Testo

Società Medico Chirurgica di Ferrara dal 1846

15° MEETING DI AGGIORNAMENTO SU ACNE E DERMATOSI CORRELATE

LA SCUOLA DELL'ACNE

Sabato 6 aprile 2019

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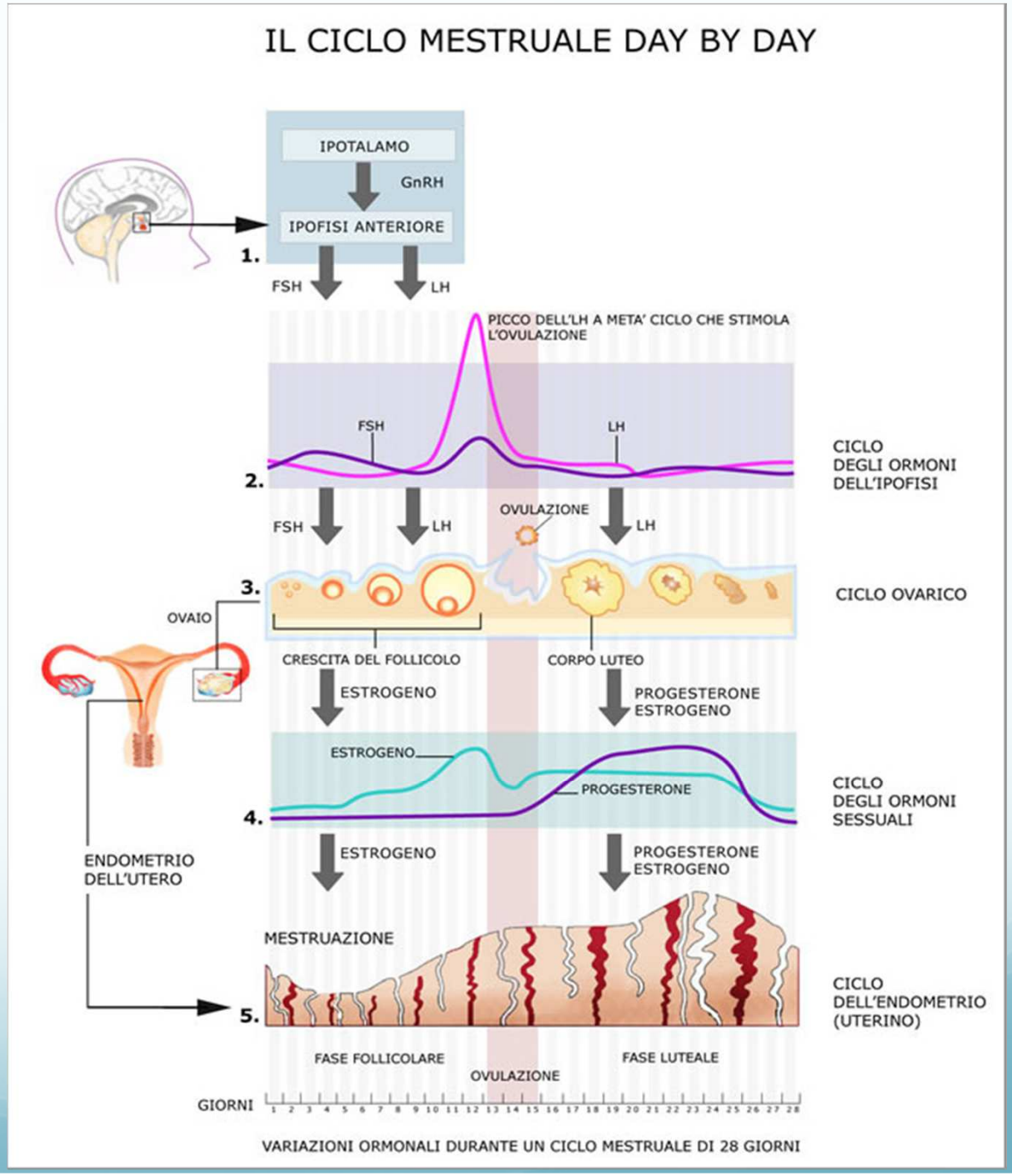
Cona, Ferrara

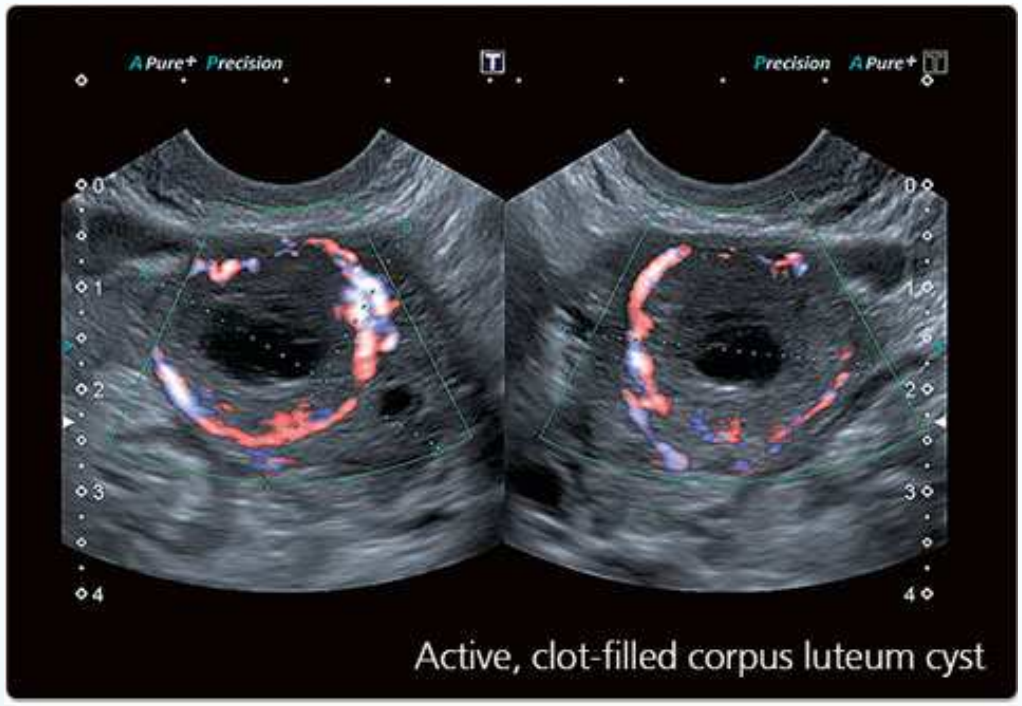
Ovaio policistico o multifollicolare ? Aspetti morfologici e correlazioni cliniche *A. Valerio* (Fe)

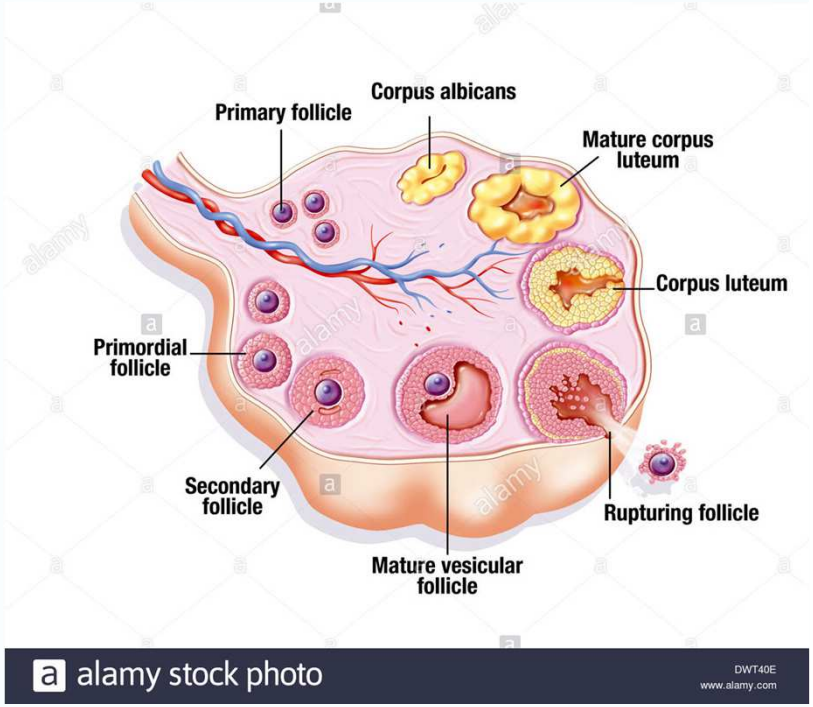
ovaio

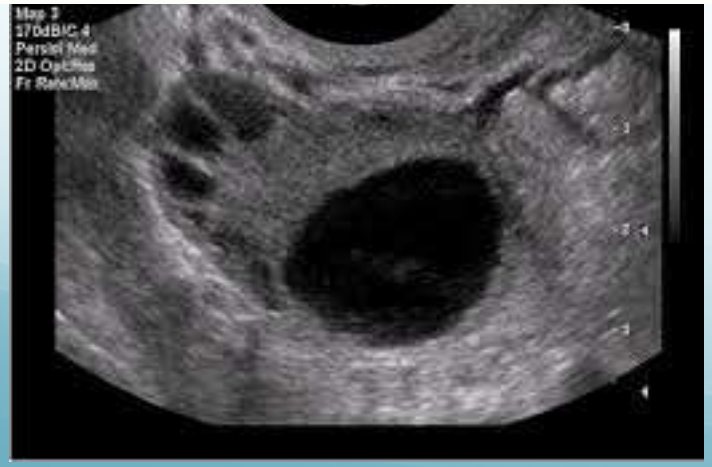
- Funzione endocrina
- Funzione riproduttiva

