PCOS: Overview from adolescence to midlife

Incidence of PCOS in women in the reproductive age group is between 5 to 15%. In women presenting with infertility the incidence is about 30% and of all women attending gynaecological clinics with irregular menstruation along with oligo/anovulation, more than 90% have PCOS. It is important to set proper criteria to diagnose PCOS with certainty, so that the health risk of these women can be assessed and follow up plans instituted.

With better understanding of the condition, the criteria for diagnosis of PCOS has been changing from time to time. The NIH/NICHD consensus conference defined this symptom complex in 1990, the Rotterdam PCOS consensus group redefined it in 2003 and the androgen excess PCOS society again defined it in 2006. However, the emphasis remained to classify PCOS in a way that the high health risk group could be identified from the lower health risk group, so that more vigorous follow up and management could be assigned to the high risk category of PCOS women. The androgen excess PCOS society labelled androgen access as the biggest indicator of high risk for metabolic diseases in PCOS woman.

Manifestations of PCOS may start at adolescence and stay with a woman through life or may start even later in life. A woman with PCOS may require special care as well as medical management of different set of problems, which keep arising at different stages of life. Accordingly, heath issues and concerns can be addressed for PCOS women by prioritizing symptom complex which occur with higher frequency at different stages of life. The 3 important stages requiring identification and management of PCOS women are as following.

1. The adolescence phase which mainly presents with menstrual irregularities comprising of menstrual delays or episodes of heavy irregular bleeding, coupled with hirsutism, acne, and hair loss.
2. The second concern need to be addressed generally when fertility is desired. Almost 60% of women go through fertility issues due to oligo ovulatory or anovulatory menstrual cycles.
3. Once the adolescent problems and fertility issue are sorted out the health risk which continue to exist for most PCOS women is due to the close association of PCOS with metabolic diseases. These do not always start at midlife, in fact may start manifesting early in life and continue till midlife or even later. Metabolic health manifestations are obesity, impaired OGTT, type2 diabetes mellitus, hypertension, hyper lipidemia, coronary vascular diseases (CVD), non-fatty liver disease with increased risk of endometrial hyperplasia or endometrial cancer.

Adolescent PCOS: This is a transitional stage of physical and psychological development in a girl's life which exists between puberty and adulthood. Signs and symptoms of PCOS overlap the physiological changes of puberty. All criteria set by various bodies for diagnosis of PCOS, pose a problem when applied to adolescent girls. To diagnose PCOS in adolescence all the 3 criteria described by the Rotterdam consensus must be met with, which means presence of anovulatory cycles, clinical or biochemical hyper-androgenism and appearance of polycystic ovaries. Having 2 features out of the 3 as defined by the Rotterdam consensus group to define an adult woman with PCOS, are not enough to classify an adolescent girl as having PCOS. Post puberty, the pituitary ovarian axis is still stabilizing in this group of young girls, which may correct itself as the hypothalamic-pituitary ovarian axis matures. Often these girls present with phases of amenorrhea followed abnormal uterine bleeding for two to three years post menarche. Moderate to severe hirsutism with or without acne indicate hyper androgenism even though acne with mild hirsutism is commonly seen in most in young adolescent girls. Ovaries may show a multi-cystic appearance around puberty with some similarity to polycystic ovarian appearance which does not qualify them as PCOS. However, scanning after eight years post-menarche still showing PCOS ovaries makes it a diagnostic criterion for definite diagnosis of PCOS. We can reserve the confirmation of her diagnosis to a later date but must start to treat this young girl based on her symptoms, especially the menstrual abnormalities.

Investigations: The test required in PCOS girls before the diagnosis is made are different from those which are used for long term follow-up of these PCOS girls.

<u>Androgen excess:</u>

Clinical feature of hirsutism or assessment of total/free testosterone levels in absence of hirsutism.

17 hydroxy progesterone and DHEAS levels must be assessed in severe cases of hirsutism to rule out other causes.

<u>Ovulatory dysfunction:</u> serum progesterone 3 to 4 weeks following menstruation to confirm ovulation. Pelvic ultrasonography to see polycystic appearance and size of the ovary with endometrial thickness assessment especially in cases where there are periods of amenorrhea or continuous episodes of bleeding.

