Polycystic ovary syndrome

- PCOS is the most common endocrine disorder affecting women during reproductive years.
- It is heterogeneous collection of signs & symptoms that together form a spectrum of disorder with vary from mild presentation to sever disturbance of reproductive, endocrine & metabolic function.

Pathophysiology

- The pathophysiology of PCOS appears to be multifactorial & polygenic.
- There is hyper secretion of androgens by the stromal cells of the ovary leading to the main manifestation of the syndrome which is hyperandrogenism.

- Hyperandrogenism is one of the mechanisms that inhibit follicular growth resulting in excess of immature follicles.
- There is hyper secretion of luteinizing hormone LH by the pituitary gland due to abnormal ovarian pituitary feedback which also stimulate testosterone secretion by the ovary.

- PCOS characterized by the presence of insulin resistance with elevated serum insulin concentration.
- Insulin resistance found in obese women with PCOS & also in many slim women with PCOS.

- Insulin is potent stimulus for androgen secretion by the ovary.
- Insulin magnify the degree of hyperandrogenism by suppressing liver production of the main carrier protein, sex hormone binding globulin(SHBG) ,thus elevating the free androgen index.

Epidemiology

- The incidence of PCOS in the general population has not been definitively determined & appears to vary considerably between population & it ranges from 4-26%.
- PCOS tend to run in families & genetic factors involved in the pathogenesis of polycystic ovaries.

- There is racial differences in expression of PCOS in which highest prevalence among South Asian women whom have high prevalence of insulin resistance & type 2 diabetes.

Clinical Presentation

- There is considerable heterogeneity in presentation & even for the same woman, the complaint may change overtime.

- The symptoms may include the followings:

1. Menstrual cycle disturbance: oligomenorrhea or amenorrhea.
2. Features of hyperandrogenism like hirsutism, acne or alopecia.
3. subfertilty.
4. Obesity.
5. Asymptomatic with PCO on ultrasound scan.

- Polycystic ovaries can exist without clinical signs of the syndrome but it may be precipitated by various factors most commonly on increase body weight.

Endocrine Abnormalities in PCOS

1.Increased fasting insulin.

2.Increased androgens (testosterone & androstenedione).

3.Decreased sex hormone binding globulin resulting in increased free androgen index.

4. Increased oestradiol & oestrone (but neither measured routinely as there is very wide range of values & it can be confirmed by finding of increased endometrial thickness)

5. Increased LH which found in 40% of patient with PCOS especially those who are slim with normal FSH (increased LH/FSH ratio).

6.Increased anti-mullerian hormone: but this is not universally accepted & still controversial.

Diagnosis of PCOS

- To diagnose PCOS, two of three criteria should be met& these called Rotterdam criteria which are:

1. Presence of clinical or biochemical features of hyperandrogenism.
2. Oligo-ovulation or anovulation (presented as oligomenorrhea or amenorrhea.
3. Polycystic ovaries by ultrasound.

- This definition of PCOS require exclusion of other causes of menstrual abnormalities like hyperprolactinemia or thyroid disorders & other causes of androgen excess such as congenital adrenal hyperplasia, Cushing syndrome or androgen secreting tumours of the ovary or adrenals.

