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Polycystic ovary syndrome in adolescents

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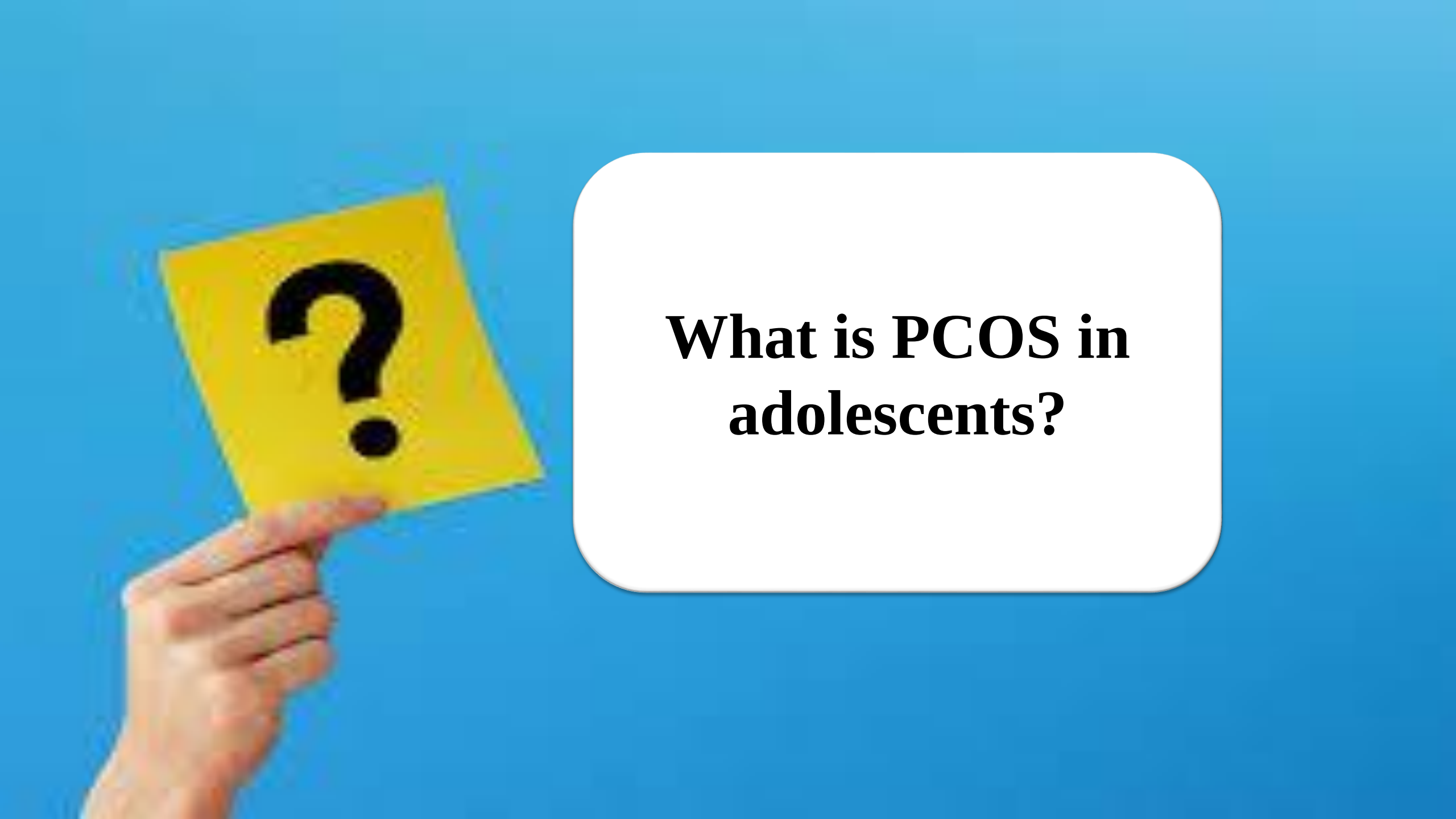
Outline

- **Definition polycystic ovary syndrome (PCOS) in adolescents**
- **Physiology of pubertal development**
- **Pathophysiology of PCOS in adolescents**
- **Prevalence and Risk factors**
- **The clinical presentation of PCOS and diagnostic criteria of PCOS in adolescents**
- **Management approach for PCOS in adolescents**



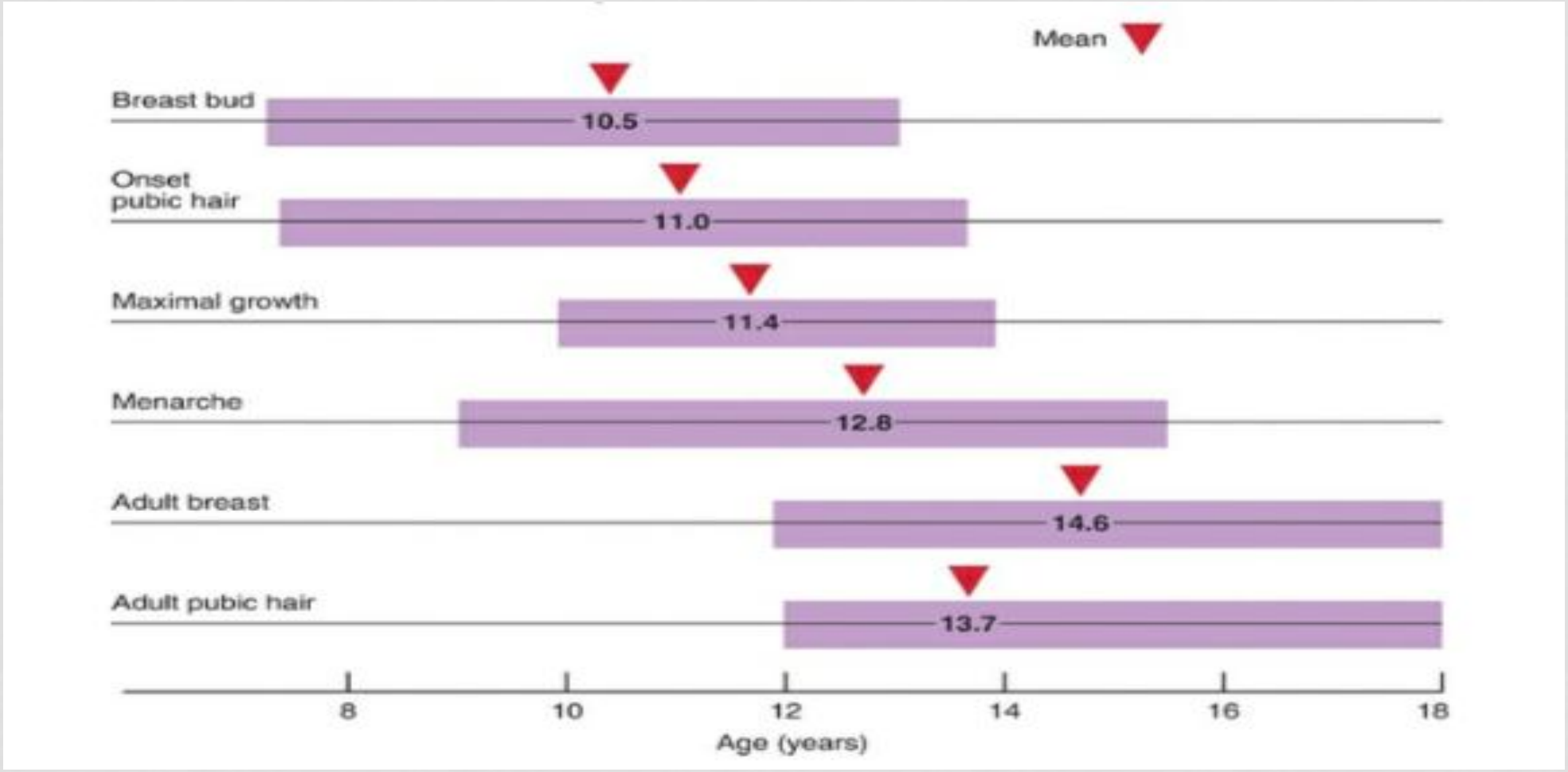
What is PCOS in adolescents?

What Is PCOS In Adolescents

- Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder during a female's reproductive lifespan.
- **PCOS is a syndrome of the 20th Century**
- Physical characteristics of PCOS often present in the **early menarcheal period of development**.
- The clinical presentation of PCOS often **mimics normal pubertal**.
- Physiologic development; this can **delay the diagnosis** of the condition and treatment of adolescents with PCOS.

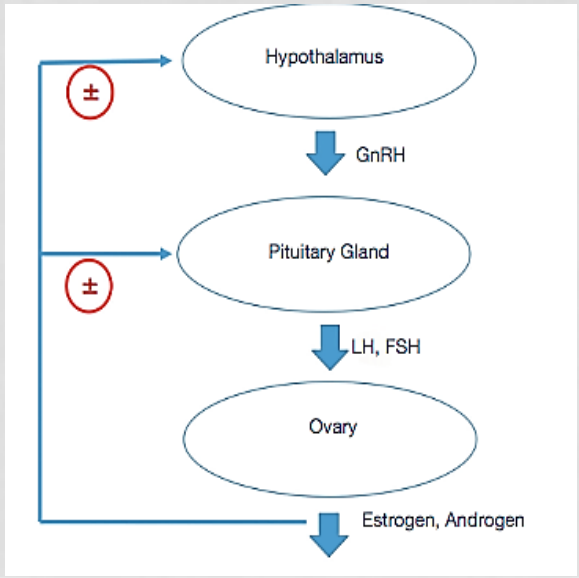
Physiology of pubertal development

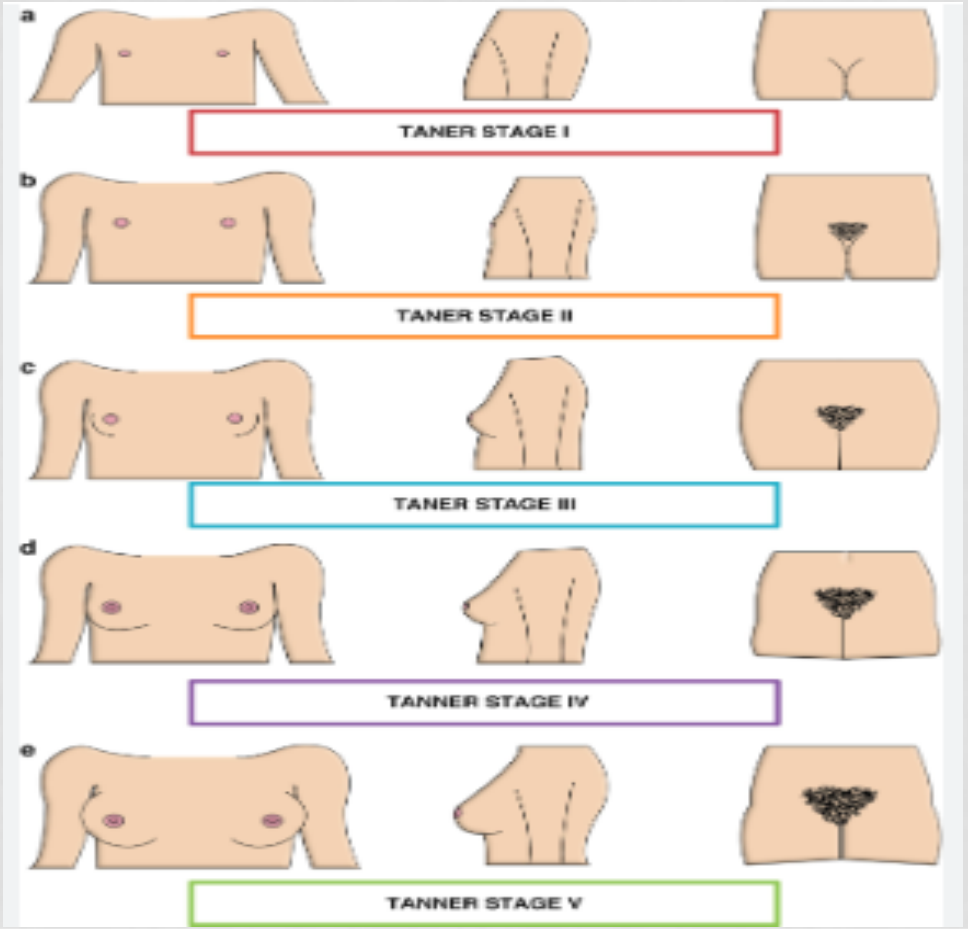
Sequence Of pubertal milestone



Thelarche

- Thelarche refers to breast growth, typically the first sign of puberty in girls, occurring around **9 or 10**.
- An increase in estrogen causes the lactiferous duct system to develop, while an increase in progesterone causes the lobular alveoli at the ends of lactiferous ducts to increase in number.





Pubarche

- Approximately six months after thelarche begins, pubarche, or growth of pubic hair, will typically occur.
- Pubic hair initially appears light, sparse and straight but will become coarse, thick, and dark throughout the course of puberty.
- Approximately two years after pubarche, axillary hair will begin to grow, a secondary sexual characteristic mediated by testosterone.

