REVIEW ARTICLE

Polycystic Ovary Syndrome in Teenage and Young Women

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Summary:

Polycystic ovary syndrome (PCOS) is an inherent ovarian dysfunction. It is a common health problem that can affect teen girls and young women. PCOS is characterized by hyperandrogenism, irregular ovulatory cycle and metabolic derangement , including glucose intolerance and hyperinsulinaemia. Hyperandrogenism is a clinical hallmark of PCOS. Hypersecretion of androgen by the stromal theca cell of polycystic ovary is cardinal clinical manifestation. Though the exact cause of PCOS is not known , the syndrome can result from disturbance in the hypothalamo pituitary ovarian axis and hyperinsulinaemia. Several definitions have been produced to describe the disease. European society of human reproduction and embryology and the American society for reproductive medicine in 2004 define PCOS as manifestation of two of the following three

1. ***Irregular Periods (intervals of more than 40 days) or amenorrhoea.***
2. ***Clinical or biochemical signs of hyperandrogenism .***
3. ***Polycystic ovaries on pelvic ultrasonography.***

PCOS patients are at risk of developing diabetes mellitus (type 2) and cardiovascular diseases. There is no cure for PCOS. The main goal of treatment is to regulate menstrual function, reduce androgen and insulin level. This review article describes cause, clinical feature, pathophysiology and management of PCOS in adolescent girls and young women.

Key words: polycystic ovary syndrome(PCOS), hyperandrogenism, hyperinsulinaemia, anovulation.

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Introduction:

Polycystic ovary syndrome (PCOS) is a common condition of teenage girls and young women. It can cause irregular menstrual periods, make periods heavier or even make period to stop. It is the most common reproductive endocrine disease among women of child bearing age, affecting 5-10% of this population[1]. Generally symptoms of PCOS begin during the teenage years around the start of menstruation and can be mild or severe[2] .

The most common symptoms are irregular period, weight gain, acne and excessive facial and body hair. The severity of the symptoms varies from girl to girl . It is not uncommon for girls with PCOS to have normal appearing ovaries but still have an imbalance in their hormone levels[2] .

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A lack of clarity regarding diagnosting criteria , etiology, natural history and optimal therapies in PCOS, causes frustration for women, clinician and researchers[3] .

Causes of polycystic ovaries:

The exact cause is not known. It is probably a combination of factors involving genetics, environmental factors as well as fetal exposure to high androgen in the womb[4] .

The PCOS has long been noted to have a familial component[5]. Those who have a mother or sister with PCOS are more likely to develop PCOS[6] . The current literature suggests that the clustering of PCOS in families resembles an antosomal dominant pattern[7] .

A number of factors that are associated with an increased risk of PCOS have been identified . Prenatal factors include high birth weight in girls born to overweight mothers, congenital virilization and low birth weight[8] . Risk factors apparent later in childhood include premature pubarche(the appearance of pubic hair in girls before the age of 8),atypical precocious puberty, obesity, acanthosis nigricans and metabolic

syndrome[8] . A history of weight gain often precedes the development. of clinical features of PCOS[9]. A high index suspicion for the diagnosis of PCOS is warranted in adolescents with persistently irregular menses and these risk factors[10].

Pathophysiology

Women with PCOS have an increase in the frequency of gonadotrophin releasing hormone (GnRH) pulses. Shorter pulse preferentially promote the production of leutinizing hormone(LH) and result in decrease in the production of follicle stimulating hormone(FSH)[11]. Elevated level of LH stimulate ovarian theca cells to produce androgenic hormone(testosterone, androstenedione and dehydroepiandrosterone) and irregular or absent menstruation. Besides this low level of FSH relative to LH, the ovarian granulosa cells cannot aromatize the androgen to estrogen. As a result , there is less oestrogen available, no LH surge and ovulation may not be able to occur[12].

Normally , progesterone is released from the corpus luteum following ovulation. Progesterone acts to slow GnRH pulsation. In PCOS , anovulation or oligoovulation causes a decrease in circulating progesterone and increase in GnRH pulsation.

Some studies have investigated the role of the regulatory genes of the cytochrome P450 (CYP)11A, FST, IVSR, 3-HSDL and CYP 17 enzyme in association with PCOS[12].Thecal cells of the ovary in PCOS have been altered whose cytochrome P450(CYP)11A, 3-HSDL and CYP 17 gene exibit elevated levels[13]. And so there is functional abnormality of the 17 – hydroxylase which is the rate limiting enzyme in androgen biosynthesis[14]. Genetic studies have identified a link between PCOS and disordered insulin metabolism and hyperinsulinaemia[15]. Hyperinsulinaemia is secondary both to insulin resistance at the periphery and to abnormal pancreatic ² cell function.

