure 16. Endometrial thickness and its distribution in PCOS versus Non-PCOS menorrhagia

UTERINE ARTERY DOPPLER INDICES AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA: In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right uterine artery PI/RI was 3.40/1 and the mean left uterine artery PI/RI was 3.44/1. Thus, the mean uterine artery PI/RI in girls with PCOS was 3.42/1.In the girls with menorrhagia but without PCOS (n=79), the mean right uterine artery PI/RI was 2.58/0.77 and the mean left uterine artery PI/RI was 2.60/0.78. Thus, the mean uterine artery PI/RI in girls with PCOS was 2.59/0.78.The difference was statistically significant (p – 0.018)

Table 28 - Uterine artery doppler and its distribution in PCOS versus Non-PCOS menorrhagia

Uterine artery Doppler	PCOS (n=11)	Non-PCOS (n=79)
Right uterine artery PI	3.40	2.58
Right Uterine artery RI	1	0.77
Left Uterineartery PI	3.44	2.60
Left Uterine artery RI	1	0.78
Mean Uterine artery PI/RI	3.42/1	2.59/0.78

Chi Square test was applied to test statistical difference in proportions and the p-value was found to be 0.018

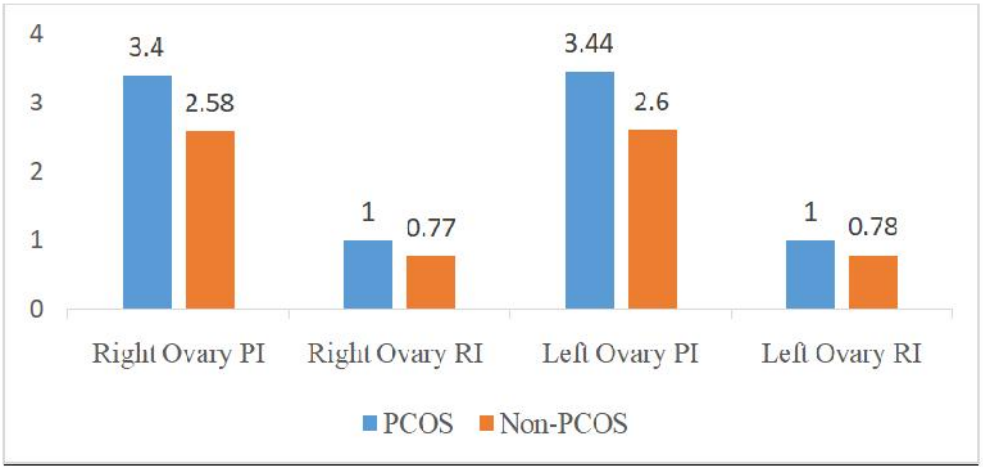

Figure 17. Uterine artery doppler and its distribution in PCOS versus Non-PCOS menorrhagia

INTRA-OVARIAN DOPPLER AND ITS DISTRIBUTION IN PCOS VERSUS NON-PCOS MENORRHAGIA: In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean Intra-ovarian PI/RI was 0.9/0.5 in both the ovaries.In the girls with menorrhagia but without PCOS (n=79), the mean right Intra-ovarian PI/RI was 1.28/0.71 and the mean left Intra-ovarian PI/RI was 1.29/0.71. Thus, the mean Intra-ovarian PI/RI in girls without PCOS was 1.29/0.71. The difference was statistically significant (p – 0.041)

Table 29. Intra-Ovarian doppler and its distribution in PCOS versus Non-PCOS menorrhagia

Intra-Ovarian Doppler	PCOS (n=11)	Non-PCOS (n=79)
Right ovary PI	0.9	1.28
Right Ovary RI	0.5	0.71
Left Ovary PI	0.9	1.29
Left Ovary RI	0.5	0.71
Mean Intra-ovarian PI/RI	0.9/0.5	1.29/0.71

Chi Square test was applied to test statistical difference in proportions and the p value was found to be 0.041.

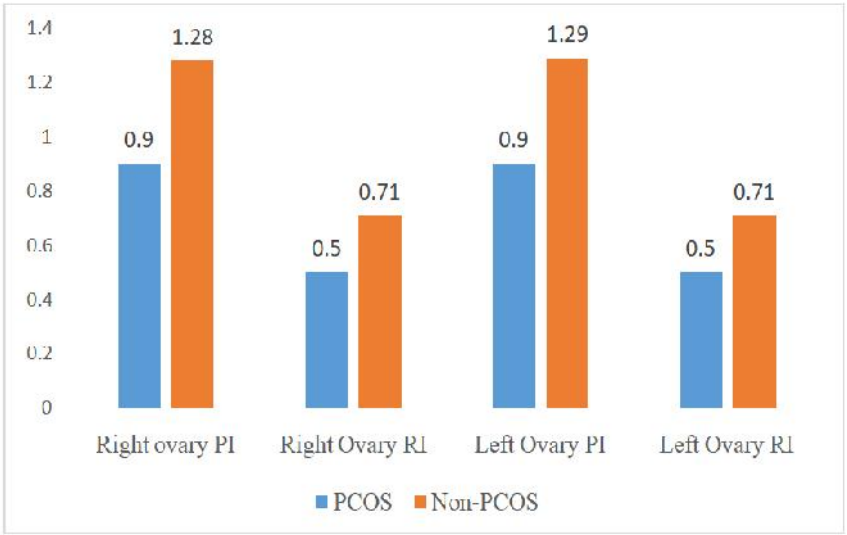

Figure 18. Intra-Ovarian doppler and its distribution in PCOS versus Non-PCOS menorrhagia

CENTRAL STROMAL BRIGHTNESS AND INTRA-OVARIAN FLOW PATTERN IN PCOS VERSUS NON-PCOS MENORRHAGIA: The central stromal brightness was increased in 100% of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) whereas it was increased in0% of the girls without PCOS (n=79).The Intra-Ovarian flow pattern on colour Doppler was present in 100% of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) whereas it was present in 0% of the girls without PCOS (n=79)

Table 30. Central Stromal Brightness and Intra-Ovarian flow pattern in PCOS versus Non-PCOS menorrhagia

Parameter	PCOS n (%)	Non-PCOS n (%)
Increased Central Stromal Brightness	11 (100%)	0 (0%)
Presence of Intra-ovarian flow pattern	11 (100%)	0 (0%)

LATERALITY OF PCOS

Both the ovaries were involved in 100% of the girls with menorrhagia who were diagnosed to have PCOS (n=11).