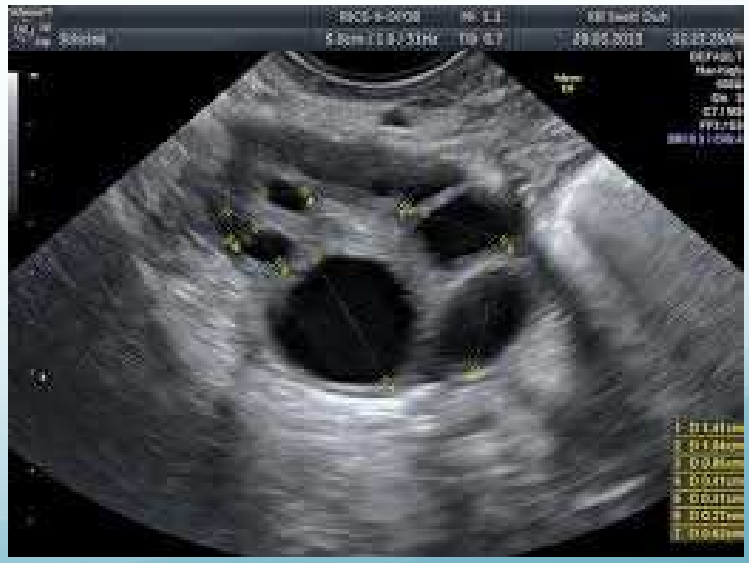


Ovaio normale









?

Dermatologo
Ginecologo
Endocrinologo
Pediatra

Principali motivazioni a valutazione ginecologica

- Irregolarità mestruali
- Acne
- Desiderio di contraccezione
- Indicazione altro specialista per valutazione annessi
- Indicazione altro specialista per contraccezione

Sindrome dell'ovaio policistico

Table 1. Criteria for Diagnosis of PCOS

Clinical finding	*National Institutes of Health criteria, 1990 (must have both of the findings marked below)*	*Rotterdam criteria, 2003 (must have any two of the findings marked below)*	*Androgen Excess and PCOS Society, 2009 (must have A plus either B or C)*
Hyperandrogenism*	X	X	A
Oligomenorrhea	X	X	B
Polycystic ovaries		X	C

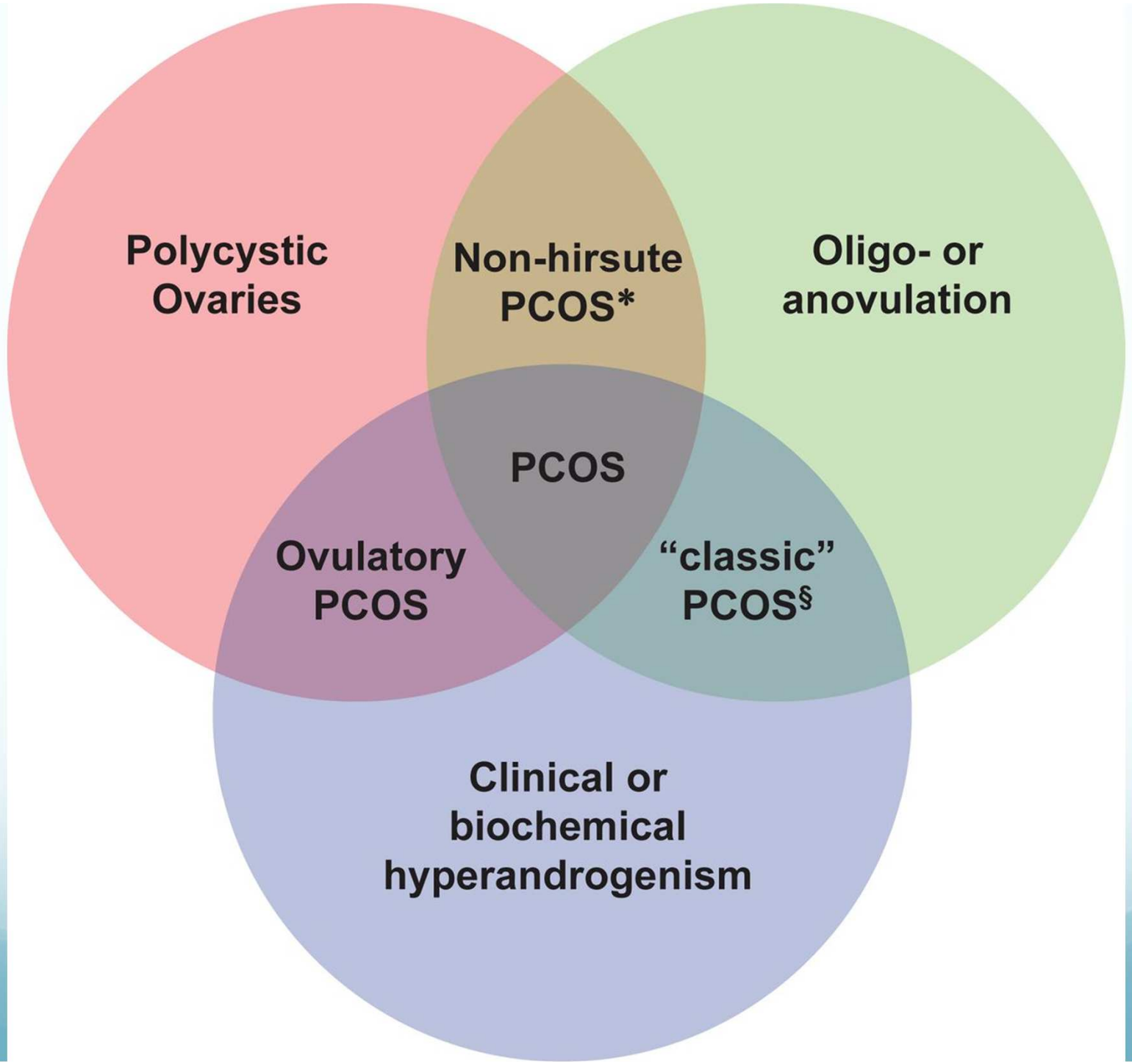
PCOS = polycystic ovary syndrome.

**—Clinical or biochemical evidence of excess androgen.*

Information from reference 19.

Polycystic ovarian syndrome (PCOS) is a common endocrinopathy typified by oligoovulation or anovulation, signs of androgen excess, and multiple small ovarian cysts. These signs and symptoms may vary widely between women as well as within individuals over time. As a result, women with PCOS may first present to various medical specialists, including gynecologists, internists, endocrinologists, or dermatologists. Thus, a familiarity with PCOS is essential for physicians in each of these specialties.

Incidence 4-12%

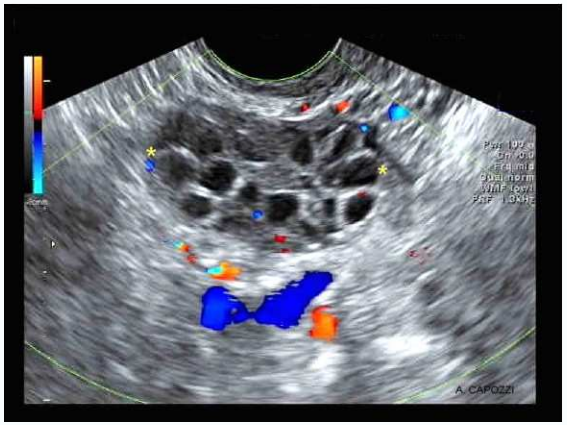

Polycystic Ovaries
Non-hirsute PCOS*
Oligo- or anovulation
PCOS
Ovulatory PCOS
"classic" PCOS§
Clinical or biochemical hyperandrogenism