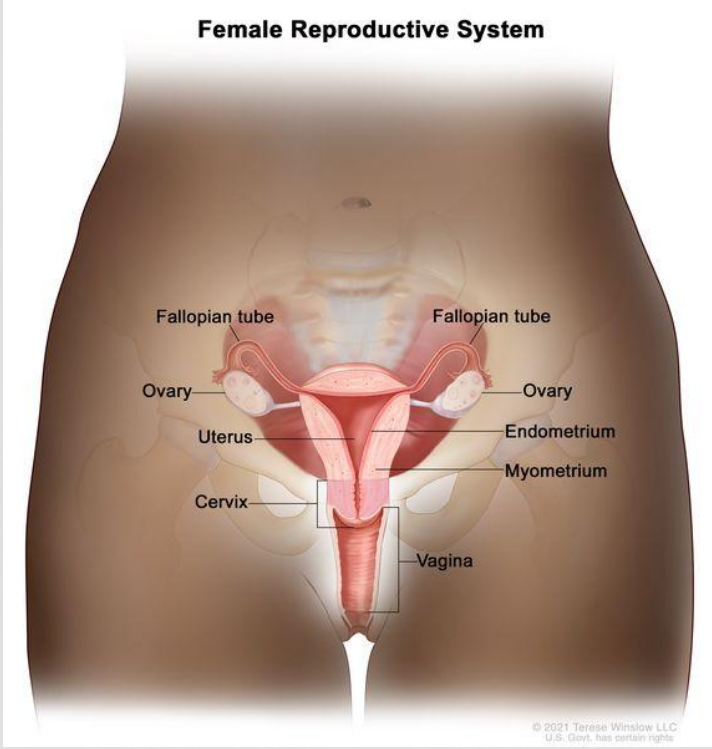
Menarche

- Menarche is the female's first menstrual period, caused by an increase in FSH and LH.
- Menarche typically occurs **1.5 to 3 years after thelarche** at approximately 12.8 years of age in White race girls and 3-8 months later in African-American girls.
- During puberty, the uterine endometrium undergoes cycles of proliferation and regression due to fluctuating **plasma estradiol levels**. This occurs until a point is reached when substantial growth occurs so that withdrawal of estrogen results in the **first menstruation** (menarche).
- Plasma **progesterone levels** remain low until a rise occurs after menarche, indicating that **ovulation** has occurred.
- The first ovulation takes place approximately 6 to 9 months after menarche due to an immature positive feedback mechanism of estrogen.

Ovarian Development

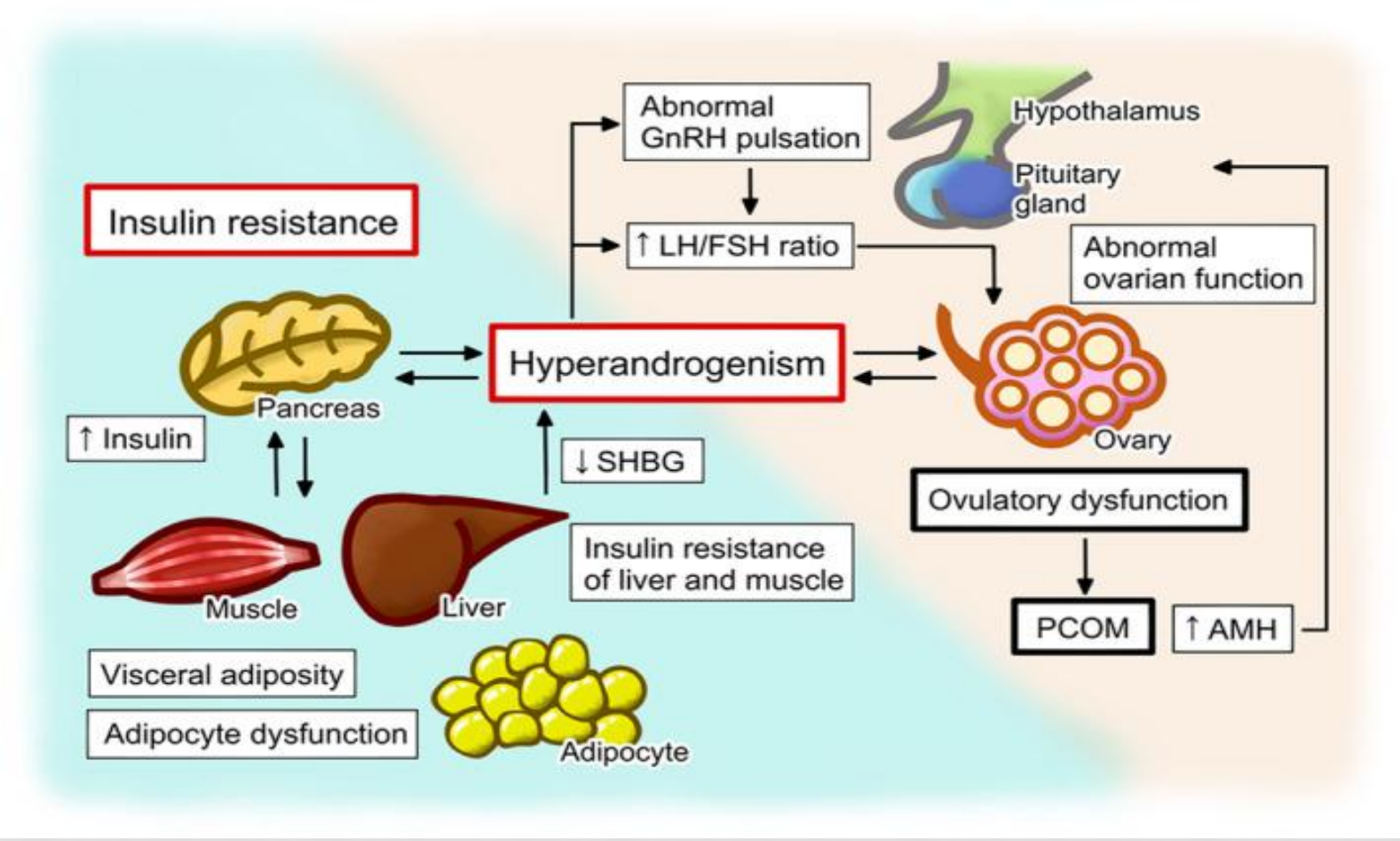
- The rise in gonadotropins during puberty stimulates the ovary to produce estradiol, which is responsible for developing secondary sexual characteristics such as thelarche, growth of reproductive organs, fat redistribution to the hips and breasts, and bone maturation.

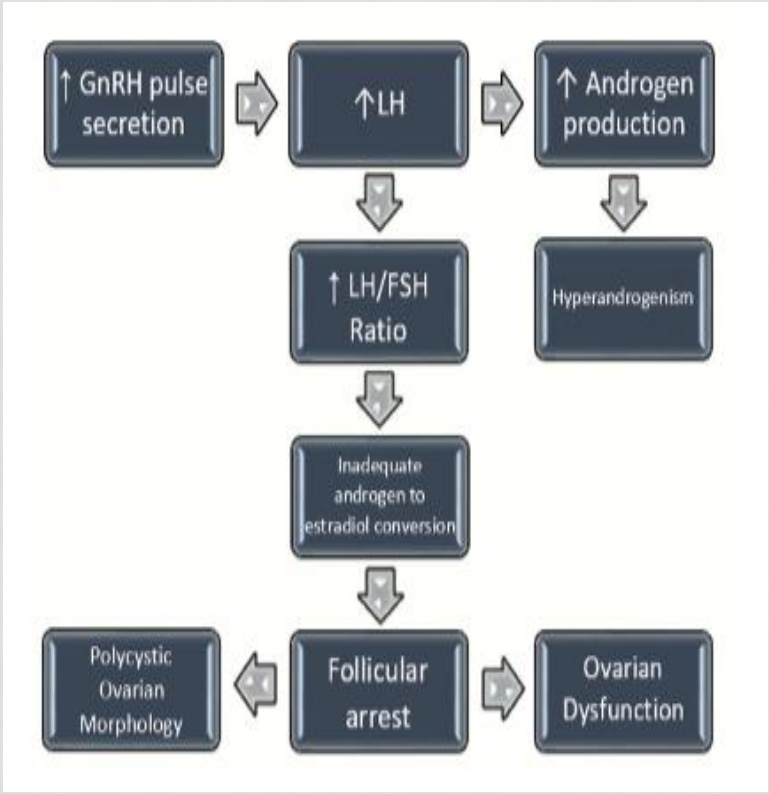
- Ovarian size increases from **prepubertal volume (approximately 0.5 cm^3)** to a **postpubertal volume (approximately 4.0 cm^3).**