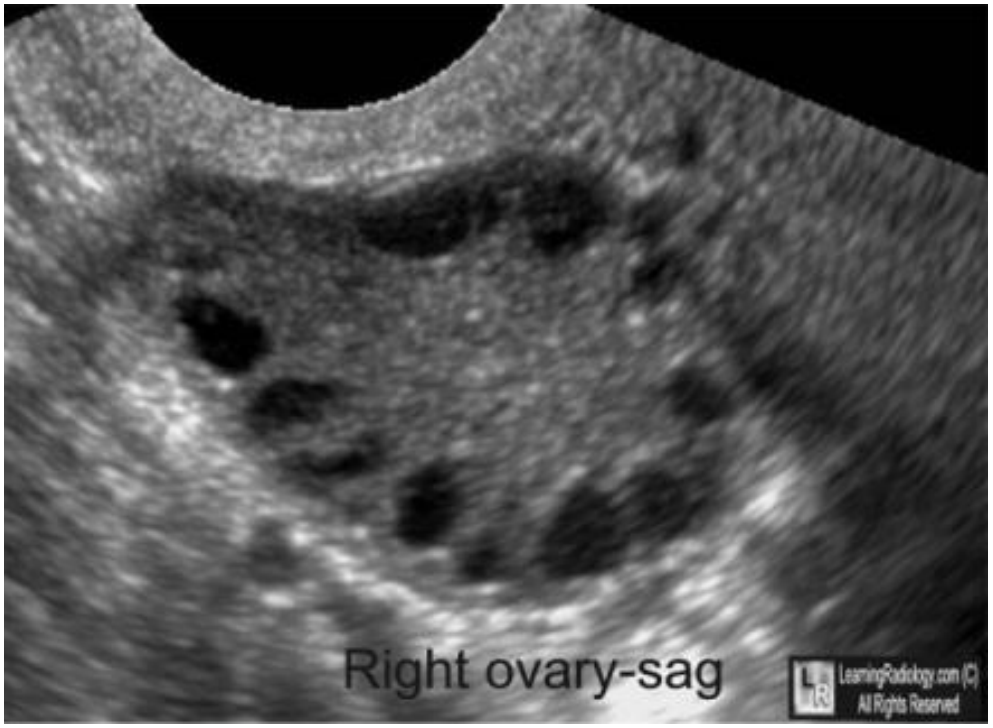
- So, the following investigations are needed for a women with suspected PCOS:

1.Pelvic ultrasound:

polycysic ovaries defined by finding ovary with 12 or more follicles measuring 2-9 mm in diameter &/or increase ovary volume more than 10 cubic cm.

This ultrasound finding present in 20-33% of the population.

increased endometrial thickness indicate increased oestrogen level & measuring oestradiol is unhelpful in the diagnosis.


Right ovary-sag
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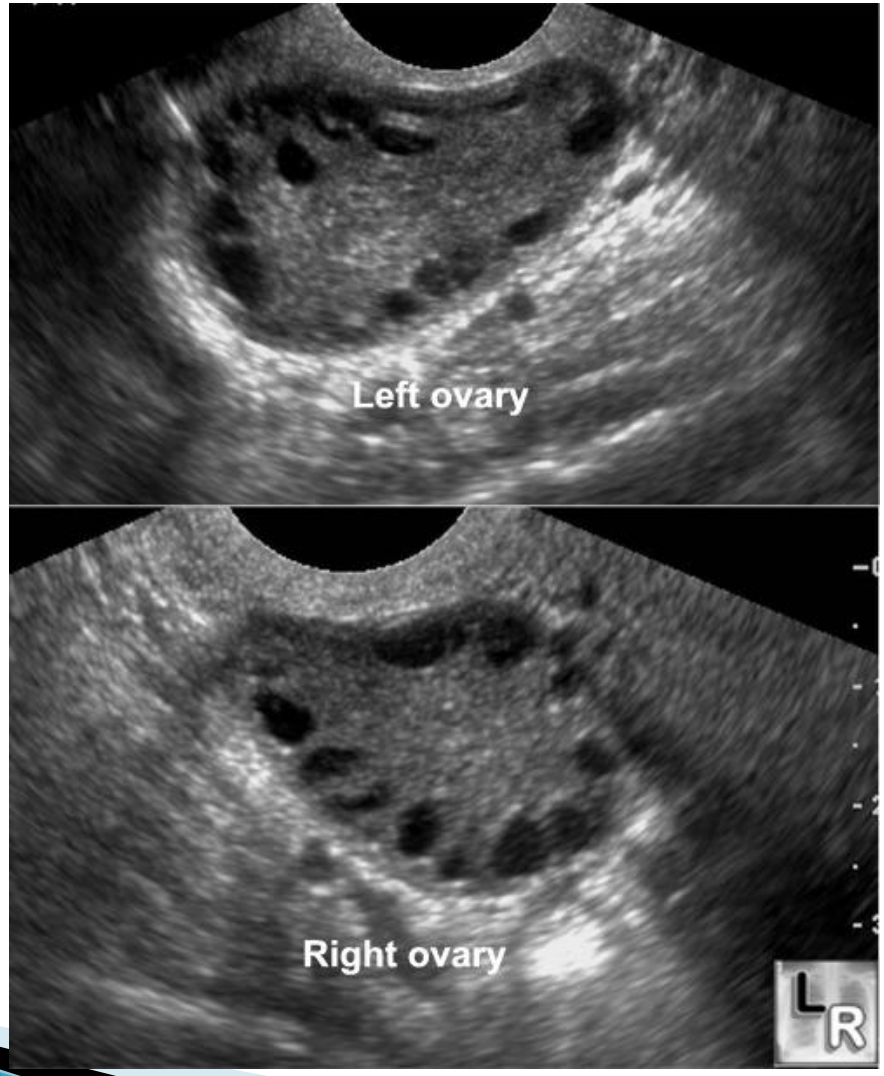
Left ovary
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L
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2.Teststerone level: (increased). It is unnecessary to measure other androgen unless total testosterone more than 5 nmol/L.