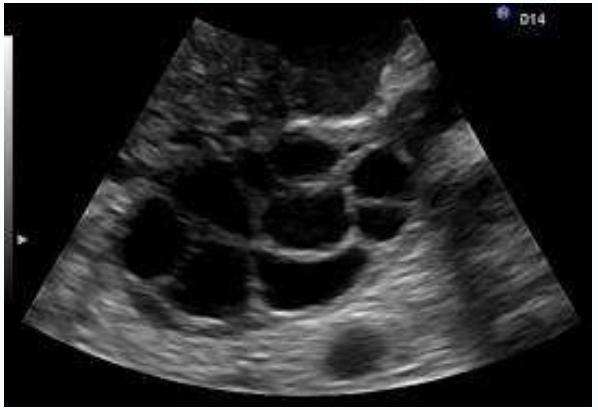
NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
1		Screening, diagnostic assessment, risk assessment and life-stage	
1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	CCR	Irregular menstrual cycles are defined as: • normal in the first year post menarche as part of the pubertal transition • > 1 to < 3 years post menarche: < 21 or > 45 days • > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year • > 1 year post menarche > 90 days for any one cycle • Primary amenorrhea by age 15 or > 3 years post thelarche (breast development) When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.	❖❖❖❖
1.1.2	CCR	In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors.	❖❖❖❖
1.1.3	CPP	For adolescents who have features of PCOS but do not meet diagnostic criteria, an “increased risk” could be considered and reassessment 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.	
1.1.4	CPP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	

Classificazione ecostrutturale delle ovaie (numero e diametri follicoli)

- Tipo 1: solido, pattern omogeneo in assenza di follicoli
- Tipo 2: microcistico, più follicoli <4mm
- Tipo 3: paucicistico, <6 follicoli 4-9mm
- Tipo 4: multicistico, >=6 follicoli 4-9mm
- Tipo 5: macrocistico, almeno 1 follicolo >9mm
- Tipo 6: cisti isolata >2cm

Ovaio multifollicolare





- Volume normale
- 6-10 cisti di 4-10mm
- Distribuzione corticomidollare
- Stroma normodenso

Ovaio multifollicolare (MFO)

- Condizione fisiologica durante il pubarca, quando aumenta l’ampiezza della pulsatilità notturna delle gonadotropina
- Pazienti affette da amenorrea secondaria e clo ponderale con regressione prepubere della secrezione di gonadotropine.

- pattern reversibile con il ripristino della pulsatilità di LH e FSH
- sono ovaie intrinsecamente normali, la cui struttura dipende da un inappropriato segnale ipotalamo-ipofisario.

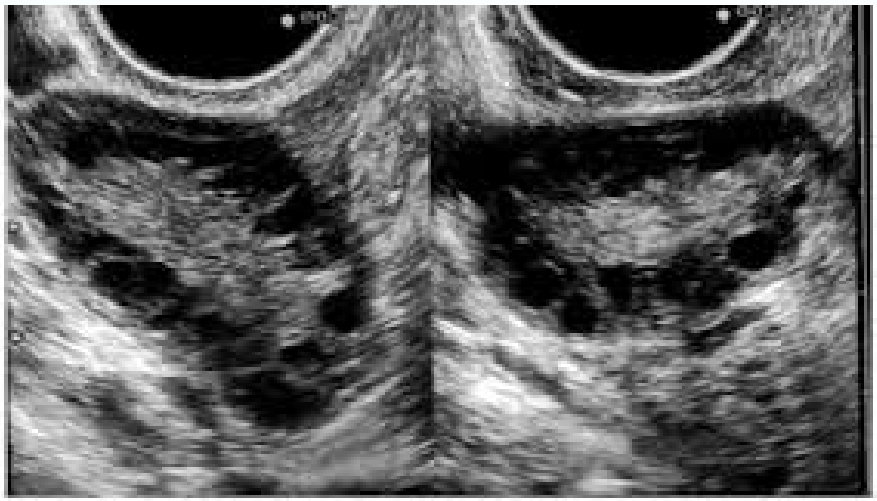
Ovaio policistico: criteri diagnosi ecografica Rotterdam 2004

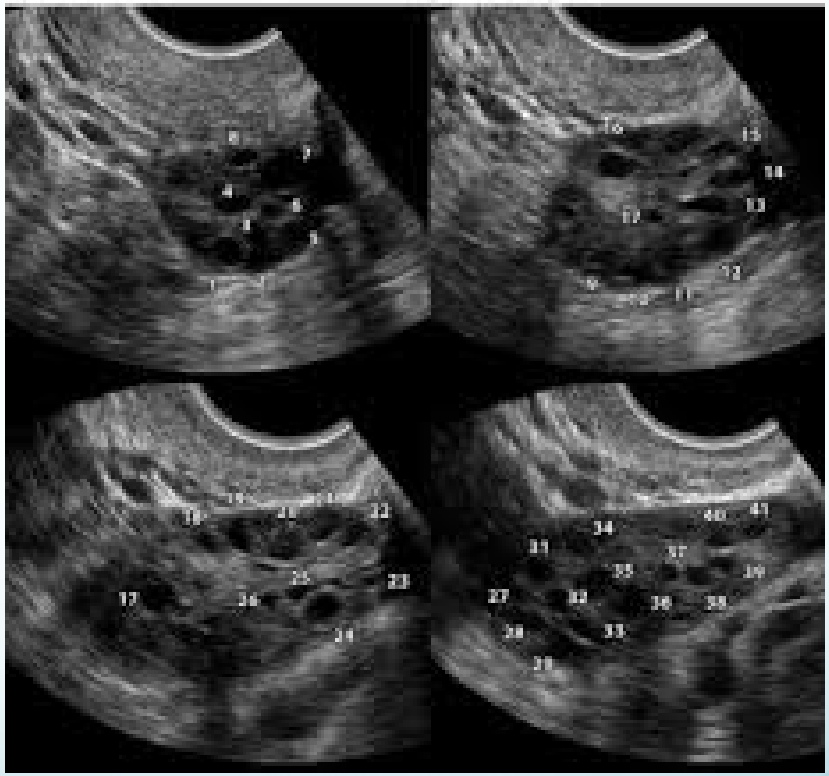
- Ovaie di volume aumentato (>10mL)
- Presenza di piccole (2-8mm), multiple (>=12) cisti

Altri aspetti ecografici:

- nucleo stromale ecodenso
- distribuzione periferica
- Ecografia 3D (VOCAL: Virtual Organ Computer-aied AnaLysis, Sono AVC: Automatic Volume Calculation)
- Rapporto volume stromale/volume ovarico
- Dopplerflussimetria 3D, vascolarizzazione dello stroma ovarico.