Table 31. Laterality of PCOS in girls presenting with menorrhagia

Laterality of PCOS	n (%)
Bilateral	11 (100%)
Unilateral	0 (0%)

DISCUSSION

The complaint of menorrhagia was verified using the modified Philip's screening tool and the presence of anaemia. It was found that 100% of the study population (n=90) had verified menorrhagia. (Table 9). The modified Ped-C consensus criteria was applied to the study population.

- Clinical/biochemical evidence of anovulation
- Clinical/biochemical evidence of hyper-androgenism
- Polycystic Ovaries on ultrasonogram

Two of the three criteria, when fulfilled was taken as diagnostic of PCOS in adolescent girls. Heavy menstrual bleeding in adolescence was taken as the clinical evidence of anovulation for the purpose of this study and 100% of the study population fulfilled the criteria of clinical anovulation. None of the study population (n=90) had moderate/severe acne, androgenic alopecia, seborrhoea or hirsutism score of MFG >16. Hence there was no clinical evidence of hyper-androgenism in the study population. (Table 10). Ultrasonogram was done and using the revised criteria for diagnosing adolescent PCOS, polycystic ovaries were found in 12.22% (n=11) of the study population (Table 13). The proportion of PCOS in puberty menorrhagia was estimated to be 12.22% based on the results.Both the ovaries were involved in 100% of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) (Table 13). The mean age group of the study population was 14.95 years. The mean age of girls with menorrhagia and diagnosed to have PCOS (n=11) was 17.18 years whereas the mean age of girls without PCOS (n=79) was 14.65 years.The difference was statistically significant with a p value of 0.0198. This shows that the proportion PCOS which tends to present as menorrhagia, occur in the later ages of adolescence rather than the immediate post-pubertal period. (Table 8 & Table 14)

The mean socio-economic class of both the PCOS (n=11) and the Non-PCOS (n=79) menorrhagia was class III (lower middle) and there was no statistically significant difference with a p value of 0.087. This could be because RGGW&CH being a public hospital, has a higher proportion of patients from the lower middle (III) and upper lower (IV) socio-economic classes. (Table 15)
The mean Body mass index of the girls with menorrhagia who were diagnosed with PCOS was 19kg/m^2 whereas the mean Body Mass Index of the girls without PCOS was 17.86kg/m^2 and the difference was not of statistical significance with a p value 0.13. This shows that the girls with menorrhagia, presenting as PCOS have a low/normal Body Mass Index. Thus, the lean PCOS variant presents more often as menorrhagia than the obese PCOS variant which presents as Oligomenorrhoea (Table 20). The anthropometric indices such as BMI, WC, WHR, WHtR and VAI are within normal limits for 100% of the study population (n=90). This shows that the risk of cardio-metabolic complications is low in the study population irrespective of the presence or absence of PCOS (Table 11). The metabolic parameters such as blood pressure, blood urea, serum creatinine, liver enzymes, blood sugar, coagulation profile and thyroid function tests are within normal limits for 100% of the study population (n=90). (Table 12) This shows that metabolic syndrome, insulin resistance and other systemic complications are relatively infrequent in the lean PCOS variant that presents with menorrhagia in adolescent girls. The mean age of menarche for girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 11.3 years whereas the mean age of menarche for girls without PCOS (n=79) was 12.54 years. The difference was statistically significant with a p value of 0.026. This shows that earlier onset of menarche is associated with a higher proportion of PCOS, possibly because of the prolonged anovulatory hyper-oestrogenism (Table 16). The mean frequency of menstrual cycles in girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 34.09 days whereas the mean frequency of menstrual cycles in girls without PCOS (n=79) was 46.54 days. The difference was significant statistically with a p value of 0.043. This shows that menorrhagia with regular cycles has a higher proportion of PCOS than that of menorrhagia with irregular cycles. This lean variant of PCOS, which presents as menorrhagia, has regular cycles and is in contrary to the obese PCOS which presents more often with Oligomenorrhoea and has irregular cycles (Table 17). The mean duration since menarche to the time of presentation with menorrhagia, in girls with PCOS (n=11) was 5.2 years whereas the mean duration since menarche to the time of presentation with menorrhagia, in girls without PCOS (n=79)was 2.47 years. The difference was statistically significant with a p value of 0.014. This shows that in PCOS, menorrhagia occurs at a much longer duration since menarche, which could be attributed to the prolonged exposure to anovulatory hyper-oestrogenism.(Table 18)

The mean duration of menorrhagia at the time of presentation in girls, who were diagnosed to have PCOS (n=11) was 8.27 months, whereas the mean duration of menorrhagia at the time of presentation in girls without PCOS (n=79) was 3.81 months.The difference was statistically significant with a p value of 0.031. This shows that duration of the complaint of menorrhagia in adolescent girls with PCOS is much longer than that of the girls without PCOS. (Table 19). Although statistically significant, this might be because of the fact that PCOS presents as menorrhagia in much older adolescents, who might not seek medical attention immediately. The girls without PCOS belong to a much younger age group and in our Indian context, the immediate post-pubertal years are more carefully supervised by parents and hence they are brought to medical attention much earlier.

The mean haemoglobin in girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 9.53 g/dl whereas the mean haemoglobin in girls without PCOS (n=79) was 8.72 g/dl. The difference was not statistically significant with a p value of 0.019. (Table 21). The mean antral follicular count in the right ovary of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 15.09 and that of the left ovary was 12.73.The mean antral follicular count in the right ovary of the girls with menorrhagia but without PCOS (n=79) was 5.63 and that of the left ovary was 5.84 (Table 22). In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right ovarian volume was 14.62ml and the mean left ovarian volume was 12.03ml. In the girls with menorrhagia but without PCOS (n=79), the mean right ovarian volume was 5.83ml and the mean left ovarian volume was 6.31ml. (Table 23) It is interesting to note that the right ovary is larger than the left in girls with PCOS whereas the left ovary is larger than the right ovary in girls without PCOS.