Pathophysiology Of PCOS

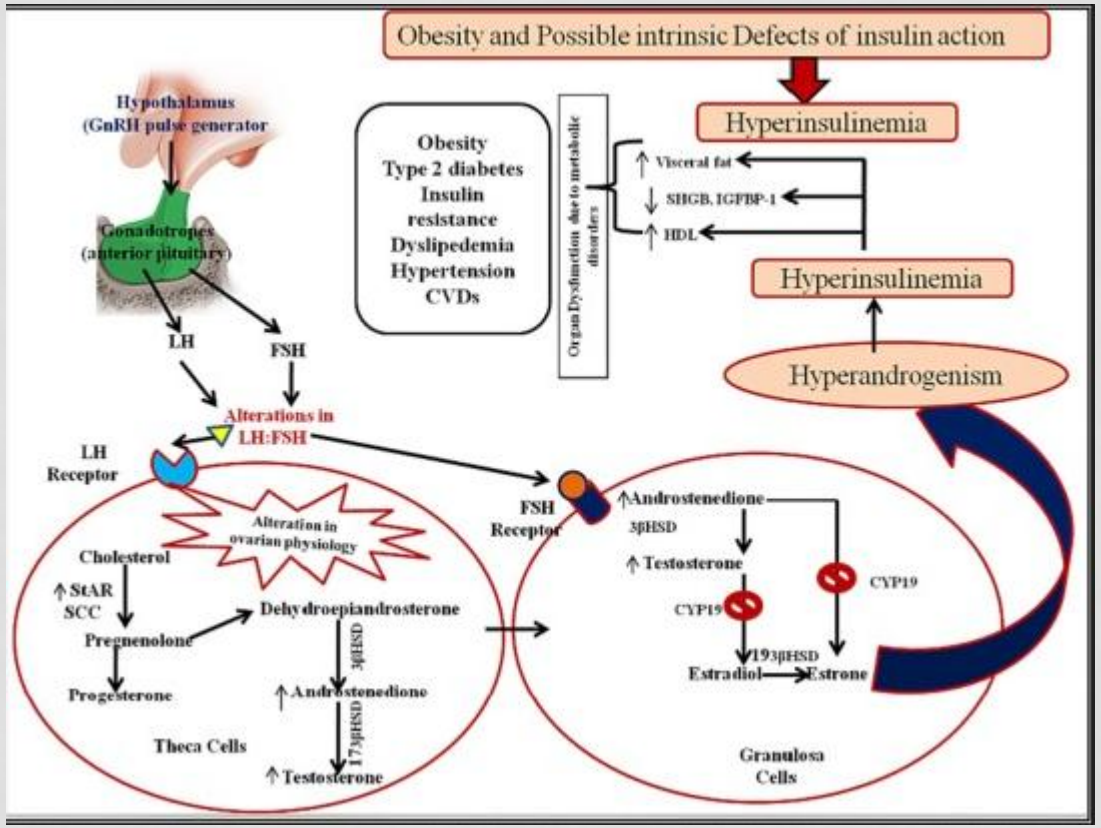
Pathophysiology Of PCOS



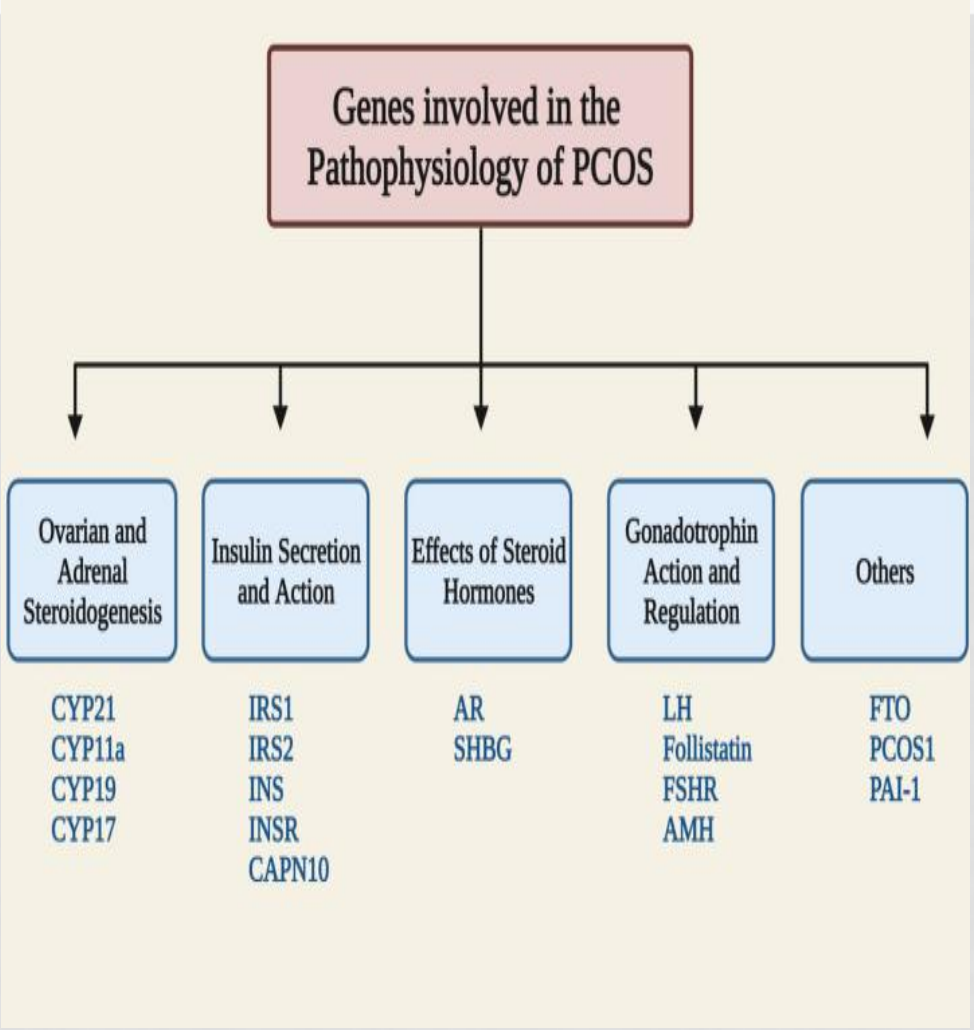


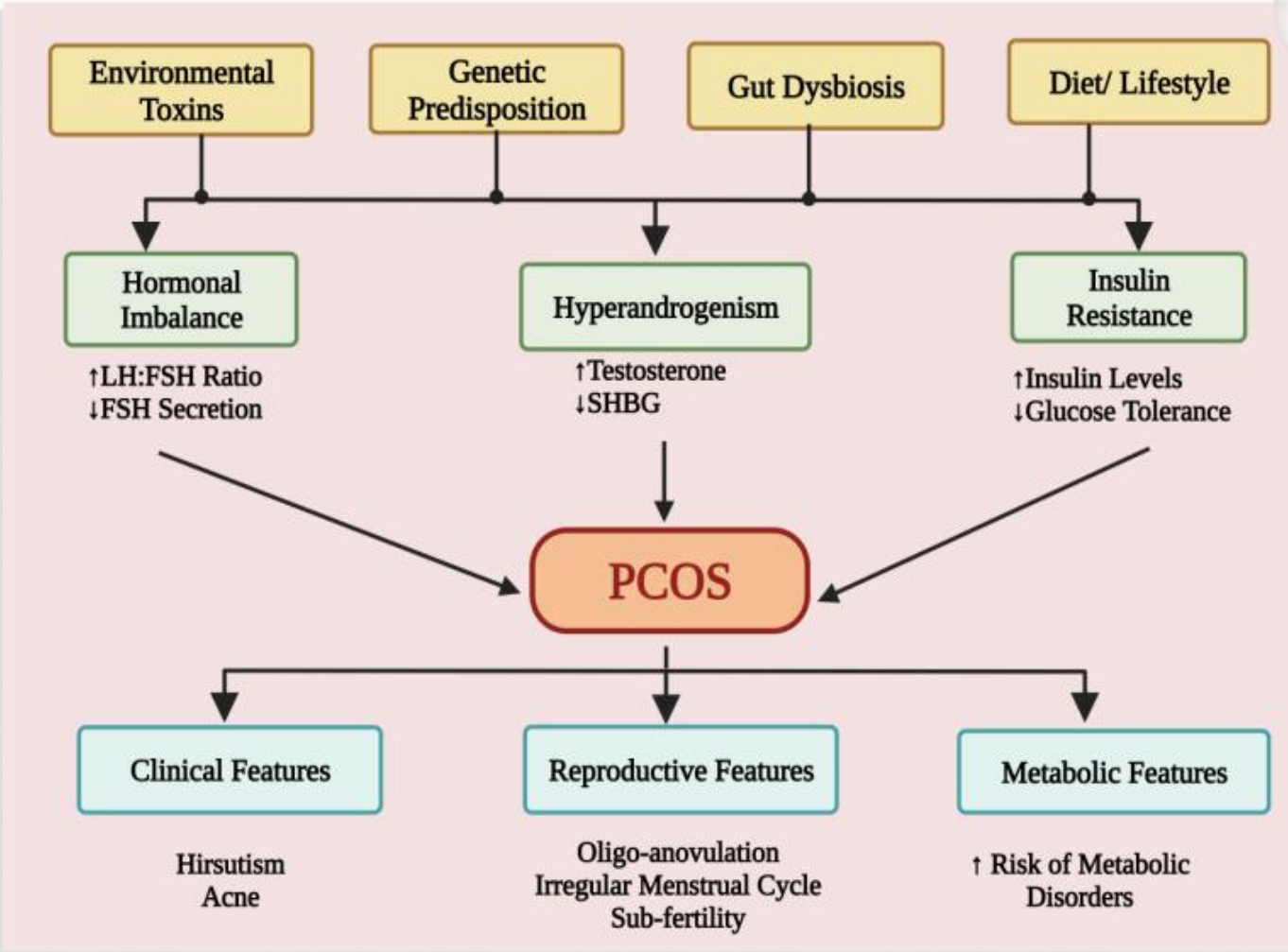
Harada M. Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. Reprod Med Biol. 2022 Oct 8;21(1):e12487. doi: 10.1002/rmb2.12487.

A review on critical appraisal and pathogenesis of polycystic ovarian syndrome



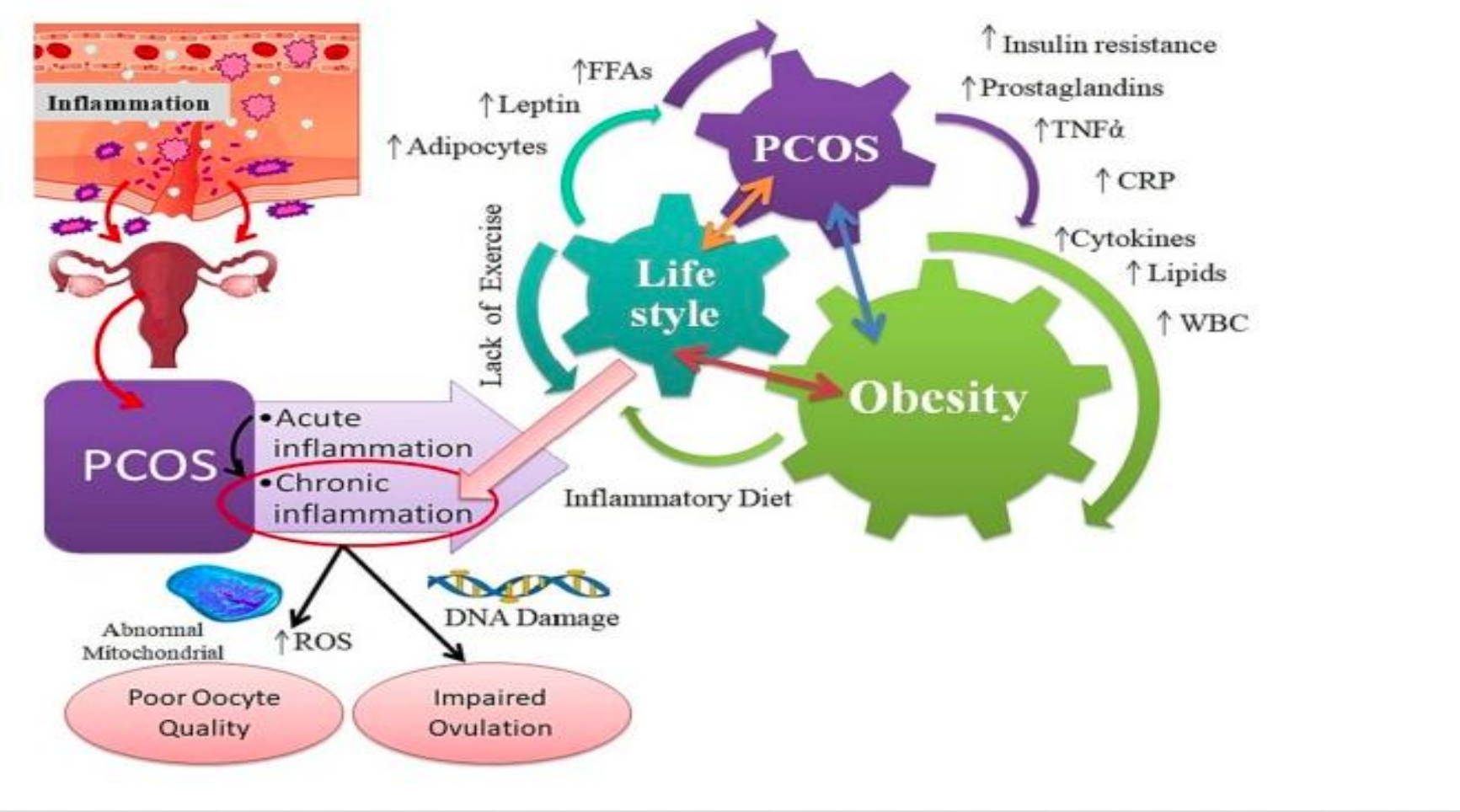
Pathophysiology Of PCOS



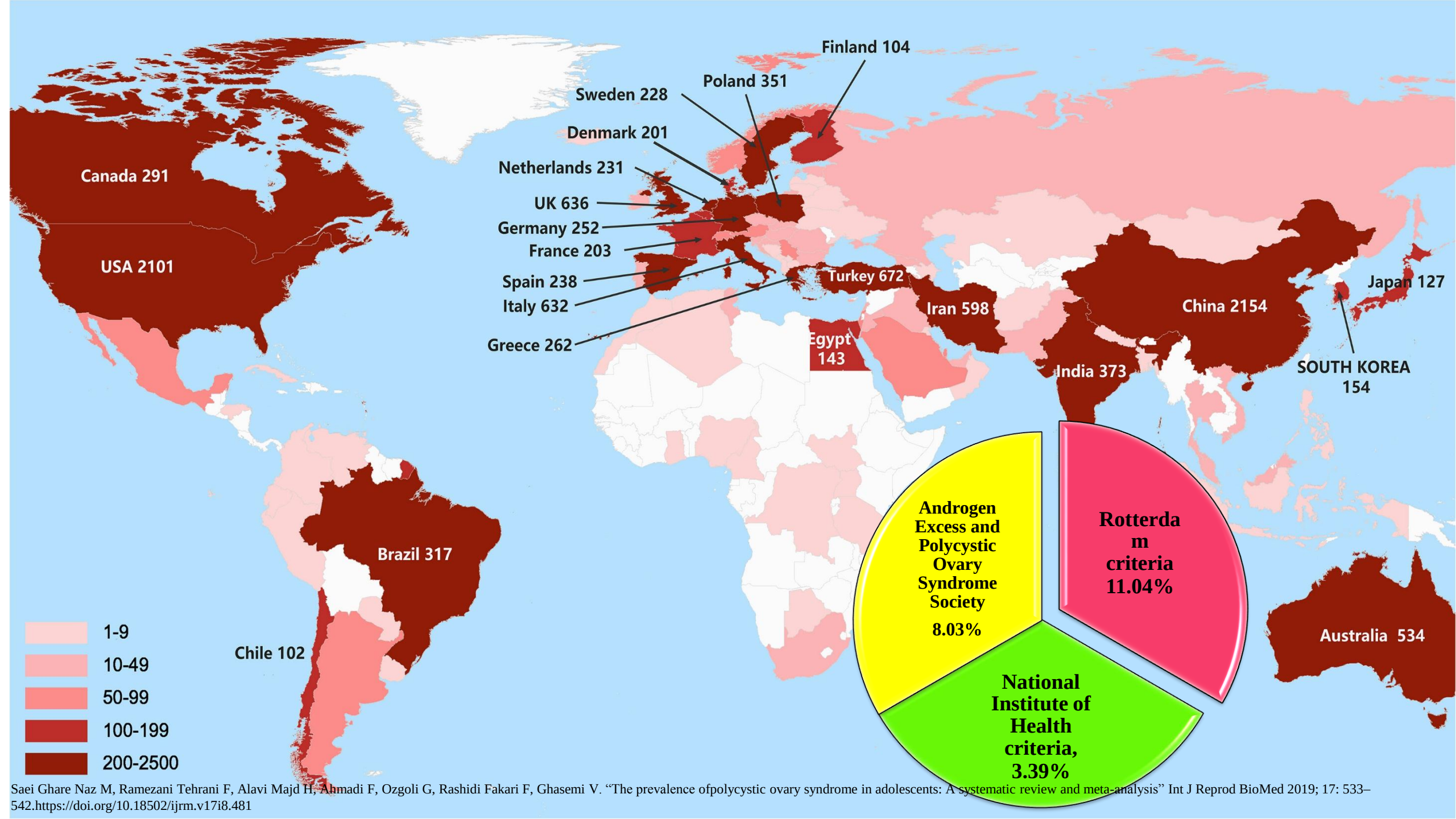


Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, Kumar M. Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics. J Clin Med. 2023 Feb 11;12(4):1454. doi: 10.3390/jcm12041454.

Biological Activities



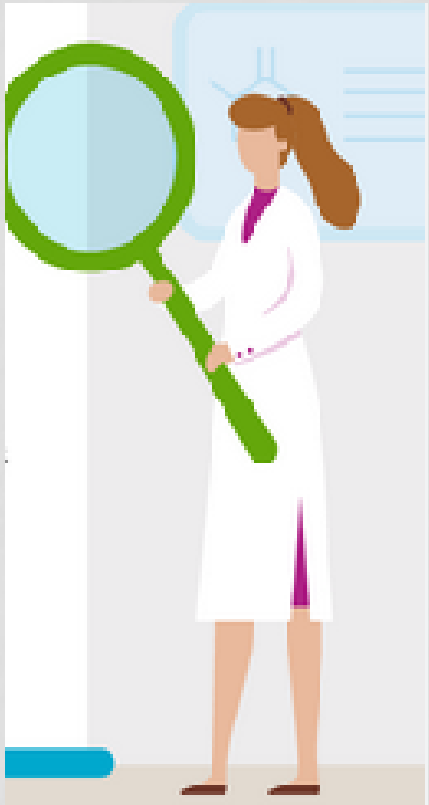
Prevalence and risk factors



Saei Ghare Naz M, Ramezani Tehrani F, Alavi Majd H, Ahmadi F, Ozgoli G, Rashidi Fakari F, Ghasemi V. "The prevalence ofpolycystic ovary syndrome in adolescents: A systematic review and meta-analysis" Int J Reprod BioMed 2019; 17: 533–542.https://doi.org/10.18502/ijrm.v17i8.481