Ovaio policistico: criteri diagnosi ecografica





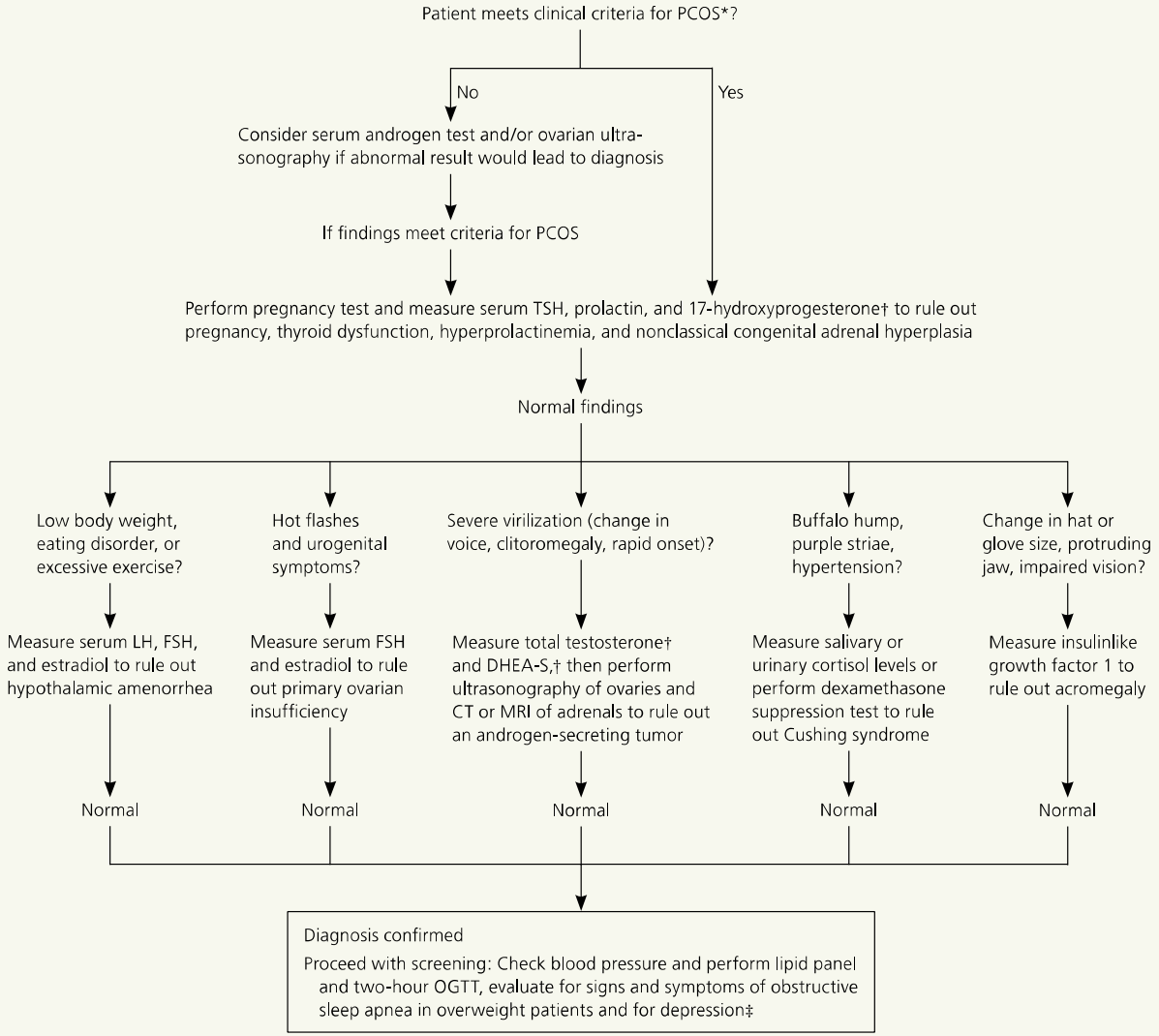
Ecografia: indicazioni

Donne giovani, <8anni dal menarca: non ancora raggiunta maturità ovarica, non indicata diagnosi di PCO per alta incidenza di ovaie multifollicolari
Rischio di sovra-diagnosi di PCOper criteri ecografici
L'utilizzo dell'ecografia in questa fascia di età è inappropriato
per la diagnosidi PCO.

L'ecografia non è strettamente indicata nelle donne adulte nelle quali siano già soddisfatti gli altri criteri per la diagnosi di PCO

1.4		Ultrasound and polycystic ovarian morphology (PCOM)	
1.4.1	CCR	Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.	❖❖❖❖
1.4.2	CCR	The threshold for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut off values for PCOM should be defined.	❖❖❖❖
1.4.3	CCR	The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.	❖❖❖❖
1.4.4	CCR	Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of > 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present.	❖❖❖
1.4.5	CPP	If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10ml on either ovary.	
1.4.6	CPP	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype.	
1.4.7	CPP	In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥ 10ml, given the difficulty of reliably assessing follicle number with this approach.	
1.4.8	CPP	Clear protocols are recommended for reporting follicle number per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards include: • last menstrual period • transducer bandwidth frequency • approach/route assessed • total follicle number per ovary measuring 2-9mm • three dimensions and volume of each ovary • reporting of endometrial thickness and appearance is preferred – 3-layer endometrial assessment may be useful to screen for endometrial pathology • other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles ≥ equal 10mm	
1.4.9	CPP	There is a need for training in careful and meticulous follicle counting per ovary, to improve reporting.	

Diagnosis of Polycystic Ovary Syndrome



*—*Patient has both hyperandrogenism (excessive acne, androgenic alopecia, or hirsutism) and ovulatory dysfunction.*

†—*Measurement to be taken in the morning, preferably during the follicular phase.*

‡—*Screen for hypertension, type 2 diabetes mellitus, dyslipidemia, depression, and obstructive sleep apnea, given their association with PCOS.*

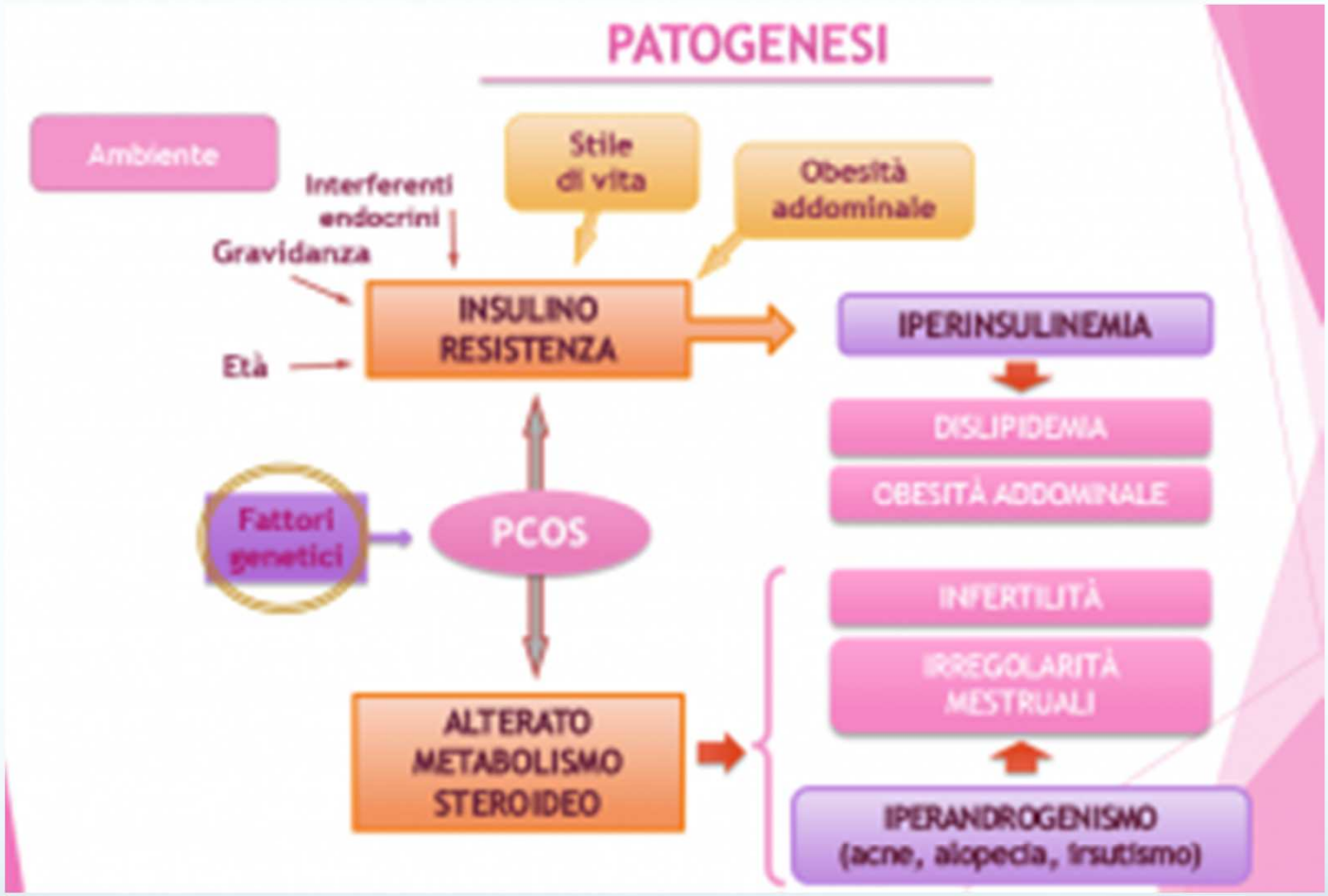
Figure 1. Diagnosis of polycystic ovary syndrome. (CT = computed tomography; DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; OGTT = oral glucose tolerance test; PCOS = polycystic ovary syndrome; TSH = thyroid-stimulating hormone.)

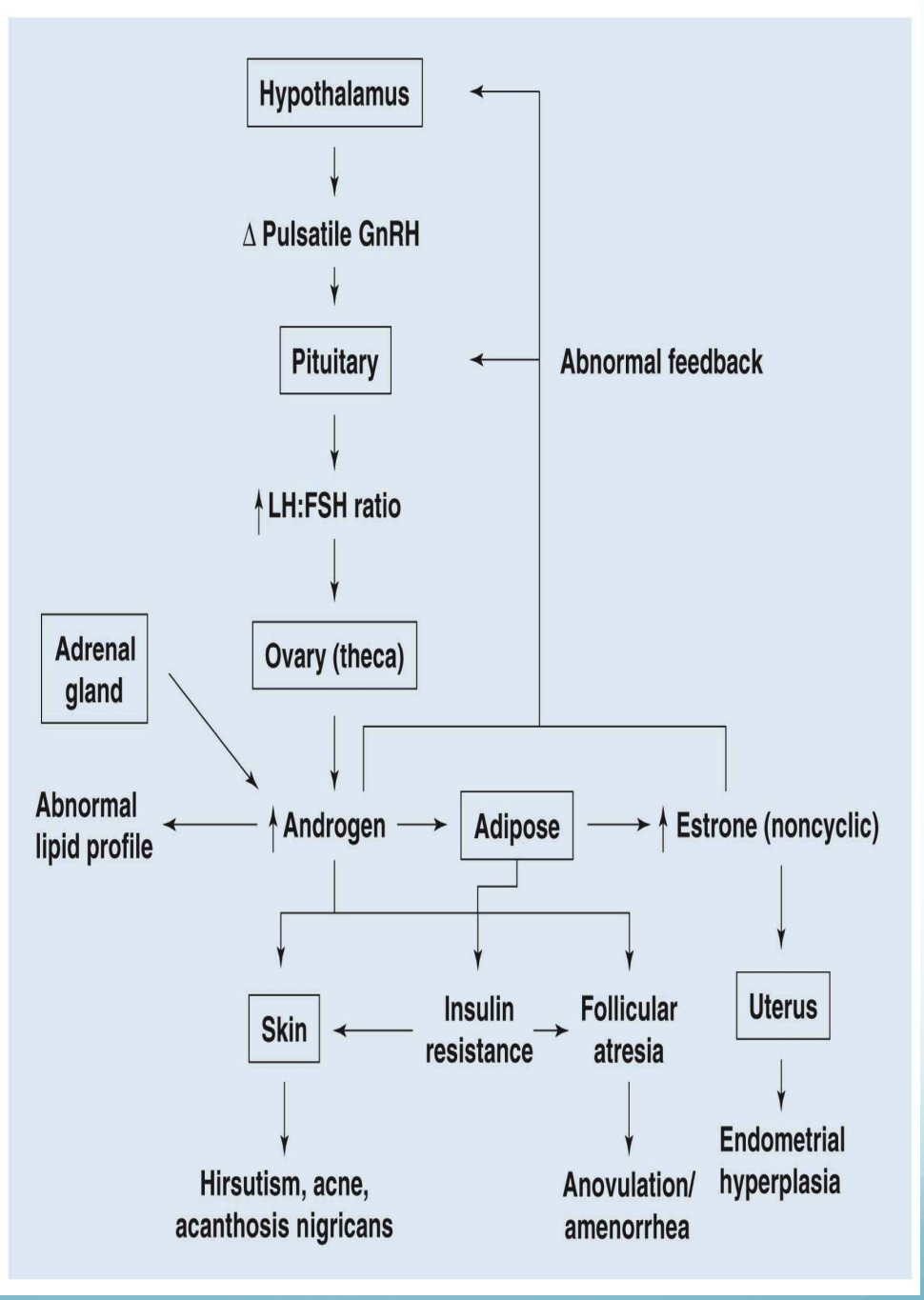
Information from reference 19.