In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right ovarian stromal thickness was 10.73mm and the mean left ovarian stromal thickness was 9.0mm. In the girls with menorrhagia but without PCOS (n=79), the mean right ovarian stromal thickness was 4.20mm and the mean left ovarian stromal thickness was 4.28mm (Table 24). In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right ovarian S/A ratio was 0.44 and the mean left ovarian S/A ratio was 0.36. In the girls with menorrhagia but without PCOS (n=79), the mean S/A ratio was 0.15 in both the ovaries. (Table 25). The central stromal brightness was increased in 100% of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) whereas it was increased in 0% of the girls without PCOS (n=79) (Table 29) This shows that there is increased central stromal brightness in girls with PCOS due to stromal hypertrophy. The Intra-Ovarian flow pattern on colour Doppler was present in 100% of the girls with menorrhagia, who were diagnosed to have PCOS (n=11) whereas it was present in 0% of the girls without PCOS (n=79).(Table 29) This shows that there is increased vascularity in the ovarian bed caused due to stromal hypertrophy in girls with PCOS. The mean endometrial thickness in girls with menorrhagia, who were diagnosed to have PCOS (n=11) was 9mm. The mean endometrial thickness in girls with menorrhagia but without PCOS (n=79) was 6.15mm. The difference was statistically significant with a p value of 0.025 (Table 26)

This shows that endometrium is thicker in girls with menorrhagia who have PCOS than those without PCOS. This could be because of the associated anovulatory hyper-oestrogenism. In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean right uterine artery PI/RI was 3.40/1 and the mean left uterine artery PI/RI was 3.44/1. In the girls with menorrhagia but without PCOS (n=79), the mean right uterine artery PI/RI was 2.58/0.77 and the mean left uterine artery PI/RI was 2.60/0.78.

The difference was statistically significant with a p value of 0.018. (Table 27) The results show that there is reduced blood flow in the uterine arteries of the girls with menorrhagia, who were diagnosed to have PCOS. This could be related to the vaso-constrictive effects of circulating androgens and the inherent atherogenic predisposition of PCOS. In the girls with menorrhagia, who were diagnosed to have PCOS (n=11), the mean Intra-ovarian PI/RI was 0.9/0.5 in both the ovaries. In the girls with menorrhagia but without PCOS (n=79), the mean right Intra-ovarian PI/RI was 1.28/0.71 and the mean left Intra-ovarian PI/RI was 1.29/0.71.(Table 28)The difference was statistically significant with a p value of 0.041. This shows that there is increased blood flow in the intra-ovarian vascular bed in girls with PCOS which could be because of the vascular re-modelling because of stromal hypertrophy caused by the hyper-oestrogenism. In girls with menorrhagia, diagnosed to have PCOS, it was observed that 100% (n=12) had bilateral PCOS and 0% (n=0) had unilateral PCOS. (Table 30)

SUMMARY

Table 32. Summary of the Descriptive statistics of the study population (n=90)

Type of study	Prospective longitudinal study
Sample size	90
Venue	RGGW&CH, Puducherry
Aim	To estimate the proportion of PCOS in puberty menorrhagia
Proportion of PCOS in puberty menorrhagia	12.22%
Mean age of study population	14.95 years
Mean SEC of the study population	Lower middle class (III)
Proportion of girls with normal Anthropometric indices in the study population	100%
Proportion of girls with normal metabolic parameters in the study population	100%
Clinical evidence of hyper-androgenism in the study population	0%
Clinical evidence of anovulation in the study population	100%
Proportion of the study population fulfilling the Ultrasonogram criteria	12.22%

Table 33. Summary of Descriptive statistics of PCOS versus Non-PCOS menorrhagia

Parameter	PCOS(n=11)	Non-PCOS(n=79)
Mean age (years)	17.18	14.65
Mean SEC	Lower middle (Class III)	Lower middle (Class III)
Mean BMI (kg/m^2')	19	17.86
Mean age of menarche (years)	11.3	12.54
Mean duration since menarche to menorrhagia (years)	5.2	2.47
Mean duration of menorrhagia (months)	8.27	3.81
Frequency of menstrual cycles (days)	34.09	46.54
Mean haemoglobin level (g/dl)	9.53	8.72

Table 34. Summary of the Ultrasonogram Parameters in PCOS versus Non-PCOS Menorrhagia

Ultrasonogram Parameter	PCOS (n=11)	Non-PCOS (n=79)
Antral follicular count	13.91	5.74
Ovarian volume (ml)	13.33	6.07
Stromal thickness (mm)	9.87	4.24
Ovarian S/A ratio	0.40	0.15
Endometrial thickness (mm)	9	6.15
Uterine artery PI/RI	3.42/1	2.59/0.78
Intra-ovarian PI/RI	0.9/0.5	1.29/0.71

STRENGTHS AND LIMITATIONS

STRENGTHS

- The complaint of menorrhagia has been analysed objectively with the modified Philip's screening tool and was confirmed as Verified Menorrhagia.
- The modified Ped-C consensus has been used to diagnose adolescent PCOS in the present study, which has a much higher negative predictive value and specificity than the Rotterdam criteria.
- The revised criteria for diagnosing clinical hyper-androgenism in adolescent girls has been used in the present study, which minimises the false-positive rate
- The newer ultrasonogram markers such as Stromal thickness, S/A ratio and central stromal brightness and the uterine and intra-ovarian Doppler indices have been used in the present study and has improved the diagnostic accuracy of adolescent PCOS.
- The Anthropometric indices and the metabolic parameters have been analysed in the present study to predict the risk of future cardio-metabolic morbidity.