3.SHBG (decreased)& free androgen index (increased)

4.LH & FSH best measured at day 1-3 of menstrual cycle (if the patient has amenorrhea or oligomenorrhea, random samples are taken).

5.Fasting insulin but this not routinely measured & insulin resistance assessed by glucose tolerance test especially if BMI more than 30.

6.Tests to exclude other causes of menstrual abnormalities by doing serum prolactin & thyroid function test.

Health Consequences of PCOS

- Insulin resistance with trunkal obesity (increased abdominal visceral fat)with dyslipidemia beside chronic unovulation all are risk factors to certain health problems which are:

1.Diabetes:

Young women with PCOS who are obese have 10-20% risk of impaired GTT& if left untreated, they have 50% risk of developing type 2 diabetes.

2. Cardiovascular diseases:

Obesity, dyslipidemia& hypertension are associated with increased visceral fat & all these will increase the risk of ischemic heart disease & this may be aggravated by having type 2 diabetes.

3.Endometrial cancer:

women with PCOS have unopposed oestrogen due to unovulation & so progesterone not released by the ovary &the endometrium is not shed as menstrual bleed.

The endometrium then may become hyperplastic& endometrial hyperplasia may progress to atypical cellular changes & with time lead to endometrial carcinoma.

- In recent years there is debate about risk of developing ovarian tumours in women with PCOS due to treatment with ovulation induction drugs but the results are conflicting.
- Obesity & subferility seen PCOS are features associate with breast cancer but PCOS does not appear to increase the risk of breast cancer.

Treatment of PCOS

- Management of a women with PCOS should be focused on the patient particular problem.

Obesity

- Obesity worsen both symptoms & endocrine profile & obese women with BMI more than 30 Kg/m should be encouraged to loose weight.
- Weight loss improve endocrine profile & the likelihood of ovulation & healthy pregnancy.
- Weight reduction can be achieved by:

1.Exercise.

2.Calorie restriction: It is sensible to decrease carbohydrate intake& avoid fatty diet. This can be helped by dietician.

3.Drugs: Orlistat may help with weight loss.

4.Surgery: Surgery for weight reduction is increasing as there is global epidemic of obesity like gastric banding or gastric bypass.

Menstrual Irregularity

- Amenorrhea in PCOS is not due to oestrogen deficiency & so there is no risk of osteoporosis.
- To treat oligomenorrhea or amenorrhea:

1.Encourage weight loss.

2.Low dose combined oral contraceptive pills:

This is the simplest way to control the menstrual cycle.

Third generation COCP should be used as they are lipid friendly. Although all COCP will suppress ovarian hyperandrogenism & cause increase SHBG, Dianette & Yasmin are preferable as they contain antiandrogenic activity.

3.Progesterone :

Medroxyprogesterone acetate(provira) can be used for 12 days every 1-3 months to induce withdrawal bleeding.