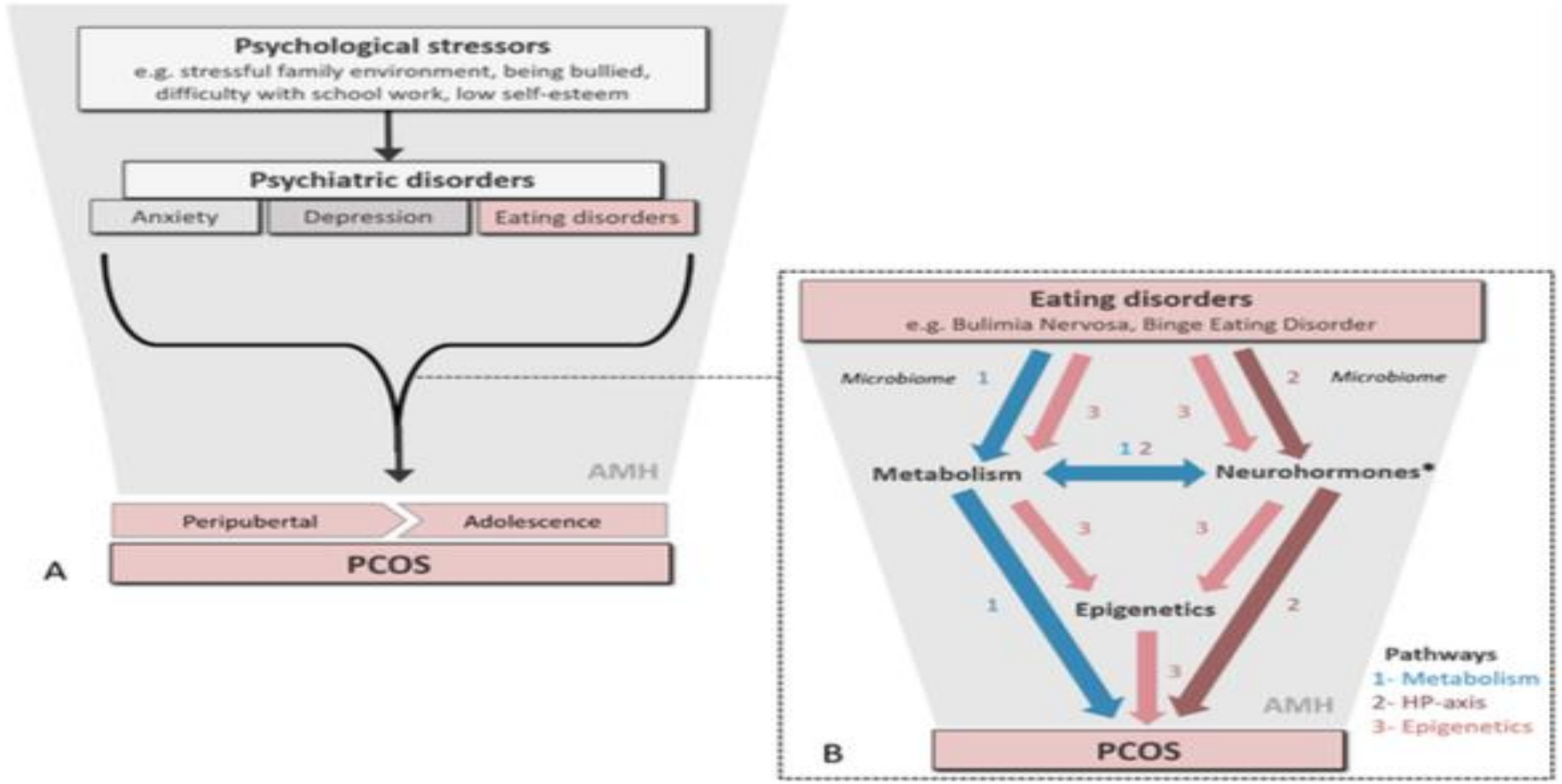
Risk Factors

obesity
premature menarche
Low birth weight
Premature pubarche
Environmental agents
Gens
inflammation
Physical inactivity



Welt CK, Carmina E. Clinical review: Lifecycle of polycystic ovary syndrome (PCOS): from in utero to menopause. J Clin Endocrinol Metab. 2013 Dec;98(12):4629-38. doi: 10.1210/jc.2013-2375. Epub 2013 Sep 24.

PCOS & Eating Problems Originating During Puberty And Adolescence



What Findings Would Be Expected In PCOS?

Menstrual irregularity

- Menstrual irregularity is common among adolescents (**first 2 years after menarche**) and is generally the result of anovulatory cycles.

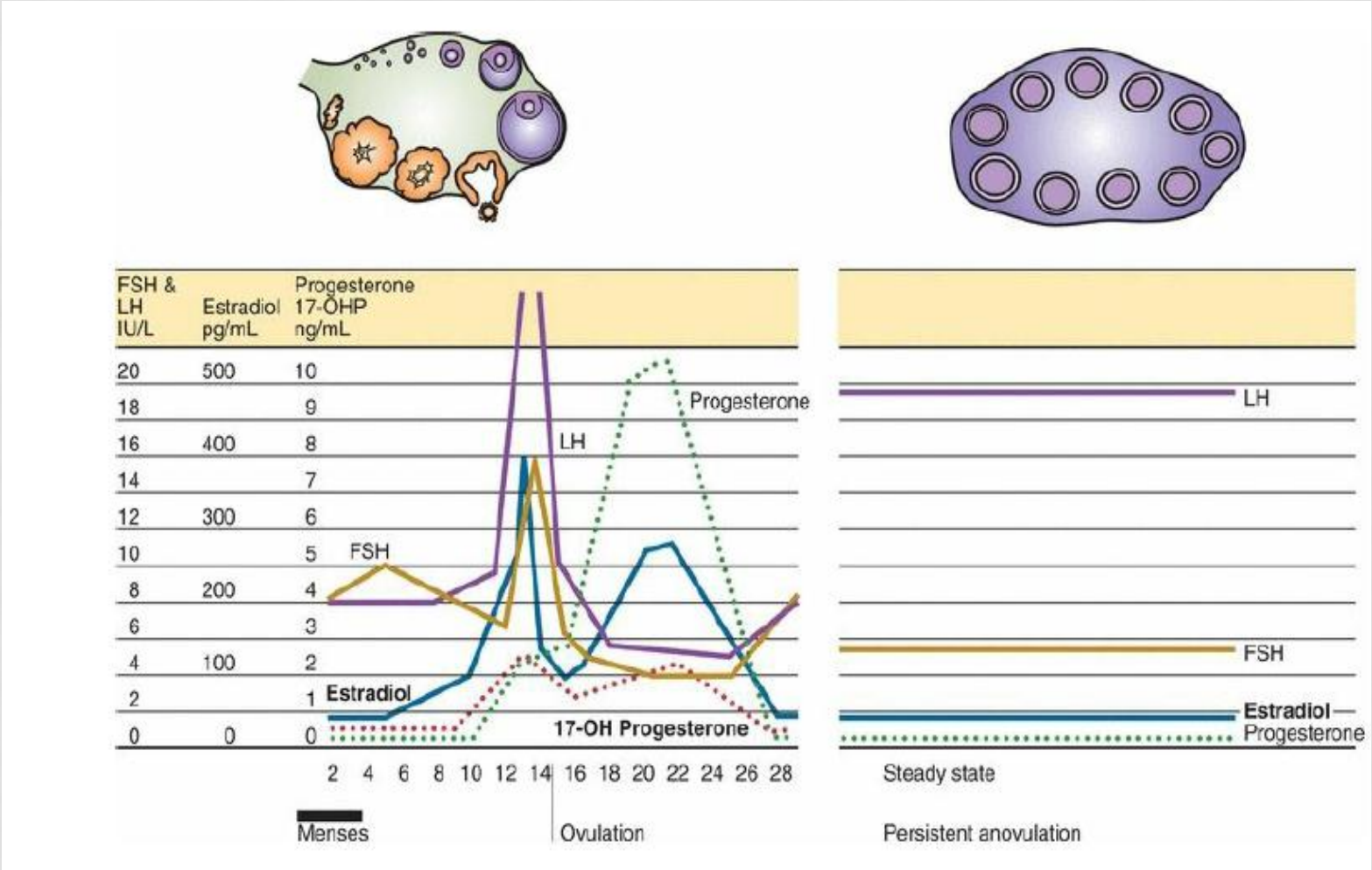
- Regular cycles (21–45 days) are established by the third year after menarche in approximately 95% of girls, but **cycles can remain irregular until the fifth year**.

Definition Of Irregular Menstrual Cycles In Adolescents

Time post menarche	Definition of irregular menstrual cycles
Less than 1 year post menarche	Irregular menstrual cycles are normal pubertal transition
> 1 to < 3 years post menarche	< 21 or > 45 days
> 3 years post menarche	< 21 or > 35 days or < 8 cycles per year
More than 1 year post menarche	> 90 days for any one cycle
-	Primary amenorrhoea by age 15 years or > 3 years post thelarche (breast development)

Peña, A.S., Witchel, S.F., Hoeger, K.M. *et al.* Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC Med* **18**, 72 (2020). https://doi.org/10.1186/s12916-020-01516-x

Persistent Anovulation



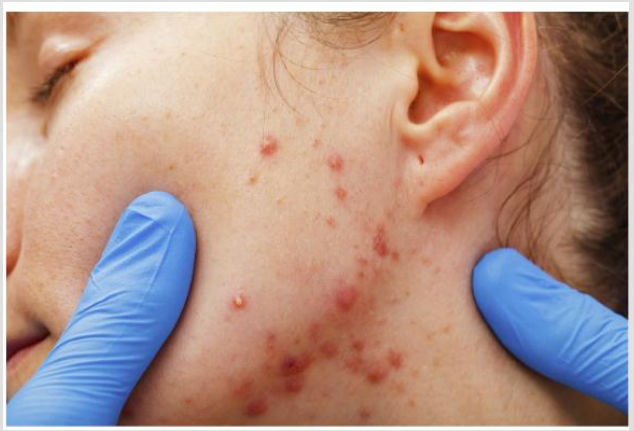
Clinical Hyperandrogenism

- A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, which in adolescents include **severe acne and hirsutism**.

- The mild comedonal acne is common in adolescent girls but moderate or severe comedonal acne (i.e. 10 or more facial lesions) in early puberty or moderate to severe inflammatory acne during the peri-menarcheal years is uncommon (less than 5%) and is more likely to relate to clinical hyperandrogenism.

Peña, A.S., Witchel, S.F., Hoeger, K.M. *et al.* Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC Med* **18**, 72 (2020). https://doi.org/10.1186/s12916-020-01516-x

Acne



Acne vulgaris is seen in 20% to 50% of adolescents with PCOS and often fails to respond to traditional topical treatments

Although acne may be associated with underlying hyperandrogenism, it cannot be used as the sole criterion for clinical hyperandrogenism, due to its high prevalence (up to 90%) in adolescence.

Hachey LM, Kroger-Jarvis M, Pavlik-Maus T, Leach R. Clinical Implications of Polycystic Ovary Syndrome in Adolescents. Nurs Womens Health. 2020 Apr;24(2):115-126. doi: 10.1016/j.nwh.2020.01.011. PMID: 32273076.

Hirsutism

- Hirsutism is considered a **more reliable marker** of hyperandrogenism in adolescents compared with acne.

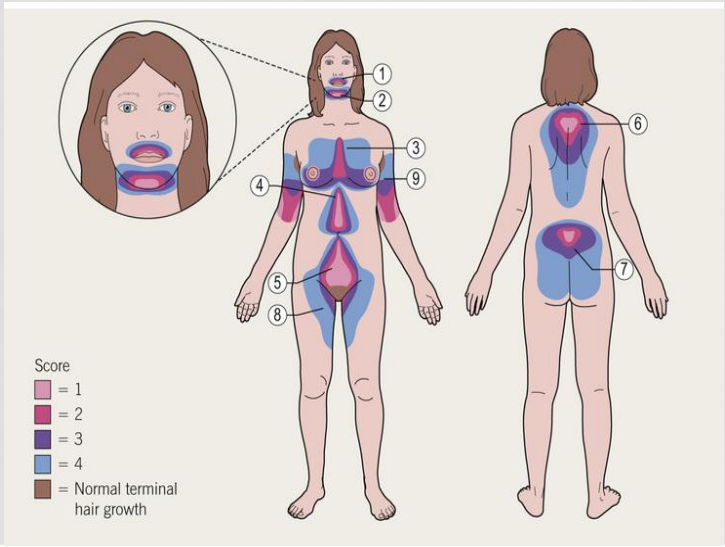
- It becomes more prominent in adulthood as the duration of exposure to androgens is increasing.

- **Mild hirsutism is considered to be normal soon after menarche**.

Hirsutism

- Standardised visual scales are preferred when assessing hirsutism, such as the modified Ferriman–Gallwey score (mFG), with a level ≥ 4–6 indicating hirsutism, depending on ethnicity, and acknowledging that self-treatment is common and can limit clinical assessment.

- The definition of ‘abnormal’ in hirsutism is controversial and varies across ethnicities. The original Ferriman–Gallwey cut-off was 4–6 and this later evolved in the literature to an arbitrary cut-off of 6–8 based on the 95th percentile of unselected women (which likely included women with PCOS)



Alopecia

- Male pattern hair loss or alopecia is another feature of clinical hyperandrogenism which manifests as a reduction in hair density over the central area of the scalp while the frontal hairline remains generally well conserved.

- There are no studies in adolescents evaluating alopecia in the context of PCOS.

Hyperandrogenemia

- The criteria used to define hyperandrogenemia in adolescent girls are confounded by developmental considerations.
- **Testosterone** levels have long been known to rise during puberty to reach a peak approximating adult levels within a few years after menarche .
- However, testosterone levels increase as adolescent anovulatory cycles lengthen in both asymptomatic and symptomatic anovulatory girls.
- Thus, there is uncertainty about whether mild hyperandrogenemia results as a normal perimenarcheal phenomenon. Additionally, how often adolescent hyperandrogenemia persists and predicts adult hyperandrogenemia is unclear.
- In most adolescents, androgen levels reach adult ranges at 12-15 years of age.

Hyperandrogenemia

- Biochemical evidence of hyperandrogenism, as indicated by **persistent elevation of serum total and/or free testosterone levels** and determined in a reliable reference laboratory, provides the clearest support for the presence of hyperandrogenism in an adolescent girl with symptoms of PCOS.

- A **single androgen** level >2 SD above the mean for the specific assay should not be considered to be evidence of hyperandrogenism in an otherwise asymptomatic adolescent girl.

Witchel SF, Oberfield S, Rosenfield RL, Codner E, Bonny A, Ibáñez L, Pena A, Horikawa R, Gomez-Lobo V, Joel D, Tfayli H, Arslanian S, Dabadghao P, Garcia Rudaz C, Lee PA. The Diagnosis of Polycystic Ovary Syndrome during Adolescence. Horm Res Paediatr. 2015 Apr 1. doi: 10.1159/000375530.