LIMITATIONS

- Biochemical hyper-androgenism has not been studied in the present study.
- The present study has been done in a public hospital, hence adolescent girls of higher socio-economic strata could not be included for analysis
- Small sample size
- Attrition bias was very high in the present study (30.23%). A total of 129 cases had to be enrolled to achieve the target sample size of 90. This could have probably been due to the socio-cultural stigma and apprehension associated with the gynaecologic well-being of the adolescent girls, consequently leading to withdrawal of parental consent for study participation.

CONCLUSIONS AND RECOMMENDATIONS

- The complaint of menorrhagia should be objectively verified before investigating the cause.
- All cases of puberty menorrhagia should be investigated before being attributed to theimmaturity of the HPO axis.
- The clinicians must be aware of the revised criteria for diagnosing clinical hyper-androgenism in adolescent girls.
- The modified Ped-C consensus 2015 should be applied to diagnose PCOS in adolescent girls as it is a much better diagnostic criteria than the Rotterdam consensus.
- Ultrasonogram of the pelvis must be done using the revised criteria for diagnosing PCOS so that it can be differentiated from MFO which is quite common in adolescence
- The newer markers such as Stromal thickness, Central Stromal Brightness, ovarian S/A ratio should be implemented as part of the Ultrasonogram to diagnose PCOS.
- The addition of Doppler indices of the uterine and intra-ovarian flow will increase the diagnostic accuracy.
- Adolescent girls with PCOS must be screened with the various anthropometric and metabolic parameters to predict the occurrence of future cardio-metabolic morbidities.
- Diagnosing PCOS in early adolescence provides the opportunity to counsel and suggest life-style modification to optimise the reproductive and metabolic health and wellbeing of these girls.

REFERENCES

1. Ebling FJP. The neuroendocrine timing of puberty. Reproduction. 2005.
2. Klein J, Vuguin PM. Precocious puberty. In: Abnormal Female Puberty: A Clinical Casebook. 2016.
3. Rogol AD, Roemmich JN, Clark PA. Growth at puberty. J Adolesc Heal. 2002;
4. Grover SR, Bajpai A. Puberty. In: International Encyclopedia of Public Health. 2016.
5. Gillani S, Mohammad S. Puberty menorrhagia: Causes and management. J Med Sci. 2012;
6. Khosla AH, Devi L, Goel P, Saha PK. Puberty menorrhagia requiring inpatient admission. J Nepal Med Assoc. 2010;
7. Rathod AD, Chavan RP, Pajai SP, Bhagat V, Thool P. Gynecological Problems of Adolescent Girls Attending Outpatient Department at Tertiary Care Center with Evaluation of Cases of Puberty Menorrhagia Requiring Hospitalization. J Obstet Gynecol India. 2016;
8. Peacock A, Alvi NS, Mushtaq T. Period problems: Disorders of menstruation in adolescents. Archives of Disease in Childhood. 2012.
9. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;
10. Tariq A, Mir MA, Babar S, Akhtar R. PCOS; Prof Med J. 2018;
11. Meier RK. Polycystic Ovary Syndrome. Nursing Clinics of North America. 2018.
12. Cochrane Database of Systematic Reviews. 1996.
13. Klein J, Craven M, Vuguin PM. Polycystic ovarian syndrome. Adolescent Medicine: State of the Art Reviews. 2015.
14. Fauser BCJM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;
15. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;
16. Wang R, Mol BWJ. The Rotterdam criteria for polycystic ovary syndrome: Evidence-based criteria? Hum Reprod. 2017;
17. Azziz R. Diagnosis of polycystic ovarian syndrome: The Rotterdam criteria are premature. J Clin Endocrinol Metab. 2006;
18. March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;
19. Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab. 2006;
20. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocrine Reviews. 2016.
21. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;
22. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. Nature Reviews Endocrinology. 2011.
23. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Medicine. 2010.
24. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;
25. Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoraka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2018.
26. Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2004.
27. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C, Dewailly D. Ultrasound examination of polycystic ovaries: Is it worth counting the follicles? Hum Reprod. 2003;
28. Balen AH, Laven JSE, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: International consensus definitions. Human Reproduction Update. 2003.
29. Youngster M, Ward VL, Blood EA, Barnewolt CE, Emans SJ, Divasta AD. Utility of ultrasound in the diagnosis of polycystic ovary syndrome in adolescents. Fertil Steril. 2014;
30. Salley KES, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Position statement: Glucose intolerance in polycystic ovary syndrome - A position statement of the androgen excess society. J Clin Endocrinol Metab. 2007;
31. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;
32. Auble B, Elder D, Gross A, Hillman JB. Differences in the Management of Adolescents with Polycystic Ovary Syndrome across Pediatric Specialties. J Pediatr Adolesc Gynecol. 2013;
33. Choudhary A, Jain S, Chaudhari P. Prevalence and symptomatology of polycystic ovarian syndrome in Indian women: is there a rising incidence? Int J Reprod Contraception, Obstet Gynecol. 2017;
34. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Position statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An androgen excess society guideline. J Clin Endocrinol Metab. 2006;
35. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2018;
36. Terrie YC. Insight into diagnosing and treating polycystic ovarian syndrome. U.S. Pharmacist. 2015.
37. Engstrom JL, Rose R, Brill AI, Polhill KM, Lukanich CM, Fritz L. Midwifery care of the woman with menorrhagia. Journal of Nurse-Midwifery. 1999.
38. O'Flynn N, Britten N. Menorrhagia in general practice - Disease or illness. Soc Sci Med. 2000;