Insulin resistance affects 50-70% of a women with PCOS[16]. Elevated insulin levels may have gonadotrophin (LH) augmenting effects on ovarian function. Insulin helps to regulate ovary function and the ovaries respond to excess insulin by producing androgen[7]. Hyperinsulinaemia also suppress generation of carrier protein sex hormone binding globulin (SHBG) which in turn increase androgenicity[17]. Hyperandrogenism a clinical hallmark of PCOS, can cause inhibition of follicular development , microcyst formation in the ovaries, anovulation and menstrual irregularity[18].

High levels of androgen and high insulin levels can affect the menstrual cycle and prevent ovulation.

Clinical Feature of PCOS

- Hyperandrogenism (Acne, hirsutism, alopecia) :

  Hirsutism is characterized by terminal hair growth in a male pattern of distribution including chin, upper lip, chest, abdomen, nipple area, upper or lower abdomen, upper arm, thigh and buttocks. Upto 60% of women with PCOS have hirsutism[19].

- Menstrual disturbance:

  Irregular menstrual periods which means period more than once a month or every few month or never having periods. Approximately 85% - 90% of women with oligomenarrhoea have PCOS while 30-40% of women with amenorrhoea will have PCOS [20] .

- Periods that is very heavy or very scanty.
- Subfertility or impaired fertility due to lack of ovulation.

Around 70% of ovulatory fertility issue are related to PCOS[6].

- Obesity (BMI > 30kg/m^2)
- Other less common features may include –
- Hair thinning
- Skin tags under the armpits or neck.
- Mood disorders are common among adolescent girls[21].Teens or a young woman often feel frustrated and/or sad if they are having a hard time losing weight, dealing with acne, excess body hair and menstrual irregularities[2].
- High blood pressure
- Pre diabetes or in some cases diabetes
- High total cholesterol and/or low HDL

Serum Endocrinology –

- Increased fasting insulin/ impaired glucose tolerance assessed by GTT
- Increased androgen (testosterone or androstenedione)

- Increased LH, Usually normal FSH.
- Increased SHBG
- Increased prolactin

Approximately 25% of patient's with PCOS have elevated prolactin levels[22].

Diagnostic Criteria of PCOS

A recent Joint ESHRE/ASRM (European Society for Human Reproduction and Embryology/ American Society for reproductive medicine – sponsored PCOS consensus workshop group 2004) consensus meeting a refined definition of the PCOS was agreed: namely the presence of two out of the following three criteria:

1. Irregular periods(intervals of more than 40days) or amenorrhoea.
2. Clinical or biochemical signs of hyperandrogenism.
3. Polycystic ovaries on pelvic ultrasonography.

The morphology of the polycystic ovary, has been redefined as an ovary with 12 or more follicles measuring 2-9 mm in diameter and increased ovarian volume (>10cm^3) on transvaginal ultrasound[23].

These criteria may not be appropriate for all adolescents as some girls with PCOS may experience regular menses or not have cysts[24].

Possible late sequelae

- Diabetes mellitus – insulin resistance is a key feature of both obese and lean PCOS. It occurs in 70-95% of people with obese PCOS and 30-75% of people with lean PCOS [25]. This can contribute to an increased risk of developing type-2 diabetes and cardiovascular disease.
- Dyslipidaemia – hyperinsulinaemia is also responsible for dyslipidemia and for elevated level of plasminogen activator inhibitor -1(PAI-1) in patients with PCOS. Elevated PAI-1 levels are a risk factor of intravascular thrombosis [26].
- Hypertension, Cardiovascular Disease.
- Endometrial Cancer- endometrial hyperplasia and endometrial cancer are possible, due to overaccumulation of uterine lining, and also lack of progesterone resulting in prolonged stimulation of uterine cells by oestrogen[27] .
- Breast cancer- Obesity, hyperandrogenism and infertility occur frequently in PCOS, and are features known to be associated with the development of breast cancer[17].

Obese women with PCOS are more insulin resistant than nonobese women with PCOS moreover pregnant women with PCOS should be informed of the increased rate of miscarriage, gestational diabetes, pre-eclampsia and premature delivery[28].

Investigations

To exclude all other disorders that can result in menstrual irregularity and hyperandrogenism, including adrenal or ovarian tumour, thyroid dysfunction, congenital adrenal hyperplasia, hyper-prolactinaemia, acromegaly and cushing syndrome[29] .