Main Laboratory Features Of PCOS In Adolescence

Hormones		Metabolic markers	
Testosterone	*high/ normal*	A1-apolipoprotein	*low*
Free Androgen Index (FAI)	*high*	Cholesterol	*normal/ high*
Sex Hormone Binding Globulin (SHBG)	*low*	HDL/ LDL cholesterol ratio	*low*
D4-Androstendione	*normal/ high*	Triglycerides	*normal/ high*
DHEAS	*normal/ high*	Insulin	*high/ normal*
LH	*normal/ high*	Hba1c	*high/ normal*
LH/FSH ratio	*normal/ high*		

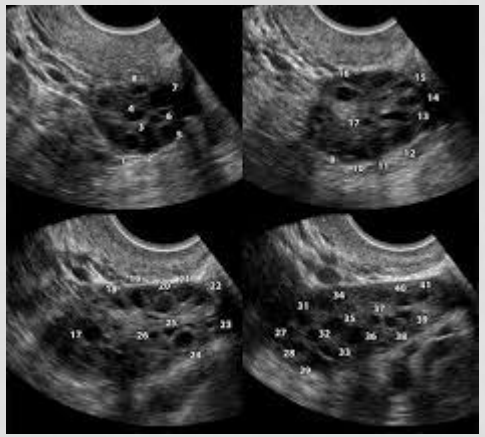
Tsikouras P, Spyros L, Manav B, Zervoudis S, Poiana C, Nikolaos T, Petros P, Dimitraki M, Koukouli C, Galazios G, von Tempelhoff GF. Features of Polycystic Ovary Syndrome in adolescence. J Med Life. 2015 Jul-Sep;8(3):291-6. PMID: 26351529

What Findings Would Be Expected In Ultrasound imaging in PCOS?

Ultrasound imaging in teens

- The ovarian volume starts to **increase with the onset of puberty**, achieves maximum volume soon after (between menarche and age 16 years), and remains stable or decreases slightly thereafter.

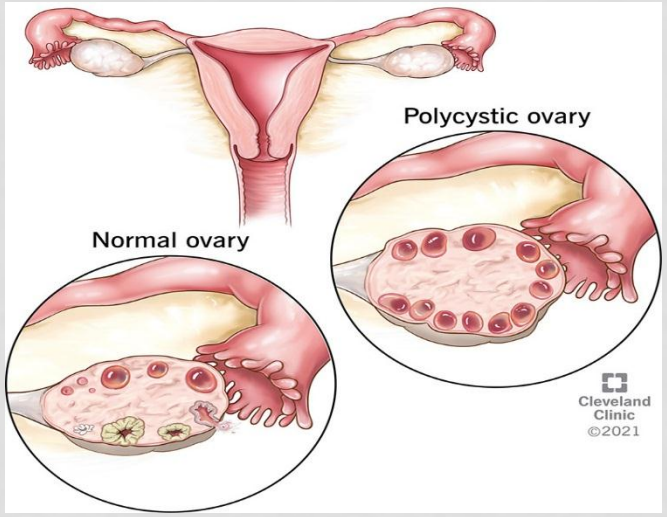
- Follicle number and size are also noted to increase with puberty, with a higher number of small follicles during adolescence and young adulthood and a decrease thereafter.



Ultrasound imaging

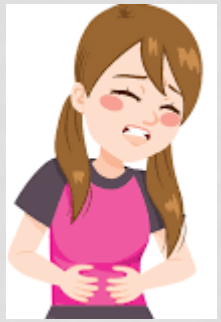
- A multifollicular pattern, which is defined by the presence of large follicles distributed throughout the ovary, does not have a relationship with hyperandrogenism, is more common in adolescents, and should not be considered a pathological finding

- Additionally, in healthy girls with regular menstrual cycles and without hyperandrogenism, PCOM does not indicate a diagnosis of PCOS.
- Abdominal ultrasound in adolescents, particularly obese girls, may yield inadequate information.



Ultrasound imaging

- **There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents; hence, it is not recommended in adolescents**

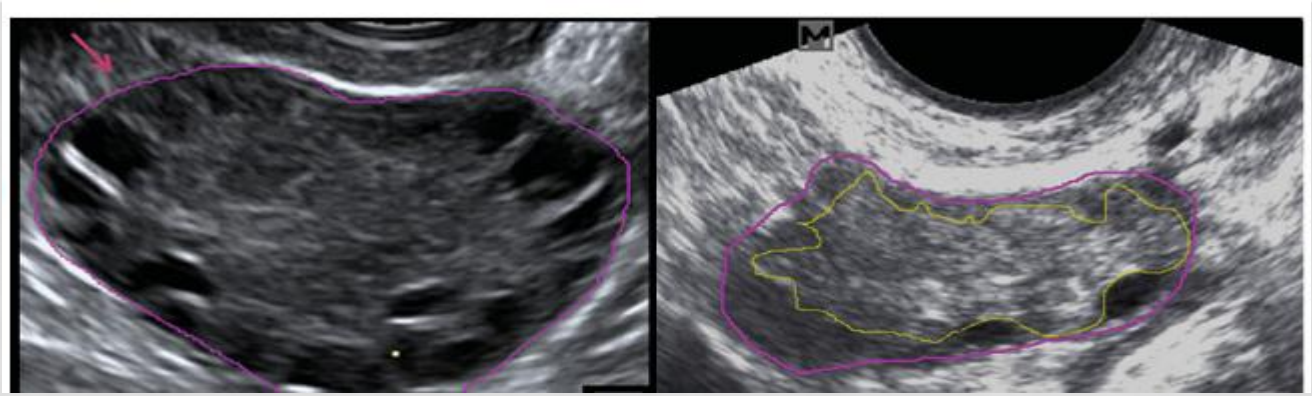


Ultrasound imaging

- Currently, ultrasonography is not diagnostic of PCOS in adolescents but provides supportive evidence, mainly in the setting of an enlarged ovarian volume.
- Ovarian volume is important to evaluate in adolescents but is not enough in making a definitive diagnosis of PCOS.
- Although morphologic sonographic features, such as peripheral distribution of follicles, increased stromal area, and vascularization are not included in the diagnostic criteria for PCOS, they may have significant potential to increase the accuracy of diagnosis of PCOS in adolescents.
- **Evaluation with ultrasound can occur after 8 years post menarche**

Senaldi L, Gopi RP, Milla S, Shah B. Is ultrasound useful in the diagnosis of adolescents with polycystic ovary syndrome? J Pediatr Endocrinol Metab. 2015 May;28(5-6):605-12. doi: 10.1515/jpem-2014-0307. PMID: 25381947.
Peña, A.S., Witchel, S.F., Hoeger, K.M. et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med 18, 72 (2020). https://doi.org/10.1186/s12916-020-01516-x

Ultrasound imaging



The ultrasound should be preferred to perform the scan on Day 2-7 of the menstrual cycle. This prevents any growing follicle from hiding smaller ones or modifying ovarian volume. In case of oligo or amenorrhoeic women, scanning may be performed at random, or 2-5 days after progesterone-induced bleeding.

Scanning should be done with an ‘optimally’ filled bladder, avoiding extremes in transabdominal sonography (TAS), and empty bladder in transvaginal sonography. Identify the ovaries in relation to iliac vessels.

Measurement of ovarian volume (length x width x thickness) should be done precisely, ensuring adequate visualisation of the ovarian contour. If possible, a follicular count should be obtained with careful meticulous sweeping of both ovaries individually.

Diagnostic Criteria For PCOS In Adolescents

TABLE 1. Diagnostic criteria for PCOS in adolescents[3,4]

Criteria	Evaluation	Considerations
Irregular menses/ovulatory dysfunction	Comprehensive history and physical/menses tracking. Irregular menses are defined as: • From 1 to 3 years postmenarche: <21 or >45 days • From 3 years postmenarche: <21 days or >35 days, or <8 cycles per year • Menstrual cycle >90 days for any one cycle >1 year postmenarche • Primary amenorrhea by age 15 years or age 13 years with absence of menses and no secondary sexual characteristics such as breast development	Generally, patients with irregular menses must be 2 years postmenarche
Hyperandrogenism: clinical or biochemical	• Clinical hyperandrogenism • Progressive hirsutism • Complete physical examination; use validated visual scale to evaluate hirsutism • Moderate to severe acne; follow-up with evaluation for biochemical hyperandrogenism • Biochemical hyperandrogenism • Use of high-quality assays for total and free testosterone	Moderate to severe acne alone is not adequate to diagnose clinical hyperandrogenism, must use follow-up testing
Rule out other disorders of hyperandrogenism	Laboratory evaluation for pregnancy, thyroid disorders, nonclassic congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor	Ultrasound is not recommended to evaluate ovarian morphology*

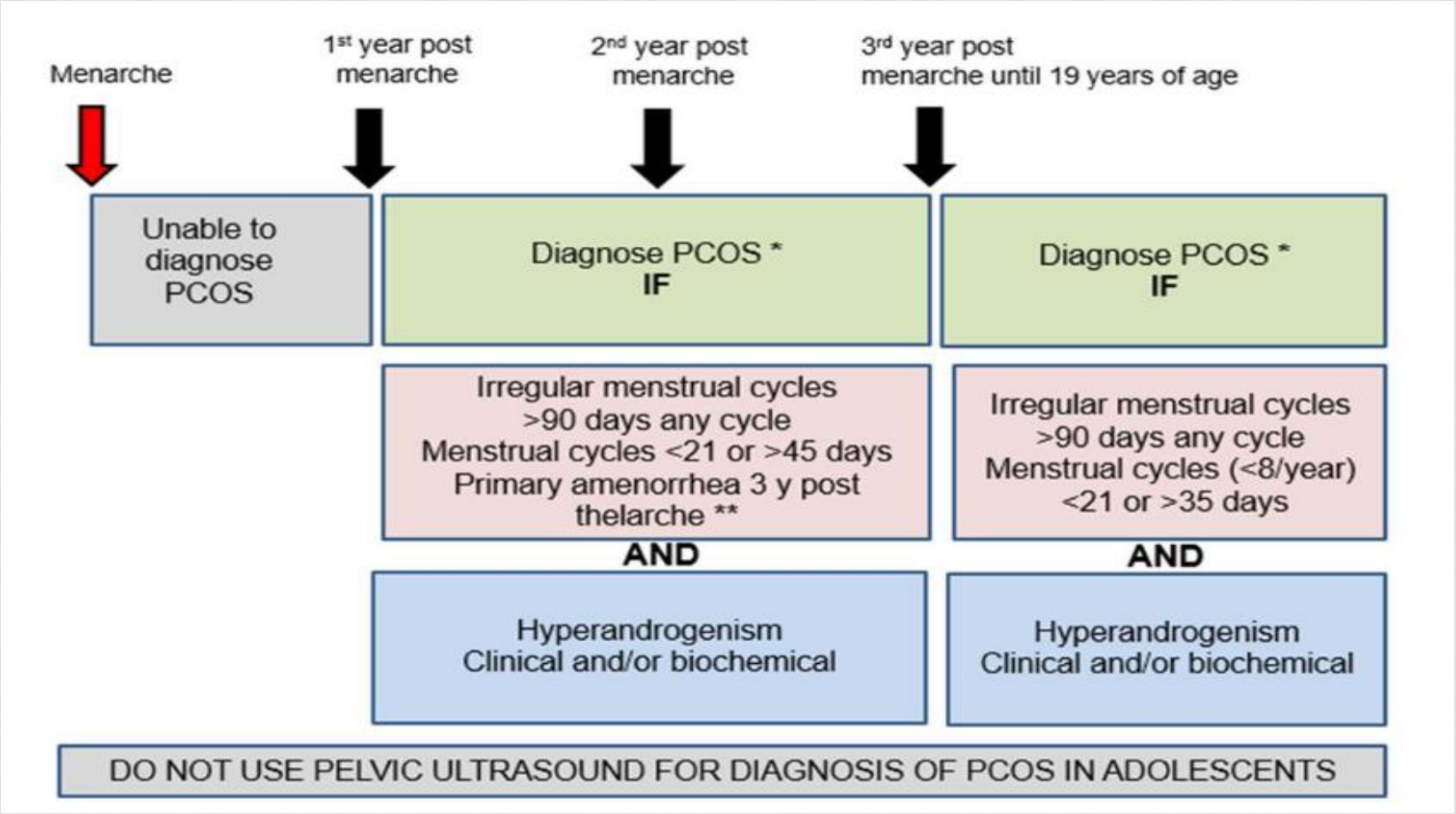
*Ultrasound should not be used to evaluate for PCOS in patients <8 years postmenarche. Ultrasound should be reserved for evaluation of other conditions as needed, such as evaluation for structural abnormalities in primary amenorrhea.

Conlon JL, Malcolm S, Monaghan M. Diagnosis and treatment of polycystic ovary syndrome in adolescents. JAAPA. 2021 Oct 1;34(10):15-22. doi: 10.1097/01.JAA.0000791468.37054.5d. PMID: 34524161.

Increased risk

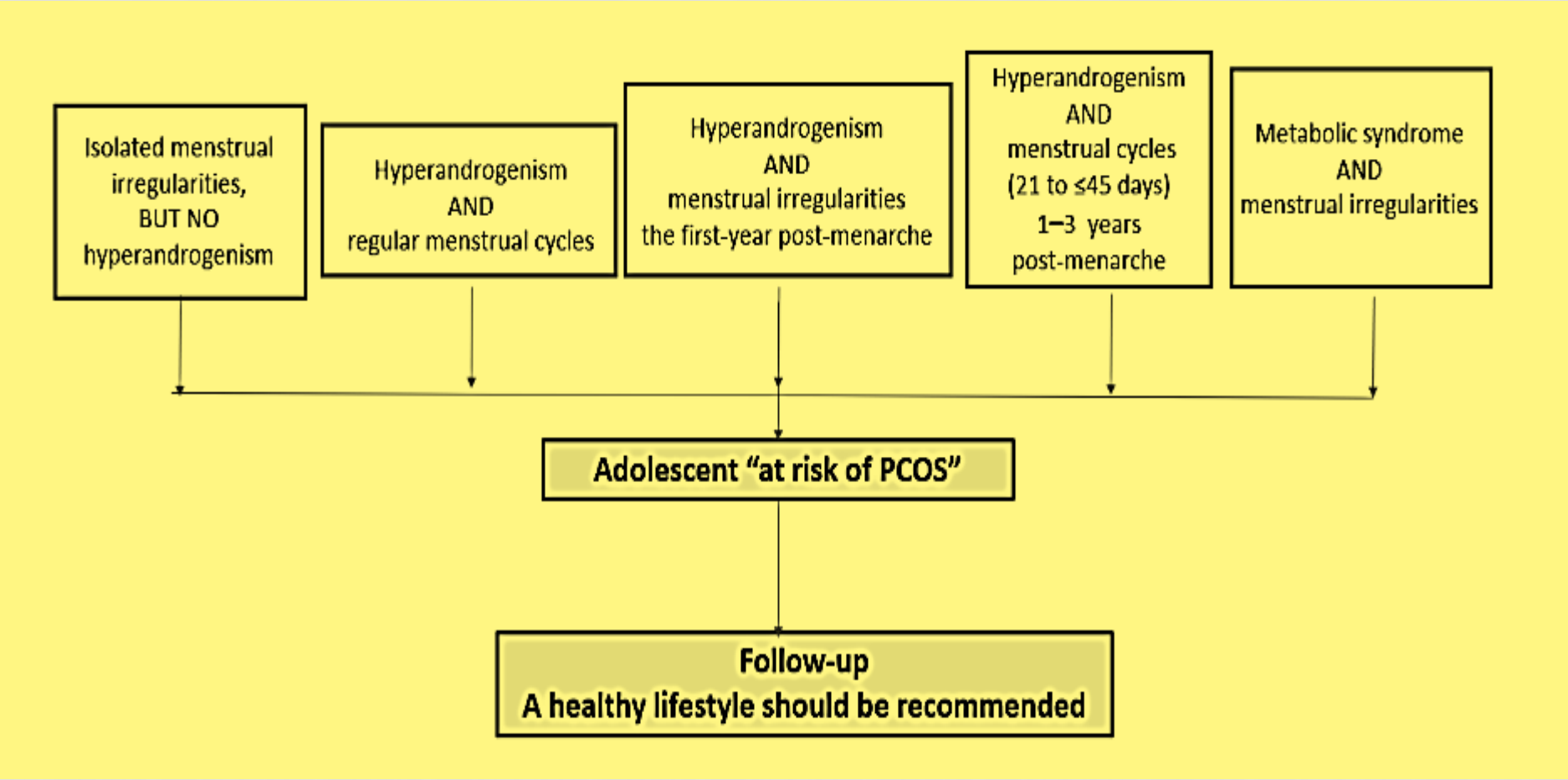
- For adolescents who have features of PCOS, but do not meet diagnostic criteria, an "**increased risk**" could be considered and reassessment is advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features, and those with significant weight gain in adolescence.