39. Puri M, Gami N. Evaluation & work up of a woman with menorrhagia. In: Journal International Medical Sciences Academy. 2009.
40. Baron YM. Menorrhagia: Risk Factors, Diagnosis and Treatment. MENORRHAGIA AND DYSMENORRHEA. 2015;
41. Rodeghiero F, Kadir RA, Tosetto A, James PD. Relevance of quantitative assessment of bleeding in haemorrhagic disorders. Haemophilia. 2008;
42. Gudmundsdottir BR, Hjaltalin EF, Bragadottir G, Hauksson A, Geirsson RT, Onundarson PT. Quantification of menstrual flow by weighing protective pads in women with normal, decreased or increased menstruation. Acta Obstet Gynecol Scand. 2009;
43. Higham JM, Shaw RW. Risk-Benefit Assessment of Drugs Used for the Treatment of Menstrual Disorders. Drug Safety. 1991.
44. P.A. C, T.C. A, V.H. F, J.C. G, S.L. H, R.R. M. Comparison of three different bleeding assessment tools for von willebrand disease in the zimmerman program. Am J Hematol. 2016;
45. B.R. G, E.F. H, G. B, A. H, R.T. G, P.T. O. Quantification of menstrual flow by weighing protective pads in women with normal, decreased or increased menstruation. Acta Obstetricia et Gynecologica Scandinavica. 2009.
46. Warrilow G, Kirkham C, Ismail KM, Wyatt K, Dimmock P, et al. Quantification of menstrual blood loss. Obstet Gynaecol. 2004;
47. Philipp CS, Faiz A, Heit JA, Kouides PA, Lukes A, Stein SF, et al. Evaluation of a screening tool for bleeding disorders in a US multisite cohort of women with menorrhagia. In: American Journal of Obstetrics and Gynecology. 2011.
48. Philipp CS, Faiz A, Dowling NF, Beckman M, Owens S, Ayers C, et al. Development of a screening tool for identifying women with menorrhagia for hemostatic evaluation. Am J Obstet Gynecol. 2008;
49. Revel-Vilk S, Paltiel O, Lipschuetz M, Ilan U, Hyam E, Shai E, et al. Underdiagnosed menorrhagia in adolescents is associated with underdiagnosed anemia. J Pediatr. 2012;
50. Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J, et al. Clinical practice guidelines on menorrhagia: Management of abnormal uterine bleeding before menopause. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2010.
51. J. W, R. O, T. M. Adherence to published guidelines for the management of menorrhagia in primary and secondary care. BJOG An Int J Obstet Gynaecol. 2012;
52. Magiakou MA, Mastorakos G, Webster E, Chrousos GP. The hypothalamic-pituitary-adrenal axis and the female reproductive system. In: Annals of the New York Academy of Sciences. 1997.
53. Davis HC, Hackney AC. The hypothalamic-pituitary-ovarian axis and oral contraceptives: Regulation and function. In: Sex Hormones, Exercise and Women: Scientific and Clinical Aspects. 2016.
54. Sanfilippo JS. An Update on Female Puberty. US Endocrinol. 2015;
55. Motta T, Laganà AS, Vitale SG. Dysfunctional uterine bleeding. In: Good Practice in Pediatric and Adolescent Gynecology. 2017.
56. Doufas AG, Mastorakos G. The hypothalamic-pituitary-thyroid axis and the female reproductive system. Ann N Y Acad Sci. 2000;
57. Kılıç SÇ, Sarper N, Zengin E, Gelen SA. Screening Bleeding Disorders in Adolescents and Young Women with Menorrhagia. Turkish J Hematol. 2013;
58. Shawn MJ. Glanzmann Thrombasthenia. In: Transfusion Medicine and Hemostasis. 2009.
59. Rae C, Furlong W, Horsman J, Pullenayegum E, Demers C, St-Louis J, et al. Bleeding disorders, menorrhagia and iron deficiency: Impacts on health-related quality of life. Haemophilia. 2013;
60. Rodeghiero F. Management of menorrhagia in women with inherited bleeding disorders: General principles and use of desmopressin. Haemophilia. 2008.
61. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet. 1998;
62. ACOG Committee Opinion No. 451: Von Willebrand Disease in Women. Obstet Gynecol. 2009;
63. Kouides PA, Kadir RA. Menorrhagia associated with laboratory abnormalities of hemostasis: Epidemiological, diagnostic and therapeutic aspects. Journal of Thrombosis and Haemostasis. 2007.
64. Singh S, Sahoo S, Das PC. A study of thyroid dysfunction in dysfunctional uterine bleeding. Int J Reprod Contraception, Obstet Gynecol. 2018;
65. I.A. S, K. S, K. G, J. H. Life-threatening menorrhagia due to profound hypothyroidism. Thyroid. 2018;
66. Sharma N, Sharma A. Thyroid profile in menstrual disorders. JK Sci. 2011;
67. Kouides PA. Menorrhagia from a haematologist's point of view. Part I: Initial evaluation. Haemophilia. 2002;
68. Wilansky DL, Greisman B. Early hypothyroidism in patients with menorrhagia. Am J Obstet Gynecol. 1989;
69. Committee A. GUIDELINES & PROTOCOLS Thyroid Function Tests : Diagnoses and Monitoring of Thyroid Function Disorders in Adults. Measurement. 2010;
70. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, et al. Disturbances of menstruation in hypothyroidism. Clin Endocrinol (Oxf). 1999;
71. Saranac L, Zivanovic S, Radovanovic Z, Kostic G, Markovic I, Miljkovic P. Hyperprolactinemia: Different clinical expression in childhood. Horm Res Paediatr. 2010;
72. dos Santos Júnior A, Henriques TB, de Mello MP, Neto APF, Paes LA, Torre OH Della, et al. Hyperprolactinemia in Children and Adolescents with Use of Risperidone: Clinical and Molecular Genetics Aspects. J Child Adolesc Psychopharmacol. 2015;
73. Ciccarelli A, Daly AF, Beckers A. The epidemiology of prolactinomas. Pituitary. 2005;
74. Deo S, Agrawal M, Jaiswar SP, Sankhwar PL, Babu S, S S, et al. Evaluation of etiological factors and management of puberty menorrhagia. Int J Biomed Res. 2018;