1.3		Clinical hyperandrogenism	
1.3.1	CCR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism and, in adolescents, severe acne and hirsutism	❖❖❖❖
1.3.2	CCR	Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity.	❖❖❖❖
1.3.3	CCR	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, acknowledging that self-treatment is common and can limit clinical assessment. (See recommendations on ethnic variation)	❖❖❖❖
1.3.4	CCR	The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.	❖❖❖❖

1.2		Biochemical hyperandrogenism	
1.2.1	EBR	Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.	❖❖❖❖ ⊕⊕◯◯
1.2.2	EBR	High quality assays such as liquid chromatography–mass spectrometry (LCMS)/mass spectrometry and extraction/chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS.	❖❖❖ ⊕⊕◯◯

Sospensione contraccettivo ormonale per almeno 3 mesi


PATOGENESI
Ambiente
Interferenti endocrini
Gravidanza
Stile di vita
Obesità addominale
INSULINO RESISTENZA
Età
IPERINSULINEMIA
DISLIPIDEMIA
OBESITÀ ADDOMINALE
Fattori genetici
PCOS
INFERTILITÀ
IRREGOLARITÀ MESTRUALI
ALTERATO METABOLISMO STEROIDEO
IPERANDROGENISMO (acne, alopecia, irsutismo)


Hypothalamus
Δ Pulsatile GnRH
Pituitary
Abnormal feedback
↑LH:FSH ratio
Adrenal gland
Ovary (theca)
Abnormal lipid profile
↑Androgen
Adipose
↑Estrone (noncyclic)
Skin
Insulin resistance
Follicular atresia
Uterus
Hirsutism, acne, acanthosis nigricans
Anovulation/ amenorrhea
Endometrial hyperplasia

Short-term consequences

Obesity
Infertility
Irregular menses
Abnormal lipid levels
Hirsutism/acne/androgenic alopecia
Glucose intolerance/acanthosis nigricans

Long-term consequences

Diabetes mellitus
Endometrial cancer
Cardiovascular disease

1.11		Endometrial cancer	
1.11.1	CCR	Health professionals and women with PCOS should be aware of a two to six-fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk of endometrial cancer remains relatively low.	❖❖❖
1.11.2	CPP	Health professionals require a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended.	
1.11.3	CPP	Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.	

Management of Polycystic Ovary Syndrome

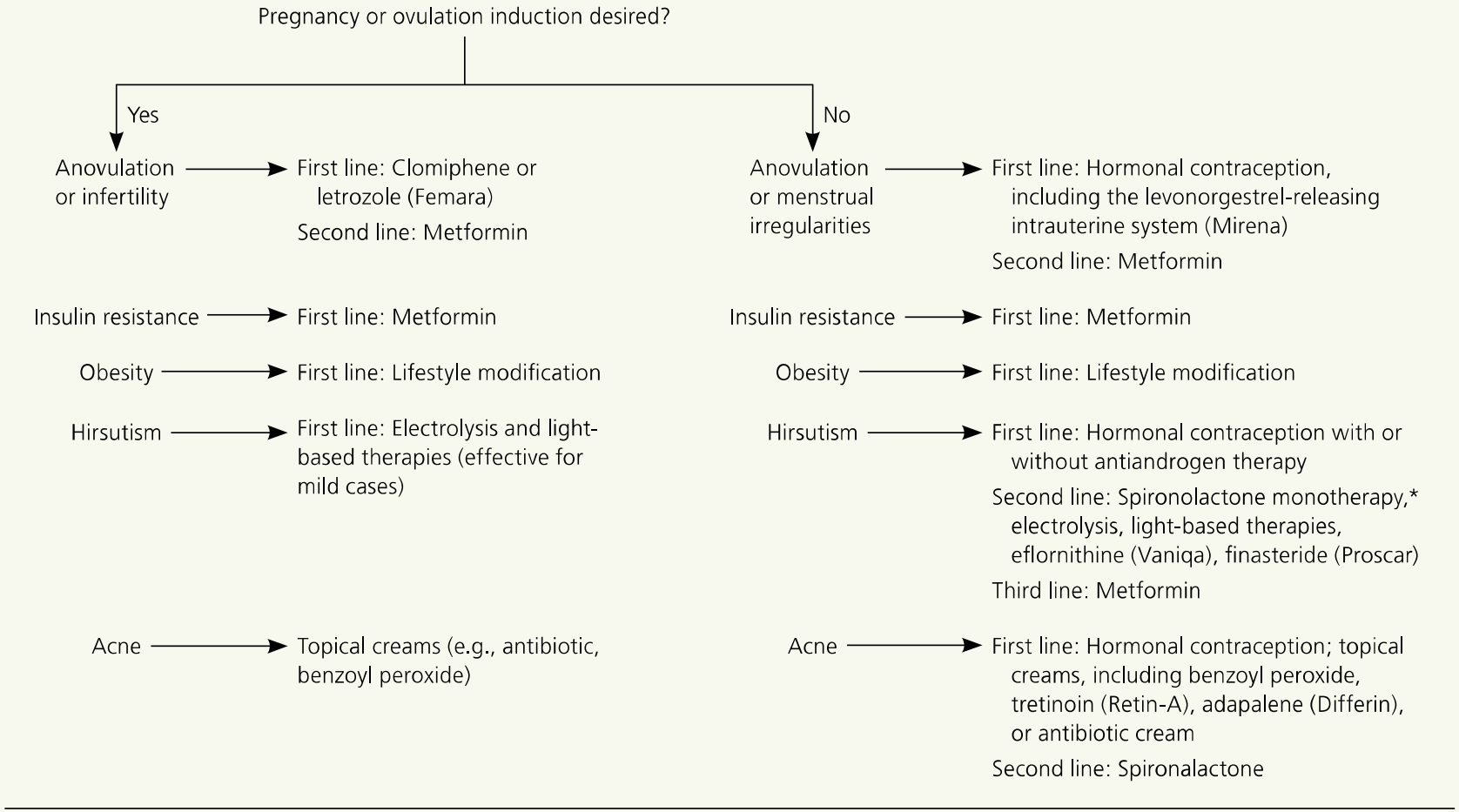


Figure 2. Management of polycystic ovary syndrome. Treatment options vary depending on patient's desire for contraception. Lifestyle modification is a central part of treatment for all manifestations of polycystic ovary syndrome.

Information from references 19, and 29 through 35.

4.2		Combined oral contraceptive pills (COCPs)	
4.2.1	EBR	The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or irregular menstrual cycles.	❖❖❖❖ ⊕⊕◯◯
4.2.2	EBR	The COCP alone should be considered in adolescents with a clear diagnosis of PCOS for management of clinical hyperandrogenism and/or irregular menstrual cycles.	❖❖❖ ⊕⊕◯◯
4.2.3	EBR	The COCP could be considered in adolescents who are deemed “at risk” but not yet diagnosed with PCOS, for management of clinical hyperandrogenism and irregular menstrual cycles.	❖❖❖ ⊕⊕◯◯
4.2.4	EBR	Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended in adults and adolescents with PCOS and practice should be informed by general population guidelines.	❖❖❖ ⊕⊕◯◯

Progestinici con effetto anti-androgeno

- ciproterone acetato (CPA);
- dienogest (dNG);
- drospirenone (dRSP);
- clormadinone acetato (CmA).