FSH, LH, thyroid profile, and serum prolactin are recommended especially in cases of amenorrhea with withdrawal bleeding or oligomenorrhea. However, when in doubt of diagnosis assessment of serum AMH can be done.

<u>Metabolic profile:</u>

These should be assessed right from the suspicion of the diagnosis of PCOS at any stage in a girl's life.
Apart from weight assessment looking out for signs of acanthosis nigricans with possibly associated HAIR-AN syndrome (hyperandrogenism, insulin resistance, acanthosis nigricans), oral glucose tolerance test (OGTT) and lipid profile is important in these girls especially if overweight.
Follow up investigations: Once the diagnosis of PCOS is confirmed we need to follow these girls with OGTT and lipid profile yearly with weight and blood pressure monitoring from time to time. Other hormonal tests are only done whenever deemed necessary based on development of new symptoms or need based such as fertility or menstrual issues.

When do we start treatment for these girls?
Definitive diagnosis of PCOS is not necessary to initiate treatment in adolescence as treatment may decrease risk of future comorbidity even in the absence of definite diagnosis. Therefore, in cases of menstrual symptoms especially excessive and intermittent bleeding one can resort to cyclical progestogens till the bleeding stops and then either continue progestogens cyclically or switch over to combined oral contraceptive pills (COCs) especially if hirsutism is also a concern. COCs containing anti androgens like cyproterone-acetate or drospirenone are preferable progestogens which also act as anti-androgens and appear to resolve hirsutism faster. These may be continued for a minimum of six months to be able to demonstrate any beneficial effects on hirsutism and can be continued for several years with or without palliative treatment to supress hirsutism and acne.

Infertile PCOS: It is important to establish the diagnosis of PCOS recommended either by the Rotterdam's consensus group or the criteria laid by AE-PCOS society.
Fertility issues in PCOS are generally resolved by induction of ovulation. Obesity coupled with insulin resistance is a common occurrence in women with PCOS which also contributes to their ovulatory disorder. Lifestyle modification is particularly important in treating women with oligo ovulation or anovulation, not only to improve their ovulatory performance but also to reduce the metabolic consequences of the syndrome. A modest loss of 5% to 10% of total body weight leads to a 30% reduction of central fat, with improvement in insulin sensitivity and helps to restore ovulation to some extent. Weight loss should be encouraged prior to ovulation induction treatment.

Once we decide to start ovulation induction, we need to ensure that the endometrium is normal, as hyperplastic endometrium is very commonly seen in these irregularly menstruating PCOS women. If endometrial thickness is found to be 4 mm or less during menstruation, one can start with ovulation induction with oral ovulogens as first line treatment for ovulation. If oral ovulogens do not lead to successful ovulation or fail to established a pregnancy despite 5 to 6 ovulatory cycles, injectable gonadotropins are recommended. However, injectable gonadotropins are to be used with utmost caution and very judiciously as these women with PCOS tend to get hyper-stimulated in response to even small doses of gonadotropin. The starting doses should be as low as 50 to 75 international units, with small increment in doses of 12.5 to 25 unit every 5 to 7 days. The number of days taken for a dominant follicle to emerge does not appear to change the outcome in terms of successful ovulation or achieving a pregnancy in these PCOS women. Ovarian hyper stimulation syndrome (OHSS) occurs very commonly in these women and must be prevented in all instances. If more than two dominant follicles form in response to induction of ovulation, sexual contact during ovulation must be avoided to prevent the risk of 0HSS as well as that of multiple pregnancy. Sometimes, resorting to ovarian drilling also helps in resuming ovulation in PCOS women who do not ovulate easily or tend to over stimulate with various methods of ovulation induction. Insulin sensitizer as well as inositol's have also been recommended as adjuvants to ovulation inducing drugs in the context of oligo ovulatory PCOS. However, despite ovulation with any of the above agents if pregnancy fails to occur, we may have to resort to in vitro fertilisation (IVF).