75. Ibrahim G, AlNowaiser D, AlAbbasi H, Abuhaimed J, AlBukhari M, AlHarthi M, et al. The relationship between lifestyle and the frequency of polycystic ovary syndrome in Saudi female residing in Riyadh. Int J Reprod Contraception, Obstet Gynecol. 2017;
76. Kalra SK, Gracia CR, Barnhart KT. Symptomatic Fibroids in Two Patients on Hormone Replacement Therapy with Primary Ovarian Failure Secondary to Prepubertal Gonadotoxic Cancer Treatment. J Women's Heal. 2008;
77. A SS, Jehan A. PUBERTAL MENORRHAGIA : EVALUATION AND MANAGEMENT. J Evol Med Dent Sci. 2015;
78. Vilos GA, Allaire C, Laberge PY, Leyland N, Vilos AG, Murji A, et al. The Management of Uterine Leiomyomas. J Obstet Gynaecol Canada. 2015;
79. Evans P, Brunsell S. Uterine fibroid tumors: Diagnosis and treatment. American Family Physician. 2007.
80. J.L. P, S.G. L, H. K, V.L.C. W. Female genital tuberculosis: The long road to diagnosis. Thorax. 2014.
81. Samal S, Gupta U, Agarwal P. Menstrual Disorders in Genital Tuberculosis. Journal of the Indian Medical Association. 2000.
82. Gupta N, Sharma JB, Mittal S, Singh N, Misra R, Kukreja M. Genital tuberculosis in Indian infertility patients. Int J Gynecol Obstet. 2007;
83. Bremer AA. Polycystic Ovary Syndrome in the Pediatric Population. Metab Syndr Relat Disord. 2010;
84. Hughesdon PE. Morphology and morphogenesis of the stein-leventhal ovary and of so-called "Hyperthecosis." Obstet Gynecol Surv. 1982;
85. Azziz R, Adashi EY. Stein and Leventhal: 80 years on. Am J Obstet Gynecol. 2016;
86. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012;
87. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Human Reproduction Update. 2009.
88. Broekmans FJ, Knauff EAH, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BCJM. PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG An Int J Obstet Gynaecol. 2006;
89. Diamanti-Kandarakis E. PCOS in adolescents. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2010.
90. Carmona-Ruiz IO, Saucedo-de la Llata E, Moraga-Sánchez MR, Romeu-Sarró A. [Polycystic ovary syndrome: is there a rise in the prevalence?]. Ginecol Obstet Mex. 2015;
91. Lizneva D, Gavrilova-Jordan L, Walker W, Azziz R. Androgen excess: Investigations and management. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2016.
92. Asunción M, Calvo RM, San Millá N JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000;
93. Pfeifer SM, Kives S. Polycystic Ovary Syndrome in the Adolescent. Obstetrics and Gynecology Clinics of North America. 2009.
94. Sanfilippo JS, Lara-Torre E. Adolescent gynecology. Obstetrics and Gynecology. 2009.
95. Aswini R, Jayapalan S. Modified Ferriman–Gallwey score in hirsutism and its association with metabolic syndrome. Int J Trichology. 2017;
96. Cook H, Brennan K, Azziz R. Reanalyzing the modified Ferriman-Gallwey score: Is there a simpler method for assessing the extent of hirsutism? Fertil Steril. 2011;
97. Liu K, Motan T, Claman P. No. 350-Hirsutism: Evaluation and Treatment. J Obstet Gynaecol Canada. 2017;
98. Coskun A, Ercan O, Arikan DC, Özer A, Kilinc M, Kiran G, et al. Modified Ferriman-Gallwey hirsutism score and androgen levels in Turkish women. Eur J Obstet Gynecol Reprod Biol. 2011;
99. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. J Am Acad Dermatol. 2005;
100. Cunliffe WJ, Holland DB, Jeremy A. Comedone formation: Etiology, clinical presentation, and treatment. Clin Dermatol. 2004;
101. Rathi S. Acne vulgaris treatment : The Current Scenario. Indian J Dermatol. 2011;
102. Ramos-e-Silva M, Coelho da Silva Carneir S. Classification of acne. Expert Rev Dermatol. 2006;
103. Misery L. Dermatite séborrhéique. EMC - Trait médecine AKOS. 2013;
104. Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. Journal of the European Academy of Dermatology and Venereology. 2014.
105. Enos C, Patel T, Patel S, França K. Seborrheic dermatitis. In: Stress and Skin Disorders: Basic and Clinical Aspects. 2016.
106. Schmidt TH, Khanijow K, Cedars MI, Huddleston H, Pasch L, Wang ET, et al. Cutaneous findings and systemic associations in women with polycystic ovary syndrome. JAMA Dermatology. 2016;
107. Cela E, Robertson C, Rush K, Kousta E, White DM, Wilson H, et al. Prevalence of polycystic ovaries in women with androgenic alopecia. Eur J Endocrinol. 2003;
108. Quinn M, Shinkai K, Pasch L, Kuzmich L, Cedars M, Huddleston H. Prevalence of androgenic alopecia in patients with polycystic ovary syndrome and characterization of associated clinical and biochemical features. Fertil Steril. 2014;
109. Akbarzadeh M, Naderi T, Dabaghmanesh MH, Tabatabaie H, Zare Z. The prevalence of hirsutism in girls 14 to 18 years old and its relationship with polycystic ovary syndrome in Shiraz, Iran. Iran J Obstet Gynecol Infertil. 2014;
110. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome: Part 1. Endocr Pract. 2015;
111. McDonough PH, Schwartz RA. Adolescent androgenic alopecia. Cutis. 2011;
112. Bogatyreva EM, Kutusheva GF, Gogotadze IN, Zernyuk AD. Hyperandrogenism. Cases of Combination of Different Variants of Hyperandrogenism in Adolescent Girls with the Peripheral Form of Hyperandrogenism. Pediatr (St Petersburg). 2016;