- TSH, FT4
- S. Prolactin
- Total and free testosterone levels
- S hCG level
- S 17 – hydroxyprogesterone levels
- Using free cortisol and creatinine levels
- Low dose dexamethasone suppression test
- S insulin – like growth factor
- S FSH and LH levels
- S Insulin level
- Lipid panel
- Ultrasonography of pelvic organs.

Treatment

There is no cure for PCOS. But there are several ways to treat and manage it. The main goal of treatment for an adolescent girl and young women with PCOS are to regulate menstrual function, reduce androgen and insulin level and improve dermatological symptoms.

Life style modifications are considered 1st line treatment for women with PCOS[24] such as:

1. Diet – keep carbohydrate content down and avoid fatty food.
2. Exercise
3. Weight loss

Pharmacologic treatments are reserved for metabolic derangement such as anovulation hirsutism and menstrual irregularities.

1. Obesity –
   Obesity worsens both symptomatology and endocrine profile and so obese women (BMI> 30Kg/m^2) should therefore be encouraged to lose weight. Weight loss improve endocrine profile and likelihood of ovulation.
2. Menstrual irregularity –
   The easiest way to control the menstrual cycle is the use of a low dose combined oral contraceptive preparation. This will result in an artificial cycle and regular shedding of the endometrium. Birth control pill works by:
   - Correcting the hormone imbalance
   - Lowering the level of testosterone.
   - Regulating menstrual periods.
   - Lowering risk of endometrial cancer.

OCP increase both c-reactive protein and LDL cholesterol level in obese adolescents with PCOS, making metformin more popular drug of choice for this population[30].

Instead of OCP progesterone only pill can also be used.

3. Hyperandrogenism –
   High level of insulin lower the production of SHBG and so increase the free fraction of androgen. 1st line therapy has traditionally been the preparation Dianette, which contains ethinyloestradiol (30μgm) in combination with cyproterone acetate (2gm)[15]. Once symptoms control have been obtained it is advisable to switch to a combined oral contraceptive pill containing a lower dose of ethiryloestradiol, because concerns about increased risk of thromboembolism with "Dianette".

   Adrogen lowering medications such as spironolactone or Flutamide also maybe prescribed but usually takes several month (6-9 months or longer) to produce results and reduce body hair growth[31].

   Dienogest is another newer progestin that has antiandrogenic properties[32].

   Physical treatment include electrolysis, waxing and bleaching maybe helpful while waiting for medical treatment to work.
4. Acne – OCP, topical cream, oral antibiotics. Studies have shown that when insulin and glucose levels are controlled and ovulation resumes, acne and other skin condition may improve greatly.
5. Infertility:
   There are new option available including medication that aim to lower insulin levels which stimulate ovulation.

For anovulation

- Clomiphene – The drug of choice for induction of ovulation in PCOS is clomiphene citrate.

  Upto 6 cycles maybe attempted before further therapy is considered.

  Antidiabetic agent – other medication may be added to clomiphene to yield a more favourable outcome for ovulation, Antidiabetic drug metformin can be used to improve fertility, decrease insulin resistance and reduce circulating androgen level beside insulin sensitivity, metformin is a safe method to regulate menses, lower androgen and improve cardiovascular health in adolescents with PCOS[33].
- Gonadotrophins – HMG and FSH can also be used to induce ovulation, if clomiphene and/or metformin therapy fails.
- Aromatase inhibitors –

  Aromatase inhibitors are considered for patients with clomiphene resistance or for women who are not candidate for clomiphene or gonadotrophins[34].

6. Some girls with PCOS may become depressed in which case it may help to talk to a therapist or other mental health professional[35].

Surgical Options

These cysts are not cancerous and do not need to be surgically removed. Surgery is laparoscopic ovarian drilling – tiny hole are made in the ovaries with reduce the amount of androgen. Ovarian drilling is treatment option for infertility.

Follow-up

It is important that girls with PCOS follow-up regularly with their doctor and take their medication. The prescribed treatment to regulate periods and lessens her chance of getting diabetics and other problems. She should test her blood sugar once a year or have a glucose challenge test (Oral glucose tolerance test) every few years[2].

Conclusion:

PCOS is a complex disorder for which multiple treatment are required, depending on the reason a patient seeks treatment. There is no miracle cure for PCOS, it can be treated, Healthy life style that include nutritious foods and daily exercise can have a profound and positive effect on endocrine system, particularly in cases when a young women is overweight or obese.

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