Adolescent PCOS Diagnosis According To Time Post-menarch



Peña AS, Codner E, Witchel S. Criteria for Diagnosis of Polycystic Ovary Syndrome during Adolescence: Literature Review. Diagnostics (Basel). 2022 Aug 10;12(8):1931. doi: 10.3390/diagnostics12081931. PMID: 36010282;

Definitions Of Adolescents “At Risk Of PCOS”



Peña AS, Codner E, Witchel S. Criteria for Diagnosis of Polycystic Ovary Syndrome during Adolescence: Literature Review. Diagnostics (Basel). 2022 Aug 10;12(8):1931. doi: 10.3390/diagnostics12081931. PMID: 36010282;

Diagnostic Approach Of PCOS In Adolescence

- A thorough medical history has to be obtained, including information on exogenous medication intake, such as androgenic steroids and anti-epileptics.
- Of note, PCOS features may be covered by medications used to treat acne.
- Furthermore, obtaining a family history is required, since a genetic component may be present. A detailed physical examination is also important.
- Acanthosis nigricans and truncal obesity may be detected as clinical signs of insulin resistance.
- The degree of hirsutism can be assessed by the Ferriman-Gallwey score , and the severity of acne can be graded based on lesion type and count.

Diagnostic Approach Of PCOS In Adolescence

- Biochemical workup in PCOS should mainly include fasting plasma glucose, lipid profile, and total or calculated fT concentrations (or FAI), preferably in the morning.
- If treatment has been initiated in the interim, androgen concentrations may be altered, and this should be taken into consideration by the clinicians.
- To discriminate between different causes of hyperandrogenemia or menstrual irregularity, additional testing may include DHEAS, Δ-androstenedione, 17-hydroxyprogesterone [17(OH)P], thyroid stimulating hormone (TSH),[4] prolactin, LH, FSH, and estradiol from the 3rd to 5th day of the menstrual cycle.
- Acosyntropin (ACTH) stimulation test should be ideally performed to screen for non-classic congenital adrenal hyperplasia (NC-CAH). However, undertaking the ACTH stimulation testing in all patients may not be practical.

Differential Diagnoses Of PCOS

- Congenital adrenal hyperplasia
- Cushing’s syndrome
- Androgen-secreting tumour
- - Adrenal origin
- - Ovarian origin
- Exogenous androgen administration
- Ovarian hyperthecosis

Conditions That Can Masquerade As PCOS

Condition	Features shared with PCOS	Unique features and methods for exclusion
Late onset congenital adrenal hyperplasia	Oligoanovulation Hyperandrogenism Hyperandrogenima	Elevated 17-OHP levels in the commonest variant due to 21-hydroxylase deficiency
Androgen secretion tomure	Oligoanovulation Hyperandrogenism Hyperandrogenima	Rapid progression of clinical symptoms of hyperandogenism Sign of virilization Markedly elevated total testosterone levels Elevated DHEA-S levels
Cushing syndrome	Oligoanovulation Hyperandrogenism Hyperandrogenima	Clinicial stigmata including hypertension, skin platheora Elevated 24-hours urine-free cortisol
hyperprolactinemia	Oligoanovulation	Elevated prolactin levels
Hypothyroidism	Oligoanovulation Hair loss	Elevated TSH levels (primary hypothyroidism) Positive antithyroid antibodies (Hashimato thyroiditis)
Sever insulin resistance syndrome	Oligoanovulation Hyperandrogenism Hyperandrogenima	Elaveted fasting insulin levels Markedly elevated provoked insulin levels during OGTT Acantosis nigricans
Iatrogenic **Androgenic agents** **Antidepressants** **Antiseizure**	Oligoanovulation Hyperandrogenism	Androgen exposure Suppressed FSH/LH levels Elevated total testosterone Hyperprolactinemia

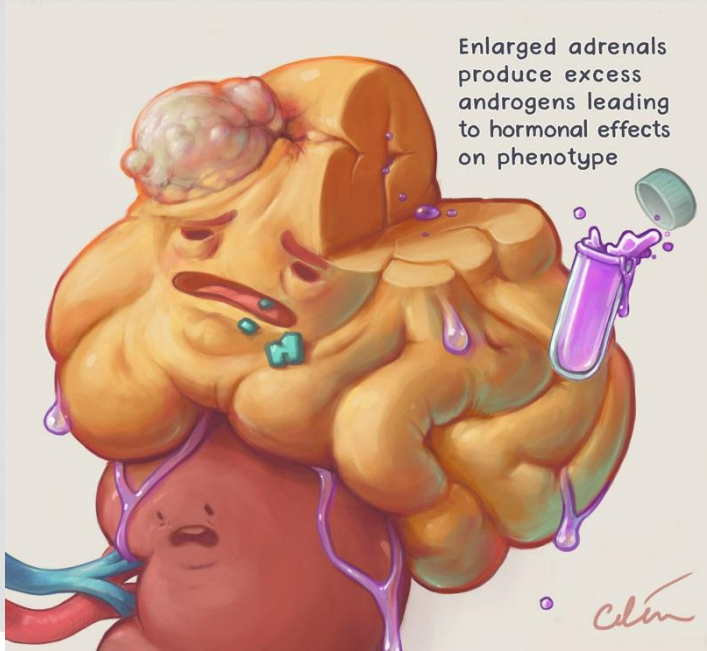
Congenital Adrenal Hyperplasia

- CAH is a group of autosomal recessive disorders, each of which involves a deficiency of one of five enzymes involved in the synthesis of cortisol in the adrenal cortex.

- In CAH, insufficient cortisol is produced, which stimulates hypothalamic CRH secretion, due to the absence of normal feedback inhibition.

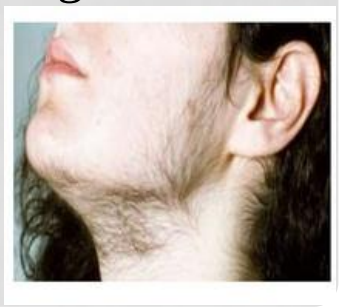
  - This leads to chronically elevated adrenocorticotrophic hormone (ACTH), which in turn stimulates the adrenal gland to become hyperplastic with excess androgen hormones and steroid precursors being produced and secreted from the normally functioning metabolic pathways.

  - The most common form of CAH is due to a deficiency of 21-hydroxylase activity, which accounts for 90–95% of cases of CAH. It is associated with a wide range of clinical effects and severity can vary depending on the mutation.



Classic 21-hydroxylase Deficiency

- Female infants can be severely virilised leading to ambiguous genitalia. Salt wasting and adrenal crises can occur in some patients and are important causes of neonatal death.
- Non-classic 21-hydroxylase deficiency tends to present in puberty, or later in adult life. In this condition, the mutated enzymes in the cortisol biosynthetic pathways maintain 20–60% of normal function.
- Typical patients have features of hyperandrogenism but have preserved cortisol and aldosterone production, so salt wasting and adrenal crises are not common features of this condition.
- Many female patients can present in early adulthood with menstrual disturbance or hirsutism. Affected males and females may exhibit precocious puberty with tall stature at pubarche, advanced bone age with early epiphyseal fusion, infertility and severe acne, which is refractory to treatment.

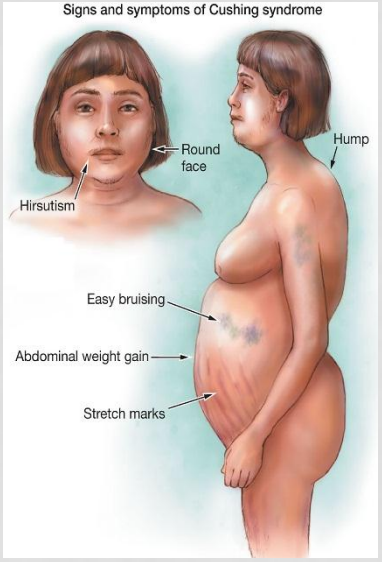


Cushing's Syndrome

- Cushing's syndrome is a rare but important cause of androgen excess. Hirsutism is present in approximately 80% of patients.

- Cushing's syndrome results from increased circulating concentrations of cortisol and can present insidiously with centripetal weight gain, facial plethora, supraclavicular fat pads, abdominal striae and signs of hyperandrogenism, such as hirsutism, acne and male pattern baldness.

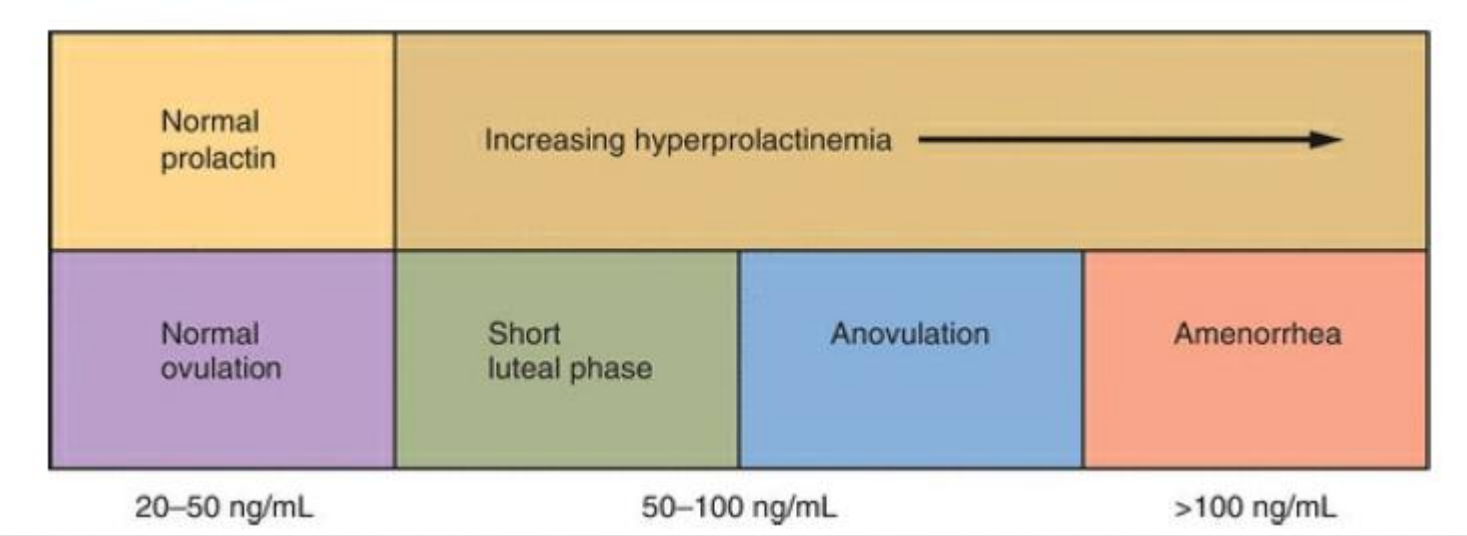
- Cushing's syndrome can be secondary to an ACTH secreting pituitary tumour (Cushing's disease), autonomous cortisol secretion by the adrenal glands due to adrenocortical neoplasms or hyperplasia, 20 exogenous administration of glucocorticoids or ectopic ACTH secretion in neoplasia including small cell lung carcinomasand carcinoid tumours.



Hyperprolactinemia

- Elevated prolactin levels can result in a spectrum of ovulatory dysfunction, ranging from a short luteal phase to anovulatory cycles to amenorrhea and hypogonadotropic hypogonadism, depending on the extent to which the gonadotropin secretion is disturbed or suppressed.

- Mild hyperprolactinemia may cause only a short luteal phase, resulting from inadequate preovulatory follicular development.