Continuous provision of progesterone by insertion Mirena intrauterine system can also be used.

4.If the endometrial thickness is more than 10mm by ultrasound & withdrawal bleeding induced by progesterone fail, then endometrial sampling should be done to exclude endometrial hyperplasia & malignancy.

Infertility

- PCOS account for 80-90% of anovulatory infertility in women.
- Various factors affect ovarian function & fertility & one of the important one is obesity.
- Hypersecretion of LH is found in 40% of women who have PCOS & it is associated with decrease fertility & increase risk of miscarriage.
- Elevated LH is found more often in slim women with PCOS.

1.Weight reduction help in resuming ovulation & it is advisable to be done before starting ovulation induction drugs,

2.Oral anti-oestrogen (clomephene citrate & tamoxifen)

- Clomephene citrate traditionally used as first line therapy for unovulatory PCOS.
- The starting dose is 50mg daily from day 2 of the cycle for 5 days.
- If no response , the dose can be increased to 100mg daily for 5 days.
- On the other hand, if excessive response found by ultrasound, the dose can be decreased to 25mg.

- The woman should be carefully monitored by ultrasound to assess follicular growth .
- Clomephene citrate induce ovulation in 70-85% of the patients& 60-70% of them will be pregnant within 6 cycles of therapy.
- On the other hand ,women with PCOS have greater risk of ovarian hyperstimulation syndrome & multiple gestation occur in 10% of the cases.

- Clomephene citrate may cause exaggeration in LH hypersecretion & has anti-oestrogenic effect on the endometrium& cervical mocus which become thick & this interfere with passage of the sperm decreasing the chance of pregnancy.

- If pregnancy not occurred after 6-9 normal ovulatory cycles, it is possible to offer the couple assisted reproductive technique.
- If no response to clomiphene citrate(failure of ovulation), either parenteral gonadotrophin therapy or laparoscopic ovarian surgery should be offered.

3.Gonadotrophin therapy:

Gonadotrophin is indicated if ovulation fail by anti-oestrogen therapy or if thought pregnancy not occurred due to effect of clomiphene citrate on LH increment or cervical mucus.

Is given as injection either recombinant FSH or human menopausal gonadotrophins which contain both FSH & LH activity.

- A low dose regimen should be used starting with 25-50 IU daily of FSH or human menopausal gonadotrophin & increasing the dose gradually if no response.
- The follicular growth should be closely monitored by ultrasound & ovulation is triggered by single injection of hCG 5000 IU when mature follicle of at least 18mm in largest diameter.

- With strict monitoring & abolishing of the trial if excessive response, the risk of multiple gestation is only 5%.

- This can be tried for 6 ovulatory cycle if the woman less than 25 years & for 12 cycles if the woman older than 25years.
- If no pregnancy in spite of ovulation, then assisted reproductive techniques are indicated.

4.Insulin sensitizing agents:

As hyperinsulinemia play major role in the pathogenesis of PCOS, it is logical to achieve decrease in insulin level to improve the symptoms.

- Biguanide metformin inhibit production of hepatic glucose& enhance insulin sensitivity leading to decrease insulin production.

- Metformin has been used for long time as treatment of infertility due to PCOS & initial studies suggest that it improve fertility but in the last decade, recent larger studies observed that no benefit from metformin either alone or with other drugs & it is now recommended it is only indicated when there is impaired glucose tolerance test or type 2 diabetes with PCOS.

5.Surgical ovulation induction:

laparoscopic ovarian diathermy (ovarian drilling) involving burning 4 holes into each ovary.

This replace the more invasive & damaging technique ovarian wedge resection which cause periovarian & peritubal adhesions.

- Ovarian drilling is an alternative to gonadotrophin therapy when there is clomiphene resistance & this will avoid the risk of hyperstimulation syndrome & multiple gestation & does not require intensive ultrasound monitoring especially if the patient is unable to attend the hospital for that.

HIRSUTISM

- Women with PCOS do not become virilized (no deepening of voice, no breast atrophy, no enlargement of the clitoris).