Accortezze per terapia CO

- Ciproterone Acetato NON prima scelta (alto rischio trombotico)
- Utilizzare dosa minima efficace della componente estrogenica (20-30 mcg EE o bioequivalente)
- Considerare nella scelta gli esgtrogeni naturali per il minore impatto metabolico
- Considerare rischi / indicazioni e controindicazioni nella prescrizione (es WHO)
- Es. Controindicazioni assolute: emicrania con aura, rischio tromboembolico anamnestico o presenza di fattori protrombotici

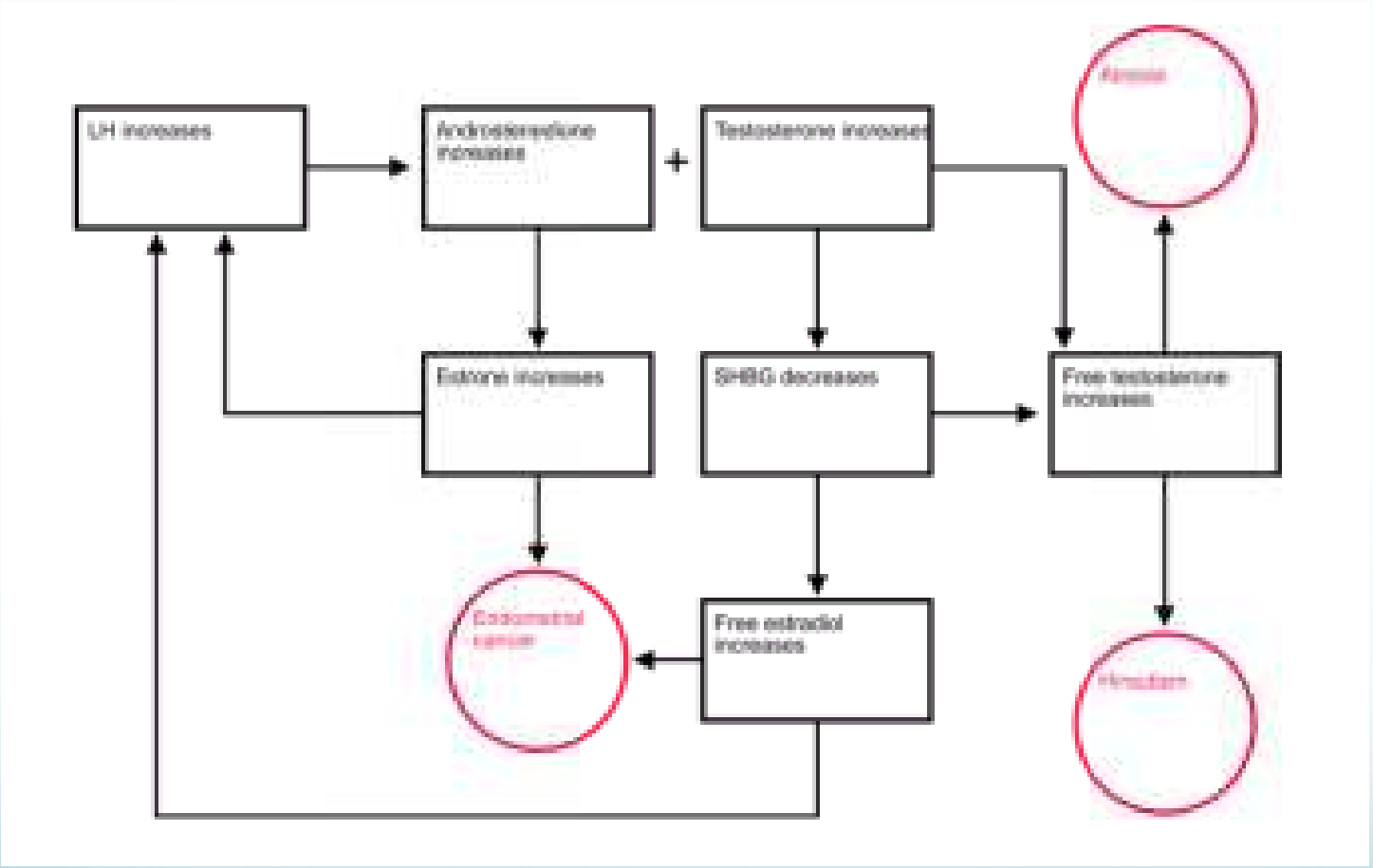
AMH
ormone anti-mulleriano

1.5		Anti-müllerian hormone (AMH)	
1.5.1	EBR	Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS.	❖❖❖ ⊕⊕◯◯
1.5.2	CPP	There is emerging evidence that with improved standardisation of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH assays will be more accurate in the detection of PCOM.	

Given the challenges with ultrasound in diagnosis of PCOS, including in the years after menarche, serum Anti-Müllerian Hormone (AMH) has been proposed as an alternative marker of ovulatory dysfunction in PCOS. AMH is a polypeptide of the transforming growth factor beta (TGF-β) family solely secreted by granulosa cells of the preantral and small antral ovarian follicles. Serum AMH levels are significantly higher in women with PCOS compared with normal ovulatory women [79, 80]. Strong correlations have been demonstrated between circulating AMH levels and antral follicle count on ultrasound in PCOS. AMH may also provide insight into the pathogenesis of PCOS and the different phenotypes. However, current literature reveals significant heterogeneity and the diagnostic value of serum AMH remains far from clear.

International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

Grazie


LH increases
Androstenedione increases
+
Testosterone increases
Estrone increases
SHBG decreases
Free testosterone increases
Free estradiol increases

The polycystic ovary is usually enlarged and is characterized by a smooth pearly white capsule. For years, it was erroneously believed that the thick sclerotic capsul acted as a mechanical barrier to ovulation. A more accurate concept is that the polycystic ovary is a consequence of the loss of ovulation and the achievement of the steady state of persistent anovulation. The characteristics of the ovary reflect this dysfunctional state: [63]

1. The surface area is doubled, giving an average volume increase of 2.8 times.
2. The same number of primordial follicles is present, but the number of growing and atretic follicles is doubled. Each ovary may contain 20–100 cystic follicles.
3. The thickness of the tunica (outermost layer) is increased by 50%.
4. A one-third increase in cortical stromal thickness and a 5-fold increase in subcortical stroma are noted. The increased stroma is due both to hyperplasia of thecal cells and to increased formation subsequent to the excessive follicular maturation and atresia.
5. There are 4 times more ovarian hilus cell nests (hyperplasia).

1.7		Menopause life stage	
1.7.1	CCR	Postmenopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism.	❖❖❖
1.7.2	CCR	A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years.	❖❖❖
1.7.3	CPP	Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.	

ecografia

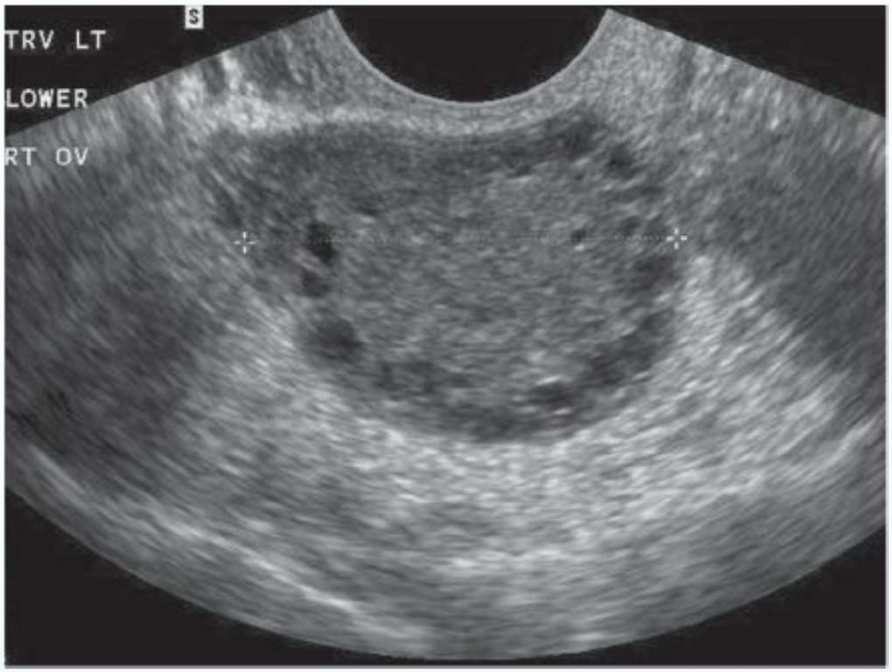
Sonography

Histologically, a polycystic ovary (PCO) displays increases in volume, number of ripening and atretic follicles, cortical stromal thickness, and number of hilar cell nests (Hughesdon, 1982). Many of these tissue changes can be seen sonographically, and pelvic sonography is commonly used to evaluate the ovaries in women with suspected PCOS. Sonography is particularly important for women with PCOS seeking fertility and in women with signs of virilization. A high-definition transvaginal approach is superior and has a higher detection rate of PCO than the transabdominal route. However, a transabdominal route is preferred for virginal adolescents.