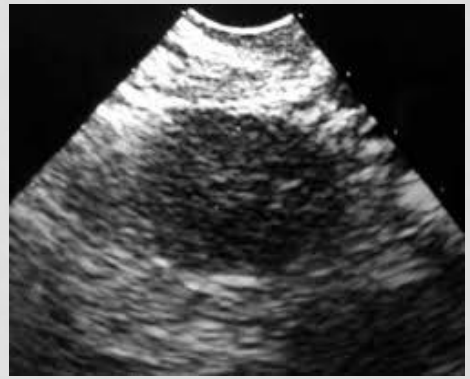
Androgen Secreting Tumours

- Androgen secreting tumours of the ovaries or adrenal glands are rare causes of hyperandrogenism that often mimic PCOS.
- Women with these tumours tend to have sudden onset and rapid progression of hyperandrogenism and early development of frank virilisation.
- The most common virilising ovarian tumours are Sertoli Leydig cell tumours and account for 0.5% of all ovarian neoplasms.
- Ovarian androgen-secreting tumours are characterised by striking elevations in serum testosterone but normal DHEA-S and urinary 17-ketosteroids.
- Androgen-secreting adrenal neoplasms are less common than ovarian neoplasms and typically present with features of Cushing's syndrome and simultaneous virilisation. Adrenal adenomas more frequently produce cortisol and aldosterone while functional adrenal carcinomas produce androgens and cortisol.
- Pure androgen-secreting adrenal tumors are rare. Adrenal carcinomas causing virilisation peak in incidence during childhood and during the fourth/fifth decades of life.
- Markedly elevated serum testosterone, DHEA-S, and urinary 17-ketosteroid levels, which are not suppressed with dexamethasone, suggest an androgen-secreting tumour.
- Significantly elevated serum testosterone levels could indicate either an androgen-secreting adrenal or ovarian tumour. Computerised tomography, magnetic resonance imaging and ultrasound are imaging techniques used to differentiate between these clinical conditions

Ovarian Hyperthecosis

- Ovarian hyperthecosis accounts for most of the cases of hyperandrogenaemia in postmenopausal women, although its prevalence in younger women is much lower, affecting <1% of women with elevated androgens in their reproductive years.

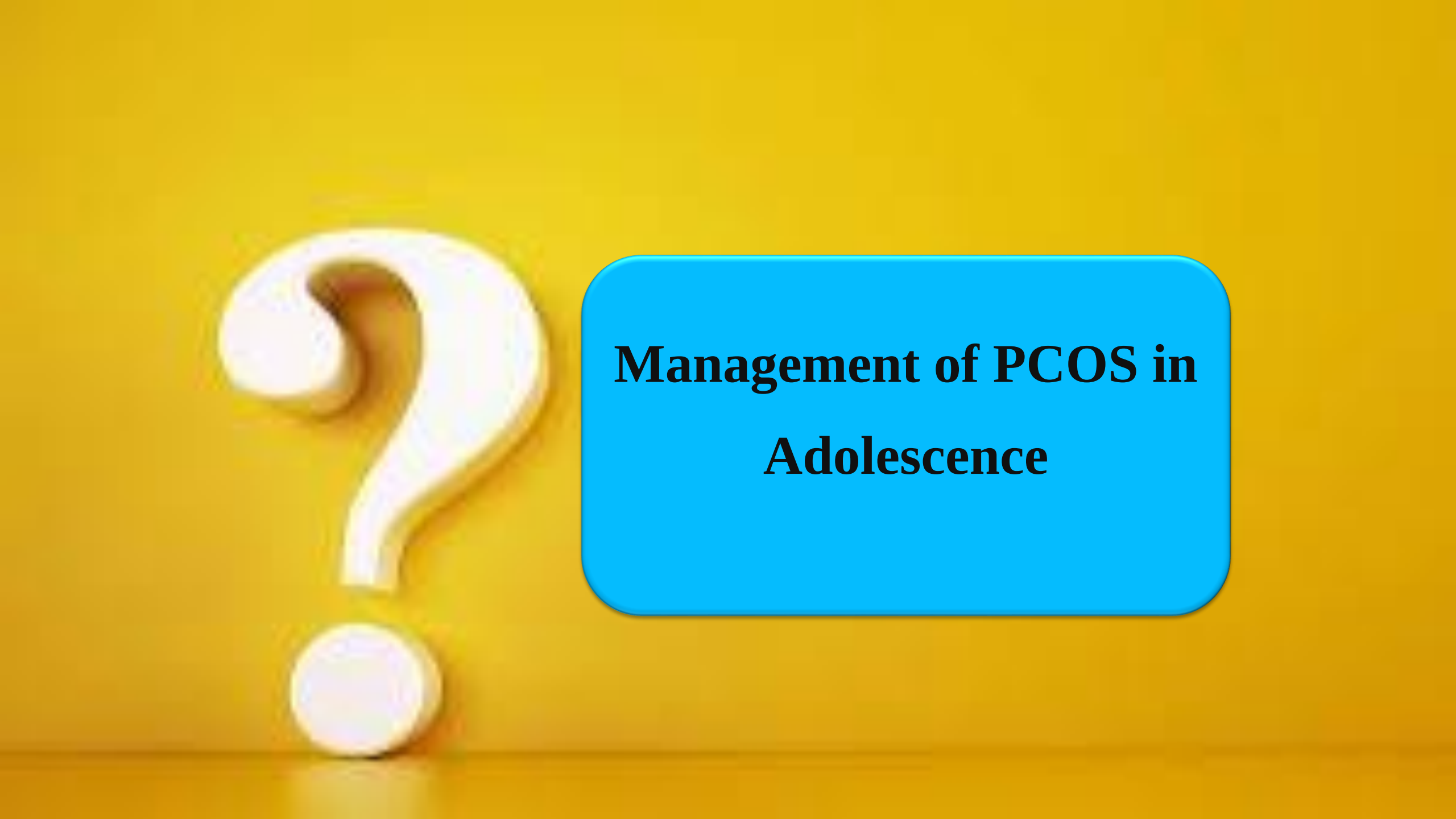
- Ovarian hyperthecosis describes the presence of luteinised theca cell nests in the ovarian stroma. When compared with the closely related condition of PCOS, hyperthecosis is typically associated with more severe hyperandrogenism and virilisation. Testosterone concentrations are much higher than in PCOS and may exceed 7 nmol/l.



Diagnosis caustion

- Great caution should be taken before diagnosing PCOS in adolescent girls with clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism if oligomenorrhea has not persisted for more than 2 years. These girls can be considered to be **at risk for PCOS**.

- To avoid misdiagnosing physiological pubertal changes as PCOS, deferred diagnostic labeling accompanied by frequent longitudinal re-evaluations of these girls considered to be at risk for PCOS is beneficial and prudent during adolescence.


Management of PCOS in Adolescence

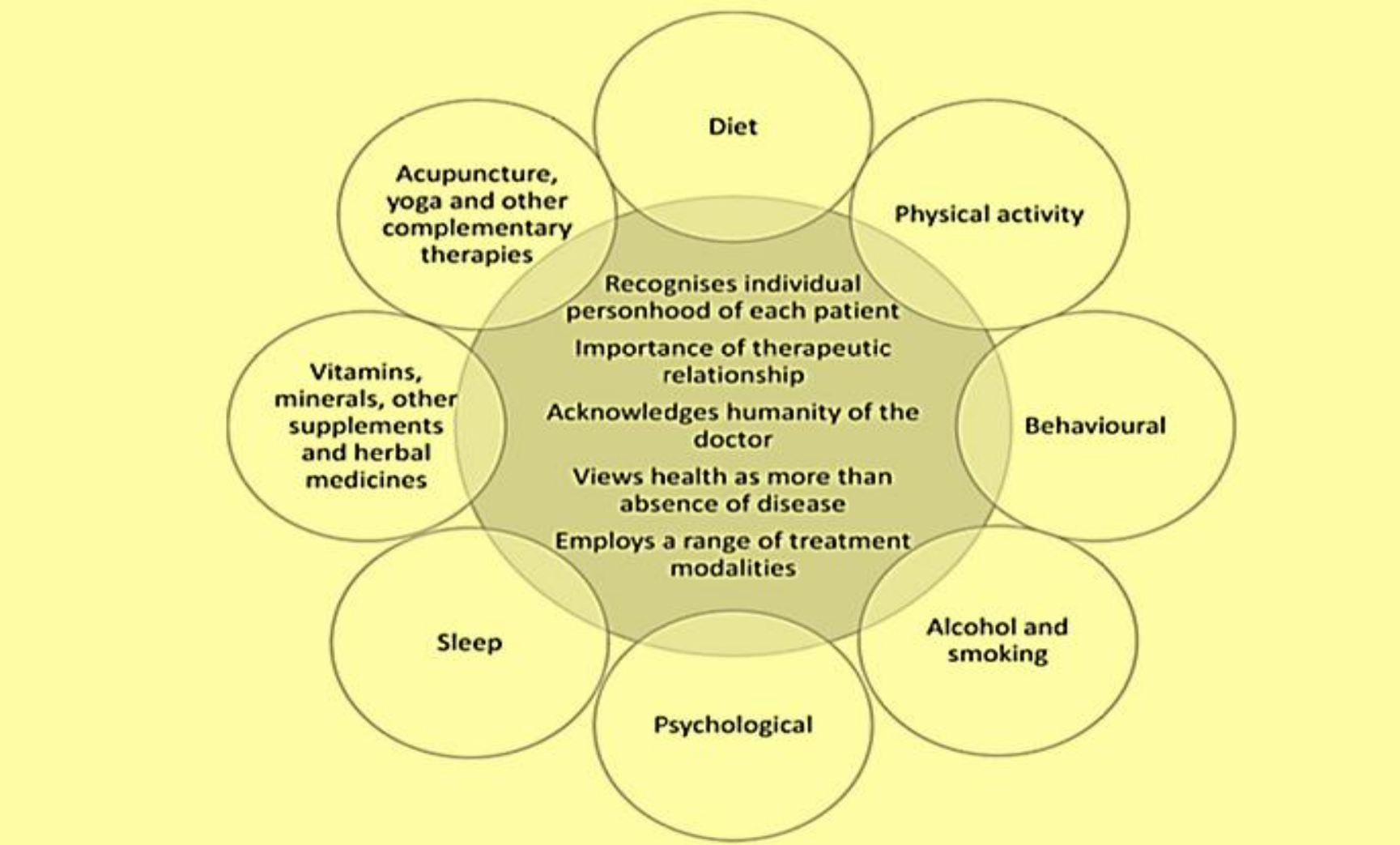
Goals And Principles Of Management

- The goals of PCOS treatment are to improve QoL and reduce the risk of long-term health outcomes.
- Individualized treatment based on the clinical presentation, needs and preferences of each patient is imperative.
- The initiation of treatment for PCOS does not require a definitive diagnosis of the syndrome, as it may decrease the risk for future comorbidities.

Lifestyle

- Lifestyle interventions (preferably multi-component, including **diet, less sedentary behaviour, exercise and behavioural strategies**) should be recommended in all those with PCOS and excess weight to achieve reductions in weight, central adiposity and insulin resistance.

Lifestyle


Diet
Physical activity
Behavioural
Alcohol and smoking
Psychological
Sleep
Vitamins, minerals, other supplements and herbal medicines
Acupuncture, yoga and other complementary therapies
Recognises individual personhood of each patient
Importance of therapeutic relationship
Acknowledges humanity of the doctor
Views health as more than absence of disease
Employs a range of treatment modalities

Diet

- There is insufficient evidence to suggest that any specific dietary approaches provide greater benefits on health outcomes.

- This advice is based on a systematic review comparing different dietary compositions (e.g. low carbohydrate, low glycaemic index (GI) and glycaemic load (GL), high protein, monounsaturated fatty acid (MUFA) enriched and fat counting diets) to best manage PCOS, identifying minimal differences between diets on anthropometric outcomes, concluding weight loss improves the presentation of PCOS regardless of dietary composition.