113. Angold A, Costello EJ, Erkanli A, Worthman CM. Pubertal changes in hormone levels and depression in girls. Psychol Med. 1999;
114. Yoo RY, Dewan A, Basu R, Newfield R, Gottschalk M, Chang RJ. Increased luteinizing hormone pulse frequency in obese oligomenorrheic girls with no evidence of hyperandrogenism. Fertil Steril. 2006;
115. Šulcová J, Hill M, Hampl R, Stárka L. Age and sex related differences in serum levels of unconjugated dehydroepiandrosterone and its sulphate in normal subjects. J Endocrinol. 1997;
116. McVeigh E. Reproductive endocrinology. In: Textbook of Clinical Embryology. 2013.
117. Van Hooff MHA, Voorhorst FJ, Kaptein MBH, Hirasing RA, Koppenaal C, Schoemaker J. Endocrine features of polycystic ovary syndrome in a random population sample of 14-16 year old adolescents. Hum Reprod. 1999;
118. Grumbach MM. The neuroendocrinology of human puberty revisited. In: Hormone Research. 2002.
119. Greenfield A. Sexual development. In: Textbook of Clinical Embryology. 2013.
120. Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. Human Reproduction Update. 2006.
121. Peper JS, Brouwer RM, van Leeuwen M, Schnack HG, Boomsma DI, Kahn RS, et al. HPG-axis hormones during puberty: A study on the association with hypothalamic and pituitary volumes. Psychoneuroendocrinology. 2010;
122. Esmaeilzadeh S, Andarieh MG, Ghadimi R, Delavar MA. Body Mass Index and Gonadotropin Hormones (LH & FSH) Associate With Clinical Symptoms Among Women With Polycystic Ovary Syndrome. Glob J Health Sci. 2014;
123. C. V, P. L, P. M, A. VV, G. I, E. C. Polycystic ovary morphology is a frequent finding in healthy postmenarchal adolescents during the second decade of life. Hum Reprod. 2010;
124. Villa P, Rossodivita A, Sagnella F, Moruzzi MC, Mariano N, Lassandro AP, et al. Ovarian volume and gluco-insulinaemic markers in the diagnosis of PCOS during adolescence. Clin Endocrinol (Oxf). 2013;
125. Fruzzetti F, Campagna AM, Perini D, Carmina E. Ovarian volume in normal and hyperandrogenic adolescent women. Fertil Steril. 2015;
126. Hickey M, Doherty DA, Atkinson H, Sloboda DM, Franks S, Norman RJ, et al. Clinical, ultrasound and biochemical features of polycystic ovary syndrome in adolescents: Implications for diagnosis. Hum Reprod. 2011;
127. Atiomo WU, Pearson S, Shaw S, Prentice A, Dubbins P. Ultrasound criteria in the diagnosis of polycystic ovary syndrome (PCOS). Ultrasound Med Biol. 2000;
128. Mastorakos G, Lambrinoudaki I, Creatsas G. Polycystic ovary syndrome in adolescents: Current and future treatment options. Pediatric Drugs. 2006.
129. Lerchbaum E, Schwetz V, Rabe T, Giuliani A, Obermayer-Pietsch B. Hyperandrogenemia in polycystic ovary syndrome: Exploration of the role of free testosterone and androstenedione in metabolic phenotype. PLoS One. 2014;
130. Buckett WM. Ovarian stromal echogenicity in women with normal and polycystic ovaries. Hum Reprod. 1999;
131. Christ JP, Vanden Brink H, Brooks ED, Pierson RA, Chizen DR, Lujan ME. Ultrasound features of polycystic ovaries relate to degree of reproductive and metabolic disturbance in polycystic ovary syndrome. Fertil Steril. 2015;
132. Galli-Tsinopoulou A, Moudiou T, Mamopoulos A, Karamouzis M, Nousia-Arvanitakis S. Multifollicular ovaries in female adolescents with cystic fibrosis. Fertil Steril. 2006;
133. Fulghesu AM, Ciampelli M, Belosi C, Apa R, Pavone V, Lanzone A. A new ultrasound criterion for the diagnosis of polycystic ovary syndrome: The ovarian stroma/total area ratio. Fertil Steril. 2001;
134. Chekir C, Nakatsuka M, Kamada Y, Noguchi S, Sasaki A, Hiramatsu Y. Impaired uterine perfusion associated with metabolic disorders in women with polycystic ovary syndrome. Acta Obstet Gynecol Scand. 2005;
135. Lam P, Johnson I, Raine-Fenning N. Endometrial blood flow is impaired in women with polycystic ovarian syndrome who are clinically hyperandrogenic. Ultrasound Obstet Gynecol. 2009;
136. Adali E, Kolusari A, Adali F, Yildizhan R, Kurdoglu M, Sahin HG. Doppler analysis of uterine perfusion and ovarian stromal blood flow in polycystic ovary syndrome. Int J Gynecol Obstet. 2009;
137. Nouh AA, Shalaby SM. The predictive value of uterine blood flow in detecting the risk of adverse pregnancy outcome in patients with polycystic ovary syndrome. Middle East Fertil Soc J. 2011;
138. Battaglia C, Regnani G, Mancini F, Iughetti L, Flamigni C, Venturoli S. Polycystic ovaries in childhood: A common finding in daughters of PCOS patients. A pilot study. Hum Reprod. 2002;
139. Özkan S, Vural B, Çalişkan E, Bodur H, Türköz E, Vural F. Color Doppler sonographic analysis of uterine and ovarian artery blood flow in women with polycystic ovary syndrome. J Clin Ultrasound. 2007;
140. Battaglia C, Mancini F, Persico N, Zaccaria V, de Aloysio D. Ultrasound evaluation of PCO, PCOS and OHSS. Reprod Biomed Online. 2004;
141. B. S, E. G, S. M. Unilateral ovarian enlargement in adolescents with polycystic ovary syndrome: A variant of bilateral disease. Journal of Pediatric Endocrinology and Metabolism. 2010.
142. Eryilmaz OG, Sarikaya E, Gulerman C, Akar S, Cicek N. Endometrial thickness measurement throughout a menstrual cycle in non-obese infertile patients with polycystic ovary syndrome. Arch Gynecol Obstet. 2012;
143. Iatrakis G, Tsionis C, Adonakis G, Stoikidou M, Anthouli-Anagnostopoulou F, Parava M, et al. Polycystic ovarian syndrome, insulin resistance and thickness of the endometrium. Eur J Obstet Gynecol Reprod Biol. 2006;
144. Shah B, Parnell L, Milla S, Kessler M, David R. Endometrial Thickness, Uterine, and Ovarian Ultrasonographic Features in Adolescents with Polycystic Ovarian Syndrome. J Pediatr Adolesc Gynecol. 2010;
145. Cheung AP. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. Obstet Gynecol. 2001;
146. Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. J Clin Endocrinol Metab. 2008;

147. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: A systematic review and meta-analysis. Obes Rev. 2013;
148. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN, et al. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;
149. Gabrielli L, Aquino EML. Polycystic ovary syndrome in Salvador, Brazil: A prevalence study in primary healthcare. Reprod Biol Endocrinol. 2012;
150. De Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: Meta-regression analysis of prospective studies. Eur Heart J. 2007;
151. WHO. Waist Circumference and Waist–Hip Ratio. WHO Expert. 2011.
152. WHO. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. World Heal Organ. 2008;
153. World Health Organization. Waist Circumference and Waist-Hip Ratio. Rep a WHO Expert Consult. 2008;
154. Singh D. Adaptive Significance of Female Physical Attractiveness: Role of Waist-to-Hip Ratio. J Pers Soc Psychol. 1993;
155. Marlowe F, Wetsman A. Preferred waist-to-hip ratio and ecology. Pers Individ Dif. 2001;
156. Vazquez G, Duval S, Jacobs DR, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: A meta-analysis. Epidemiologic Reviews. 2007.
157. Bener A, Yousafzai MT, Darwish S, Al-Hamaq AOAA, Nasralla EA, Abdul-Ghani M. Obesity index that better predict metabolic syndrome: Body mass index, waist circumference, waist hip ratio, or waist height ratio. J Obes. 2013;
158. Dalton M, Cameron AJ, Zimmet PZ, Shaw JE, Jolley D, Dunstan DW, et al. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. Journal of Internal Medicine. 2003.
159. Bacopoulou F, Efthymiou V, Landis G, Rentoumis A, Chrousos GP. Waist circumference, waist-to-hip ratio and waist-to-height ratio reference percentiles for abdominal obesity among Greek adolescents. BMC Pediatr. 2015;
160. Escobar-Morreale HF, Millán JLS. Abdominal adiposity and the polycystic ovary syndrome. Trends in Endocrinology and Metabolism. 2007.
161. Riscimanna ANC. Visceral Adiposity Index. Diabetes Care. 2010;
162. Zheng SH, Li XL. Visceral adiposity index as a predictor of clinical severity and therapeutic outcome of PCOS. Gynecol Endocrinol. 2016;
163. Amato MC, Giordano C. Visceral adiposity index: An indicator of adipose tissue dysfunction. International Journal of Endocrinology. 2014.
164. Ehsani B, Moslehi N, Mirmiran P, Ramezani Tehrani F, Tahmasebinejad Z, Azizi F. A visceral adiposity index-related dietary pattern and the cardiometabolic profiles in women with polycystic ovary syndrome. Clin Nutr. 2016;
165. Bates GW, Legro RS. Longterm management of Polycystic Ovarian Syndrome (PCOS). Molecular and Cellular Endocrinology. 2013.
166. Wani R. Socioeconomic status scales-modified Kuppuswamy and Udai Pareekh's scale updated for 2019. J Fam Med Prim Care. 2019;
167. Mohd Saleem S. Modified Kuppuswamy socioeconomic scale updated for the year 2019. Indian J Forensic Community Med. 2019;
168. Deepthi K, Srinivasan V, Vasanthakumar V, Rajiv S, Victoria J, Mahasampath GS, et al. Measuring poverty in southern India: A Comparison of socio-economic scales evaluated against childhood stunting. PLoS One. 2016;
169. Rzońca E, Bień A, Wdowiak A, Szymański R, Iwanowicz-Palus G. Determinants of quality of life and satisfaction with life in women with polycystic ovary syndrome. Int J Environ Res Public Health. 2018;
170. Joshi S, Chella H, Shrivastava D. Study of puberty menorrhagia in adolescent girl in a rural set-up. J SAFOG. 2012;
171. S. G, S. M. Puberty menorrhagia: Causes and management. J Med Sci. 2012;
172. Dolui S, Mukherjee G, Masroor F, Minj J, Biswas PK, Pain SK, et al. STUDY OF AETIOLOGICAL FACTORS OF PUBERTY MENORRHAGIA. J Evol Med Dent Sci. 2015;
173. Roychowdhury J, Chaudhuri S, Sarkar A, Biswas PK. A study to evaluate the aetiological factors and management of puberty menorrhagia. Online J Heal Allied Sci. 2008;
174. Goswami P, Ahirwar G, Mishra P, Agrawal V. ADOLESCENT GYNAECOLOGICAL PROBLEMS: A PROSPECTIVE STUDY. J Evol Med Dent Sci. 2015;
175. A.D. R, R.P. C, S.P. P, V. B, P. T. Gynecological Problems of Adolescent Girls Attending Outpatient Department at Tertiary Care Center with Evaluation of Cases of Puberty Menorrhagia Requiring Hospitalization. J Obstet Gynecol India. 2016;
176. Bentley-Lewis R, Seely E, Dunaif A. Ovarian hypertension: Polycystic ovary syndrome. Endocrinology and Metabolism Clinics of North America. 2011.
177. Bunag R. Essential hypertension. In: xPharm: The Comprehensive Pharmacology Reference. 2011.
178. Manneras-Holm L, Baghaei F, Holm G, Janson PO, Ohlsson C, Lönn M, et al. Coagulation and fibrinolytic disturbances in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2011;
179. Gozukara IO, Gozukara KH, Kucur SK, Karakılıc EU, Keskin H, Akdeniz D, et al. Association of glomerular filtration rate with inflammation in polycystic ovary syndrome. Int J Fertil Steril. 2015;
180. Barber TM, Dimitriadis GK, Andreou A, Franks S. Polycystic ovary syndrome: Insight into pathogenesis and a common association with insulin resistance. Clin Med J R Coll Physicians London. 2016;
181. Singla R, Gupta Y, Khemani M, Aggarwal S. Thyroid disorders and polycystic ovary syndrome: An emerging relationship. Indian J Endocrinol Metab. 2014;

****