Sonographic criteria for polycystic ovaries from the 2003 Rotterdam conference include ≥12 small cysts (2 to 9 mm in diameter) or an increased ovarian volume (>10 mL) or both (Fig. 17-11). Often there is an increased amount of stroma relative to the number of follicles (Balen, 2003). Only one ovary with these findings is sufficient to define PCOS. However, criteria do not apply to women taking combination oral contraceptive pills (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

In contrast, other findings are not valuable diagnostically. For example, the typical “black pearl necklace” appearance, in which follicles are distributed just underneath the capsule in a row, and the perceived increase in stromal echogenicity have been eliminated as diagnostic criteria. Moreover, a polycystic ovary should not be confused with a multicystic ovary, which is normal size, contains six or more follicles without peripheral displacement, and lacks an increase in central stromal volume.

Remarkably, studies using sonography have shown that at least 23 percent of young women have ovaries that exhibit PCO morphology, yet many of these women have no other symptoms of PCOS (Clayton, 1992; Polson, 1988). In addition, a polycystic appearance of the ovaries can often be found in other conditions of androgen excess, such as congenital adrenal hyperplasia, Cushing syndrome, and exogenous use of androgenic medications. For this reason, PCO morphology found during sonographic examination is not used solely to make the diagnosis of PCOS.


S
TRV LT
LOWER
RT OV

Diagnosis of PCOS in Adolescence

Several independent *prepubertal* risk factors for PCOS have been identified. These include above average or low birthweight for gestational age, premature adrenarche, atypical sexual precocity, and obesity with acanthosis nigricans (Rosenfield, 2007). That said, diagnosing PCOS in adolescence is difficult due to the fact that adolescents frequently have irregular menses for 2 to 4 years after menarche, and acne is common. Moreover, in adolescence, transabdominal rather than transvaginal pelvic sonography is generally performed, and image resolution is poorer. In adolescents with incomplete criteria for a firm diagnosis of PCOS, careful surveillance is warranted as they may be diagnosed at a later time (Carmina, 2010).

TREATMENT

The choice of treatment for each symptom of PCOS depends on a woman's goals and the severity of endocrine dysfunction. Thus, anovulatory women desiring pregnancy will undergo significantly different treatment than adolescents with menstrual irregularity and acne. Patients often seek treatment for a singular complaint and may see various specialists from dermatologists, nutritionists, aestheticians, and endocrinologists prior to evaluation by a gynecologist.

Observation

Women with PCOS who have fairly regular cycle intervals (8 to 12 menses per year) and have mild hyperandrogenism may choose not to be treated. In these women, however, periodic screening for dyslipidemia and diabetes mellitus is prudent.

Weight Loss

For obese women with PCOS, lifestyle changes focused on diet and exercise are paramount to treatment at each stage of life. Even a modest amount of weight loss (5 percent of body weight) can result in restoration of normal ovulatory cycles in some women. This improvement results from reductions in insulin and androgen levels, the latter mediated through increases in SHBG levels (Huber-Buchholz, 1999; Kiddy, 1992; Pasquali, 1989).

The optimal diet that best improves insulin sensitivity is not known. Diets high in carbohydrates increase insulin secretion rates, whereas diets high in protein and fat lower those rates (Bass, 1993; Nuttall, 1985). However, very-high-protein diets are concerning with respect to stresses on kidney function. Moreover, they afford only short-term weight loss initially with lesser benefits over time (Legro, 1999; Skov, 1999). Thus, it appears that a well-balanced hypocaloric diet offers the most benefit in treating obese women with PCOS.

Exercise

Exercise is known to have a beneficial effect in treating patients with type 2 DM (Nestler, 1998). The most dramatic effect of lifestyle intervention was published in 2002 as the Diabetes Prevention Program. Women and men at risk for diabetes were asked to lose at least 7 percent of their weight and to exercise for 150 minutes each week. This group had a twofold greater benefit in delaying the onset of diabetes compared with a group given metformin alone. Both groups fared better than a placebo group (Knowler, 2002). Few studies, however, have looked specifically at the effect of exercise on insulin action and reproductive function in women with PCOS (Jaatinen, 1993; Nybacka, 2011). In addition to DM, women with PCOS may have comorbid risk factors for CVD. In patients with PCOS, exercise has been shown to improve cardiovascular capacity (Vigorito, 2007).

Treatment of Oligoovulation and Anovulation

Women with oligoovulation or anovulation typically have fewer than eight menses per year, often skip menses for several months at a time, or simply have amenorrhea. Flow may be scanty or may be very long and heavy, resulting in anemia.

Combination Oral Contraceptive Pills

A first-line treatment for menstrual irregularities is combination oral contraceptive pills (COCs), which will induce regular menstrual cycles. In addition, COCs reduce androgen levels. Specifically, COCs suppress gonadotropin release, which results in decreased ovarian androgen production. Moreover, the estrogen component increases SHBG levels. Lastly, the progestin component antagonizes the endometrial proliferative effect of estrogen, thus reducing risks of endometrial hyperplasia due to unopposed estrogen.

Theoretically, COCs that contain progestins with fewer androgenic properties are preferred. Such progestins include norethindrone; a third-generation progestin, such as norgestimate or desogestrel; or the newer progestin drospirenone. However, no COC pill has shown superiority compared with another in reducing hirsutism (Sobbrio, 1990). Alternative combination hormonal contraceptive options include the contraceptive patch and vaginal ring (Chap. 5, p. 152).

In initiating therapy, if a woman's last menses was more than 4 weeks prior, a pregnancy test is indicated. If negative, progesterone is given to produce a withdrawal bleed prior to COC initiation. Typical regimens include: medroxyprogesterone acetate (MPA) (Provera), 10 mg orally daily for 10 days; MPA, 10 mg orally twice daily for 5 days; or micronized progesterone (Prometrium), 200 mg orally daily for 10 days. Patients are counseled that bleeding is expected to begin after completion of the progestin course.

Cyclic Progestogens

In patients who are not candidates for combination hormonal contraception, progesterone withdrawal is recommended every 1 to 3 months. Examples of regimens used include: MPA, 5 to 10 mg orally daily day for 12 days, or micronized progesterone, 200 mg orally each evening for 12 days. Patients should be counseled that intermittent progestins will not reduce symptoms of acne or hirsutism, nor will they provide contraception.

Insulin Sensitizing Agents

Although the use of insulin sensitizers in PCOS has not been approved by the Food and Drug Administration (FDA), they have been found to be increasingly beneficial for both metabolic and gynecologic issues. Of these agents, metformin is the most commonly prescribed, particularly in women with impaired glucose tolerance and insulin resistance. This drug improves peripheral insulin sensitivity by reducing hepatic glucose production and increasing target tissue sensitivity to insulin. Metformin decreases androgen levels in both lean and obese women, leading to increased rates of spontaneous ovulation (Batukan, 2001; Essah, 2006; Haas, 2003).

A number of studies have demonstrated that up to 40 percent of anovulatory women with PCOS will ovulate, and many will achieve pregnancy with metformin alone (Fleming, 2002; Neveu, 2007). Metformin is a category B drug and is safe to use as an ovulatory induction agent. As such, it may be used alone or in concert with other medications such as clomiphene citrate (Chap. 20, p. 533). Specifically, metformin has been shown to increase the ovulatory response to clomiphene citrate in patients who were previously clomiphene resistant (Nestler, 1998). Despite these positive findings regarding metformin and ovulation induction, in a randomized prospective study of 626 women, Legro and colleagues (2007) found higher live-birth rates with clomiphene citrate alone (22 percent) than with metformin alone (7 percent).

A rare adverse side effect of metformin is lactic acidosis, which is almost exclusively found in patients with renal insufficiency, liver disease, or congestive heart failure. More common side effects are gastrointestinal, and these can be minimized by starting at a low dose and gradually increasing the dose over several weeks to an optimal level. In clinical studies, 1500 to 2000 mg in divided doses daily with meals is typically used.

The thiazolidinediones, also known as glitazones, are another class of medications used for patients with diabetes mellitus and include rosiglitazone (Avandia) and pioglitazone (Actos). These agents bind to insulin receptors on cells throughout the body, causing them to become more responsive to insulin and thereby lowering serum glucose and insulin levels. Similar to metformin, rosiglitazone and pioglitazone have been shown to improve ovulation in some patients (Azziz, 2001; Dunaif, 1996b; Ehrmann, 1997). However, the glitazones are category C drugs and thus should be used as ovulation induction agents in rare cases and discontinued once pregnancy is achieved.