Diet

- The growing number of clinical trials related to the effect of micronutrients (zinc, chromium, selenium, vitamin D, inositol, and vitamin E) and macronutrients interventions (manipulation of fat, carbohydrate, protein, and MedDiet, Calorie restriction, Low Glycemic Diet) have been demonstrated to be practical approaches for managing clinical and biochemical features of PCOS, however the potential benefit of micronutrient and macronutrient approaches could be different from one by one, particularly in different phenotypes of PCOS.
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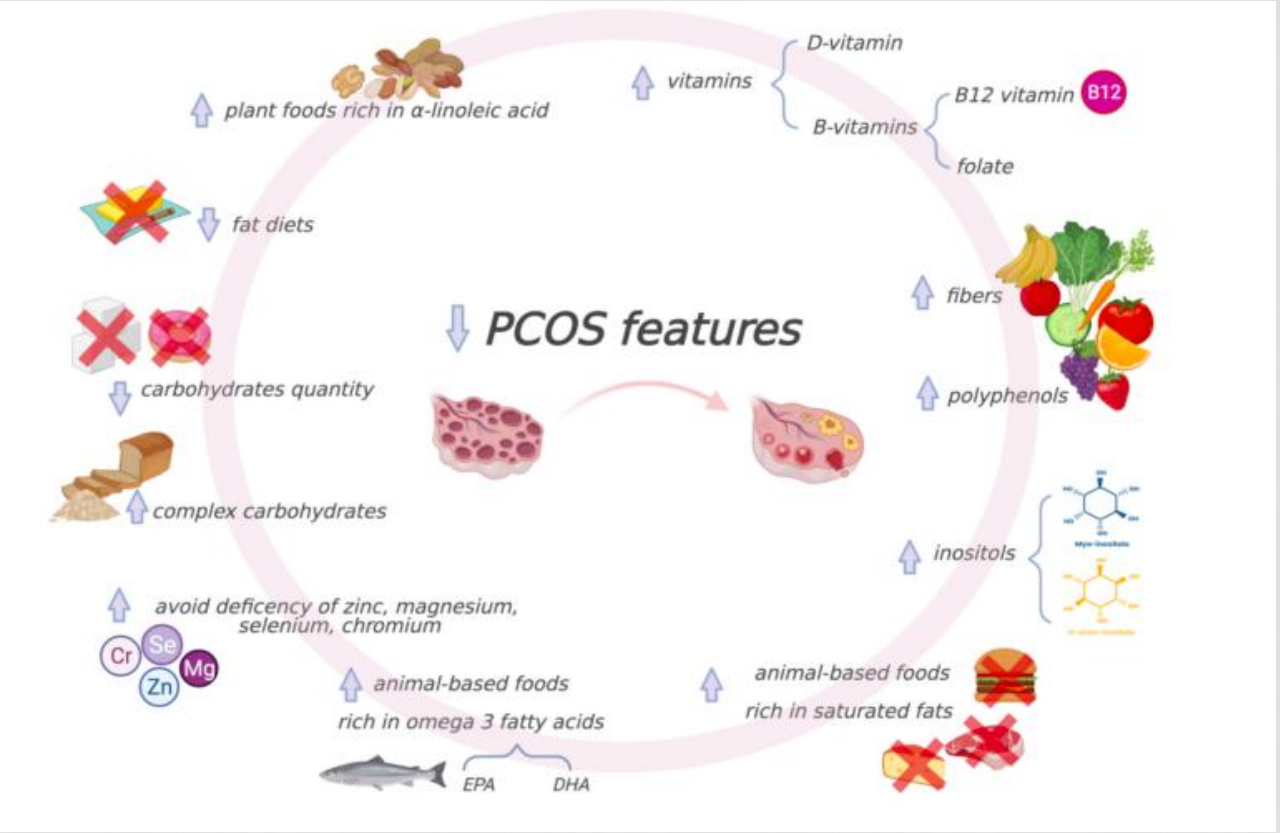
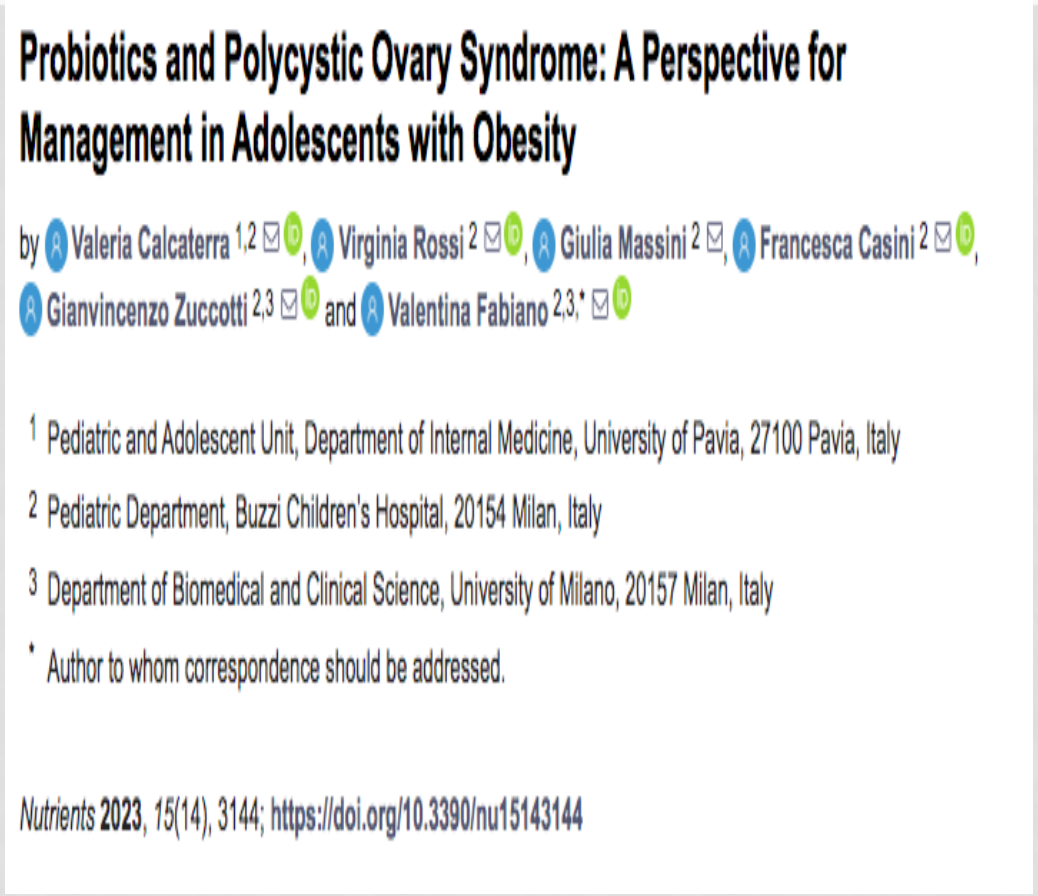


Saei Ghare Naz M, Jahanfar S, Ramezani Tehrani F. An overview on effects of micronutrients and macronutrients interventions in management of polycystic ovary syndrome. Clin Nutr ESPEN. 2022 Dec;52:218-228.

Diet

The literature suggests that probiotic supplementation may ameliorate hormonal profiles, inflammatory indicators, and lipid metabolism disturbances caused by PCOS. Studies also show improvements in weight, BMI, insulin, and HOMA-IR, including a potential role it plays in protecting fertility.



Probiotics and Polycystic Ovary Syndrome: A Perspective for Management in Adolescents with Obesity

by Valeria Calcaterra [1,2], Virginia Rossi [2], Giulia Massini [2], Francesca Casini [2], Gianvincenzo Zuccotti [2,3] and Valentina Fabiano [2,3,*]

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Weight Management

- In women with excess weight, a weight loss of 5-10% is advised, aiming for an energy deficit of 30% or 500-750 kcal/day (1200-1500 kcal/day).

- While weight management is seen as a **core component of lifestyle** interventions, the guideline recognises that a healthy lifestyle provides benefits that occur independent of weight change.

- Weight management (weight gain prevention, weight maintenance and weight loss) is found to reduce the severity of associated PCOS symptoms, decrease the risk of chronic disease and improve the quality of life in PCOS.

- Lifestyle therapy (nutrition, physical activity and behavioural strategies) for weight management is therefore an important part of optimal PCOS care.

Physical Activity

- Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day, including activities that strengthen muscle and bone at least 3 times per week.

Emotional Wellbeing

- Teenagers go through extreme amounts of emotional changes during puberty. This leads to stress and anxiety, especially in young females who show rapid growth.
- Being stress-free is an important aspect of the treatment of this disorder.
- Communicating openly with friends and family can give the patient strength and a **sense of support in dealing with the psychological and emotional components of the syndrome.**
- The management of symptoms and long-term complications in teenagers is essential. Counseling and therapy help in stress management and thereby in managing some of the few symptoms. The recognition of signs and symptoms of PCOS even before the onset of adolescence is essential.

Pharmacological Principles Of Treatment In PCOS

COCP (oestrogen and progestin preparations)

- The COCP alone should be considered in adolescents with a clear PCOS diagnosis or could be considered in those deemed ‘at risk’ but not yet diagnosed with PCOS in both groups for the management of clinical hyperandrogenism and/or irregular menstrual cycles.

- The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.

- Although the COCP is relatively safe, there are absolute medical contraindications to consider according to World Health Organisation Guidelines such as history of migraine with aura, deep vein thrombosis, pulmonary embolism, known thrombogenic mutations, multiple risk factors for cardiovascular disease, breast cancer, neuropathy, severe cirrhosis and malignant liver tumours.

Metformin

- Metformin in addition to lifestyle interventions could be considered in adolescents with a clear PCOS diagnosis or with symptoms of PCOS before a diagnosis is made.

- Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence. (Suggested maximum daily dose is 2 g in adolescents)

Combined COCP And Metformin

- The COCP in combination with metformin could be considered in adolescents with PCOS and a BMI > 25 kg/m 2 where the **COCP and lifestyle changes** do not achieve desired goal.

- Although the combination of metformin and the COCP offers additional benefits, these did not surpass the impact of the COCP plus lifestyle interventions and hence the combination was indicated when the COCP and lifestyle interventions have failed to meet the treatment goals.

- Since the COCP in combination with metformin lead **to mild gastrointestinal side effects**, these potential side effects need to be discussed with the adolescent and her family.

Antiandrogens

- Recommendations suggest the use of the COCP alone with cosmetic therapy for at least 6 months prior to considering antiandrogens.
- Where COCPs are contraindicated or poorly tolerated, and in the presence of effective forms of contraception, antiandrogens could be considered to treat hirsutism or androgen-related alopecia.
- The use of effective contraception is essential due to the teratogenic potential of antiandrogens and their impairment of external genital development in male foetuses.

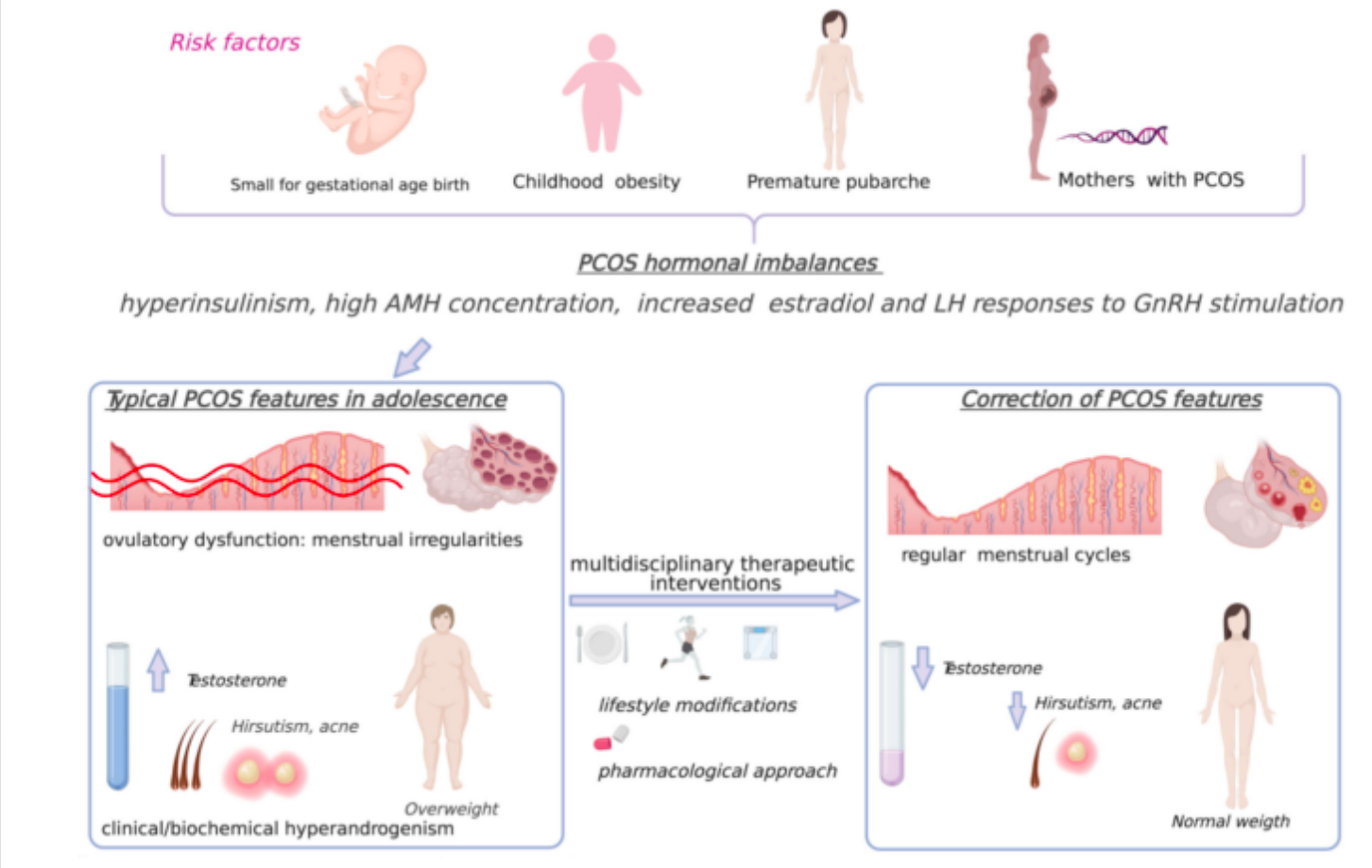
Classical Treatment Options

Chart 2 Classical treatment options (nonpharmacological and pharmacological) for polycystic ovary syndrome

Lifestyle interventions (weight loss and physical activity)	
Indications	- 1st line nonpharmacological treatment - Recommended to all adolescents with polycystic ovary syndrome
Advantages	Weight loss: ✔ ↓ BMI ✔ ↓ FG score Physical Activity: ✔ Menstrual cycle regulation (↓ LH and ↓ AMH)
Disadvantages	✗ Suboptimal adherence ✗ High relapse rate
Combined Oral Contraception (estrogen and progestin combinations)	
Indications	- 1st line pharmacological treatment - Menstrual irregularities and hirsutism - Contraception
Advantages	✔ Menstrual cycle regulation (↓ LH) ✔ ↓ Hyperandrogenemia ✔ ↓ Clinical manifestations of hyperandrogenism (seborrhea, acne, and hirsutism)
Disadvantages	✗ IR remains unchanged ✗ At least 6 to 9 months for measurable effects on hirsutism
Antiandrogens (Spironolactone/Finasteride)	
Indications	- Adjuvant to COC in severe hirsutism cases - COC contra-indication or not tolerated
Advantages	✔ ↓ FG score
Disadvantages	✗ Less effective for pre-existing hair ✗ Teratogenic
Eflornithine (topical)	
Indications	- Adjuvant to photoepilation in patients with laser-resistant facial hirsutism - Monotherapy whenever photoepilation is not recommended
Advantages	✔ ↓ Hirsutism
Disadvantages	✗ Relapse after discontinuation
Metformin	
Indications	- 2nd line pharmacological treatment - Ineffective lifestyle interventions - COC contraindication or not tolerated
Advantages	✔ ↓ IR and hyperinsulinemia ✔ Menstrual cycle regulation ✔ ↓ Hyperandrogenemia ✔ ↓ Cardiovascular risk
Disadvantages	✗ Most symptoms relapse after discontinuation ✗ Side effects: gastrointestinal symptoms; lactic acidosis (extremely rare).

Manique MES, Ferreira AMAP. Polycystic Ovary Syndrome in Adolescence: Challenges in Diagnosis and Management. Rev Bras Ginecol Obstet. 2022 Apr;44(4):425-433. doi: 10.1055/s-0042-1742292. Epub 2022 May 27. PMID: 35623621; PMCID: PMC9948137.

SUMMARY


Risk factors
Small for gestational age birth
Childhood obesity
Premature pubarche
Mothers with PCOS
PCOS hormonal imbalances
hyperinsulinism, high AMH concentration, increased estradiol and LH responses to GnRH stimulation
Typical PCOS features in adolescence
ovulatory dysfunction: menstrual irregularities
Testosterone
Hirsutism, acne
Overweight
clinical/biochemical hyperandrogenism
multidisciplinary therapeutic interventions
lifestyle modifications
pharmacological approach
Correction of PCOS features
regular menstrual cycles
Testosterone
Hirsutism, acne
Normal weigth


Thank you!