PCOS with Metabolic diseases: Once a woman with PCOS has crossed adolescent problems and overcome her fertility issues, yet she remains almost lifelong in the high-risk group for medical issues which, are commonly encountered in men and women with metabolic syndrome. Historically, the treatment of PCOS was short term and mainly under the domain of a gynaecologist and dermatologist. Oral contraceptives or progestogens were given for irregular menstruation, anti-androgens for hirsutism and ovulation induction for infertility. In recent years, a lot of research has gone into this syndrome, and these women have been linked to have higher risk for metabolic complications. In PCOS women the commonly encountered problems are obesity (50 to 60% of PCOS woman), impaired glucose tolerance test (OGTT), hypertension, cardiovascular disease, hyperlipidaemia, obstructive sleep apnoea and non-alcoholic fatty liver disease NAFLD.
Besides the metabolic complications endometrial hyperplasia and endometrial carcinoma is a real threat to these irregularly menstruating PCOS women.

Although adverse health consequences associated with PCOS are formidable and many folds, regrettably most woman and clinicians are not aware of these risks. Recommendation is that PCOS should be viewed as chronic condition that requires longitudinal treatment perspectives.

Screening of metabolic consequences in PCOS: Screening consists of monitoring blood pressure, BMI (weight in kilograms divided by height in metres square), waist circumference, OGTT and lipid profile. These need to be followed up every six months for PCOS women with borderline risk and annually for women with normal profiles. The prevalence of NAFLD in PCOS woman is approximately 15 to 60%. However, even though routine screening is not suggested, it is important to be aware of this condition, especially in obese PCOS with insulin resistance to be able to carry out appropriate screening with assessment with SGOT and SGPT whenever required.

Prevention of metabolic complications of PCOS? The most important component for prevention of metabolic consequences is by keeping one's weight under control by lifestyle modifications. However, one must have realistic expectations towards weight loss. The minimum weight reduction to have any beneficial effect on health statistics would only be if one is able to lose 5% to 10% of weight. Dietary modifications are important and reduction in 30% of calorie intake means 500 to 750 kcal reduction per day. If this can be achieved and maintained, it may lead to the desired weight loss. Physical activity of moderate to intense exercise of at least 150 minutes per week is recommended. Drugs to help reduce weight such as metformin or orlistat have been used in addition to lifestyle modification. This is possibly is most beneficial in high risk obese group which is prone to developing metabolic syndrome. Multi-disciplinary approach may be needed to treat such PCOS women constituting of a diabetologist, endocrinologist, cardiologist, and gastroenterologist for the manifold presentations of these woman with metabolic syndrome.

Prevention of Endometrial hyperplasia and adenocarcinoma: There is a 2 to 6-fold increase risk of endometrial cancer in women with PCOS, which often presents before menopause. Even one episode of prolonged or heavy bleeding warrants ultrasound for endometrial thickness in these women. Healthcare professionals should have a low threshold for investigation of endometrial cancer in women with PCOS for which endometrial aspirate with histopathology is important. Transvaginal ultrasound for endometrial thickness followed by endometrial biopsy is recommended if persistently thick endometrium is seen on ultrasound or there is abnormal vaginal bleeding following amenorrhea. It is suggested to use progestin therapy in PCOS women with cycles longer than 90 days leading to at least 4 menstrual episodes in one

year, resulting from progesterone withdrawal to prevent the risk of endometrial cancers.

Take home points

Diagnosis of PCOS in adolescents should have all three diagnostic criteria met with at least 2 to 3 years after menarche. Treatment for menstrual irregularity and or hyperandrogenism should start even in the absence of confirmation of diagnosis of PCOS. Combined OCPs or progestin can continue through reproductive life with regular follow-up for adverse effects of these drugs. Approximately 70% of PCOS women have fertility issues mainly due to scanty ovulation and the first line treatment is to induce ovulation with oral ovulogens. If these fail to induce ovulation, then gonadotropins are recommended under expert monitoring as these can lead to OHSS and multiple pregnancy. Ovarian drilling is an option for few patients only presenting with infertility. IVF is the last option for these PCOS women if they fail to conceive with all the above treatment. There is need to follow all PCOS with metabolic issues and treated accordingly. There is two to six-fold higher incidence of endometrial hyperplasia and cancer so screening is a must for women if they do not enter menopause.

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