Hirsutism

In the treatment of hirsutism, a primary goal is lowering androgen levels to halt further conversion of vellus hairs to terminal ones. However, medical therapies will not eliminate abnormal hair growth already present. Moreover, treatments may require 6 to 12 months before clinical improvement is apparent. For this reason, clinicians should be familiar with temporary hair removal methods that may be used in the interim. Permanent cosmetic therapies may then be implemented once medications have reached maximal therapeutic effect.

Combination Oral Contraceptives

As described earlier, COCs are effective in establishing regular menses and lowering ovarian androgen production. As an additional effect, the estrogen component of these pills leads to increased SHBG levels. With higher SHBG levels, a greater amount of free testosterone is bound and thus becomes biologically unavailable at the hair follicle.

Gonadotropin-Releasing Hormone Agonists

As described in Chapter 9 (p. 255), GnRH agonists effectively lower gonadotropin levels over time and in turn subsequently lower androgen levels. Despite their effectiveness in treating hirsutism, administration of these agents is not a preferred long-term treatment method due to associated bone loss, high cost, and menopausal side effects.

Eflornithine Hydrochloride

This antimetabolite topical cream is applied twice daily to areas of facial hirsutism and is an irreversible inhibitor of ornithine decarboxylase. This enzyme is necessary for hair follicle cell division and function, and its inhibition results in slower hair growth. It does not permanently remove hair, and thus women are required to continue routine methods of hair removal while using this medicine.

Clinical results from eflornithine hydrochloride (Vaniqa) may require 4 to 8 weeks of use. However, clinical trials have shown that approximately one third of patients have marked improvement after 24 weeks of eflornithine use compared with placebo, and 58 percent showed some overall improvement in hirsutism scores (Balfour, 2001).

Androgen-Receptor Antagonists

Androgen-Receptor Antagonists

Antiandrogens are competitive inhibitors of androgen binding to the androgen receptor. Although these agents are effective in the treatment of hirsutism, they carry a risk for several side effects. Metrorrhagia may frequently develop. In addition, as antiandrogens, these drugs bear a theoretical risk of pseudohermaphroditism in male fetuses of women using such medications in early pregnancy. Accordingly, these drugs are commonly used in conjunction with oral contraceptive pills, which prompt regular menses and provide effective contraception.

None of the antiandrogen agents are approved by the FDA for treatment of hyperandrogenism and thus are used off-label. Spironolactone (Aldactone), in a dosage of 50 to 100 mg orally twice daily, is the primary antiandrogen used currently in the United States. In addition to its antiandrogen effects, this drug also affects hair conversion from vellous to terminal by its direct inhibition of 5α-reductase. Spironolactone is also a potassium-sparing diuretic. As such, it should not be prescribed for chronic use in combination with agents that can also raise blood potassium levels, such as potassium supplements, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal antiinflammatory drugs such as indomethacin, or other potassium-sparing diuretics.

In Europe, Canada, and Mexico, the preferred antiandrogen is cyproterone acetate, usually marketed in an oral contraceptive pill. However, this agent is not approved by the FDA (Van der Spuy, 2003). Flutamide is another nonsteroidal antiandrogen marketed for the treatment of prostate cancer, but is rarely used for hirsutism due to its potential hepatotoxicity.

5α-Reductase Inhibitors

Conversion of testosterone to DHT may be effectively decreased by the 5α-reductase inhibitor finasteride. This drug is available as a 5-mg tablet for prostate cancer (Proscar) and a 1-mg tablet for the treatment of male alopecia (Propecia). Most studies have used 5-mg daily doses and have found finasteride to be modestly effective in the treatment of hirsutism (Fruzzetti, 1994; Moghetti, 1994).

Side effects are low with finasteride, although decreased libido has been noted. However, as with other antiandrogens, the risk of male fetal teratogenicity is present, and effective contraception must be used concurrently.

Hair Removal

Hirsutism is often treated by mechanical means, and these include both depilation and epilation techniques. In addition to hair removal, lightening hair color with bleach is an additional cosmetic option.

Gonadotropins

Anovulation in women with PCOS is characterized by inappropriate gonadotropin secretion (Fig. 17-1). Specifically, alterations in gonadotropin-releasing hormone (GnRH) pulsatility lead to preferential production of luteinizing hormone (LH) compared with follicle-stimulating hormone (FSH) (Hayes, 1998; Waldstreicher, 1988). It is currently unknown whether hypothalamic dysfunction is a primary cause of PCOS or is secondary to abnormal steroid feedback. In either case, serum LH levels rise, and increased levels are observed clinically in approximately 50 percent of affected women (Balen, 2002; van Santbrink, 1997). Similarly, luteinizing hormone:follicle-stimulating hormone (LH:FSH) ratios are elevated and rise above 2:1 in approximately 60 percent of patients (Rebar, 1976).

Increased intrafollicular androgen levels result in follicular atresia. Increased circulating androgen levels contribute to abnormalities in patient lipid profiles and the development of hirsutism and acne. Increased circulating androgens can also be derived from the adrenal gland.

Elevated serum androgens (primarily androstenedione) are converted in the periphery to estrogens (primarily estrone). As conversion occurs primarily in the stromal cells of adipose tissue, estrogen production will be augmented in obese PCOS patients. This conversion results in chronic feedback at the hypothalamus and pituitary gland, in contrast to the normal fluctuations in feedback observed in the presence of a growing follicle and rapidly changing levels of estradiol. Unopposed estrogen stimulation of the endometrium may lead to endometrial hyperplasia.

Insulin resistance due to genetic abnormalities and/or increased adipose tissue contributes to follicular atresia in the ovaries as well as the development of acanthosis nigricans in the skin.

Lack of follicular development results in anovulation and subsequent oligo- or amenorrhea.

Note that this syndrome may develop from primary dysfunction of any one of a number of organ systems. For example, elevated ovarian androgen production may be due to an intrinsic abnormality in enzymatic function and/or abnormal hypothalamic-pituitary stimulation with LH and FSH.

The common denominator is development of a self-perpetuating noncyclic hormonal pattern.

Sindrome multifattoriale poligenica
Familiarità
Geni conivolti nella sintesi degli androgeni e nell'insulino-resistenza
Cicli anovulatori per alterata secrezione gonadotropine
Alterazione nel GnRH che porta aaumento LH rispetto a FSH
Disfunziona ipotalamica primitiva / secondaria (?)
LH/FSH > 2:1 nel 60% dei casi
Aumento di androgeni endofollicolari comporta atresia follicolare
Aumento androgeni circolanti comporta alterato profilo lipidico
Androstenedione periferico è convertito in estrone neo tessuto adiposo
con feedback cronico ipotalamo ipofisario
Stimolazione estrogenica non antagonizzata su endometrio può portare a iperpla
La resistenza all'insulina può portare a atresia follicolare e acantosis nigricans
Mancato sviluppo follicolare porta ad amenorrea
La sindroma pió svilupparsi come disfunzione primaria di uno qualunque di componenti periferiche
Fattore comune è l'automantenimento del quadro ormonale non ciclico.

Sia insulina che LH stimolano la produzione di androgeni
da parte delle cellule della teca ovariche
Le ovaie quindi secernono alti livelli di testosterone e androstenedione
Alti livelli di androstenedione contribuioscono all'aumento di livelli di estrone
per conversione eriferica da aromatasi
Ridott SHBG circolanti, la sintesi della proteina è soppressa dall'insulina
 e da androgeni, coritoidi, progestinici, e GH
Mafggiore ormone circolante libero
Basse SHBG sono correlate a diabete tipo 2

Anovulation

Although androgen levels are typically elevated in women with PCOS, progesterone levels are low due to anovulation. The precise mechanism leading to anovulation is unclear, but hypersecretion of LH has been implicated in menstrual irregularity.

In addition, anovulation may result from insulin resistance, as a substantial number of anovulatory patients with PCOS may resume ovulatory cycles when treated with metformin, an insulin sensitizer (Nestler, 1998). It has been suggested that oligoovulatory women with PCOS exhibit a milder phenotype of ovarian dysfunction than anovulatory PCOS patients and have a more favorable response to ovulation induction agents (Burgers, 2010).

Finally, the large antral follicle cohort seen in PCOS may contribute to anovulation. Some patients who have undergone ovarian wedge resection or laparoscopic ovarian drilling have found significant improvement in their menstrual regularity. One study demonstrated that 67 percent of PCOS patients developed regular menses following such surgery compared with only 8 percent prior to surgery (Amer, 2002).

Progestinici con effetto anti-androgeno

- ciproterone acetato (CPA);
- dienogest (dNG);
- drospirenone (dRSP);
- clormadinone acetato (CmA).

1.2.3	EBR	Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however, these provide limited additional information in the diagnosis of PCOS.	❖❖❖ ⊕⊕○○
1.2.4	CCR	Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyperandrogenism in PCOS, as they demonstrate poor sensitivity, accuracy and precision.	❖❖❖❖
1.2.5	CPP	Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production.	
1.2.6	CPP	Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time.	
1.2.7	CPP	Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent.	
1.2.8	CPP	Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotyped healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages.	
1.2.9	CPP	Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism.	