Amenorrhea

Dr. Ala'a Shallal Farhan
M.B.Ch.B/F.I.C.O.G/C.A.B.O.G

Amenorrhea: is defined as the absence of menstruation.

• **Primary amenorrhea** is when girls fail to menstruate by 16 years of age.

- • **Secondary amenorrhea** is absence of menstruation for more than six months in a normal female of reproductive age that is not due to pregnancy, lactation or the menopause.
- **The causes may be hypothalamic, pituitary, ovarian or endometrial**

Causes of amenorrhea

Hypothalamic disorders

- Hypothalamic disorders will give rise to hypogonadotrophic hypogonadism, with the following causes:
- • Excessive exercise, weight loss and stress.
- • Hypothalamic lesions (craniopharyngioma, glioma), which can compress hypothalamic tissue or block dopamine.
- • Head injuries.
- • Kallman's syndrome (X-linked recessive condition resulting in deficiency in GnRH causing underdeveloped genitalia).
- • Systemic disorders including sarcoidosis, tuberculosis resulting in an infiltrative process in the hypothalamo-hypophyseal region.
- • Drugs: progestogens, HRT or dopamine antagonists.

Pituitary disorders

- Pituitary disorders will also give rise to hypogonadotrophic hypogonadism, with the following causes:
- • Adenomas, of which prolactinoma is most common.
- • Pituitary necrosis (e.g. Sheehan's syndrome, due to prolonged hypotension following major obstetric haemorrhage).
- • Iatrogenic damage (surgery or radiotherapy).
- • Congenital failure of pituitary development.

Ovarian disorders

- Anovulation is often due to polycystic ovary syndrome (PCOS), described below. Ovarian failure is the cause of hypergonadotrophic hypogonadism.
- Premature ovarian failure (POF) is defined as cessation of periods before 40 years of age.

Endometrial disorders

- Primary amenorrhoea may result from Müllerian defects in the genital tract including an absent uterus, or outflow tract abnormalities, leading to a haematocolpos like transverse vaginal septum or imperforated hymen.
- Secondary amenorrhoea may result from scarring of the endometrium called Asherman syndrome.

Findings from the history should guide the examination:

- Developmental history :including Menarche Delayed/incomplete may indicate Congenital malformation or chromosomal abnormality
- Menstrual history: Oligomenorrhoea, PCOS

Secondary amenorrhoea: POF,

- Reproductive history: Infertility may occure with PCOS or Congenital malformation
- Cyclical symptoms: Cyclical pain without menstruation may indicate Congenital malformation or Imperforate hymen
- Hair growth : Hirsutism may indicate PCOS
- Weight: Dramatic weight loss may indicate Hypothalamic malfunction
- Difficulty losing weight :PCOS
- Lifestyle: Exercise, stress may indicate Hypothalamic malfunction
- Past medical history: Systemic diseases, e.g. sarcoidosis may idicate Hypothalamic malfunction
- Past surgical history: Evacuation of uterus occure with Asherman's syndrome
- Drug history: Dopamine agonists, HRT with Hypothalamic malfunction
- Headache: Pituitary adenoma
- Galactorrhoea: Prolactinoma
- Visual disturbance: Pituitary adenoma

- A general inspection of the patient should be carried out to assess body mass index (BMI), secondary sexual characteristics (hair growth, breast development) and signs of endocrine abnormalities (hirsutism, acne, abdominal striae, moon face, skin changes). If the history is suggestive of a pituitary lesion, an assessment of visual fields is indicated. External genitalia and a vaginal examination should be performed to detect structural outflow abnormalities or demonstrate atrophic changes consistent with hypo-oestrogenism.

Investigation of amenorrhoea/oligomenorrhoea

- Findings from the history and examination should guide the choice and order of investigations.
- A pregnancy test should be carried out if the patient is sexually active. Blood can be taken for LH, FSH and testosterone; raised LH or raised testosterone could be suggestive of PCOS; raised FSH may be suggestive of POF. A raised prolactin level may indicate a prolactinoma.
- Thyroid function should be checked if clinically indicated.
- An ultrasound scan can be useful in detecting the classical appearances of polycystic ovaries.
- Magnetic resonance imaging (MRI) of the brain should be carried out if symptoms are consistent with a pituitary adenoma.
- Hysteroscopy is not routine, but is a suitable investigation where Asherman or cervical stenosis is suspected.
- Karyotyping is diagnostic of Turner's and other sex chromosome abnormalities.

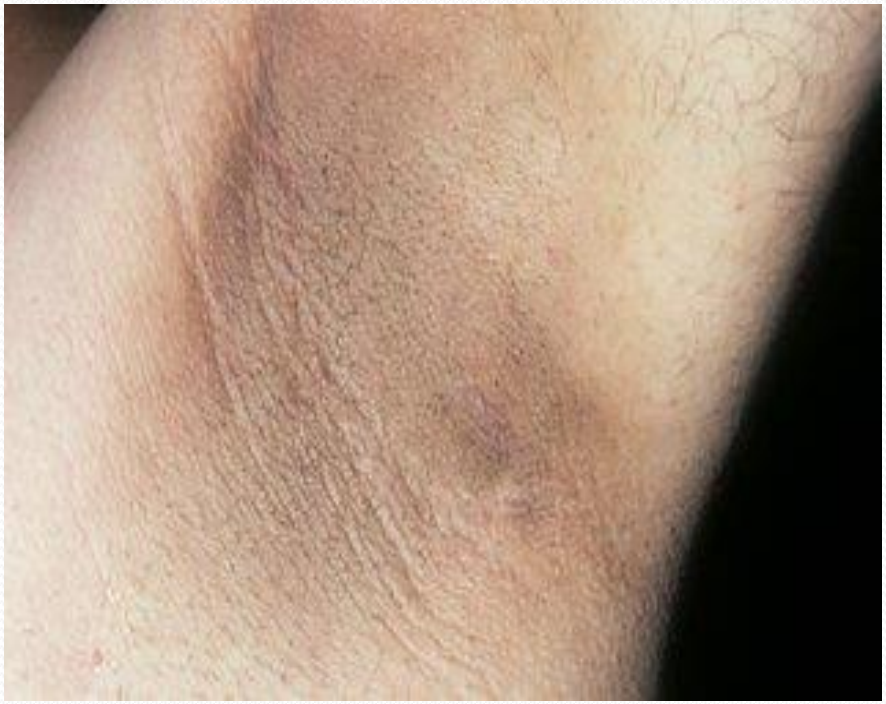
Polycystic ovary syndrome

- PCOS is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and polycystic ovary morphology.
- The prevalence of polycystic ovaries seen on ultrasound is
- around 25% of all women but is not always associated with the full syndrome.
- Clinical manifestations include menstrual irregularities, signs of androgen excess (e.g. hirsutism and acne) and obesity. Elevated serum LH levels, biochemical evidence of hyperandrogenism and raised insulin resistance are also common features.
- PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events.
- It affects around 5–10% of women of reproductive age. The etiology of PCOS is not completely clear, although the frequent familial trend points to a genetic cause.

Clinical features

- •Oligomenorrhoea/amenorrhoea in up to 75% of patients, predominantly related to chronic anovulation.
- • Hirsutism.
- • Subfertility in up to 75% of women.
- • Obesity in at least 40% of patients.
- •Acanthosis nigricans (areas of increased velvety skin pigmentation occur in the axillae and other flexures).
- • May be asymptomatic.

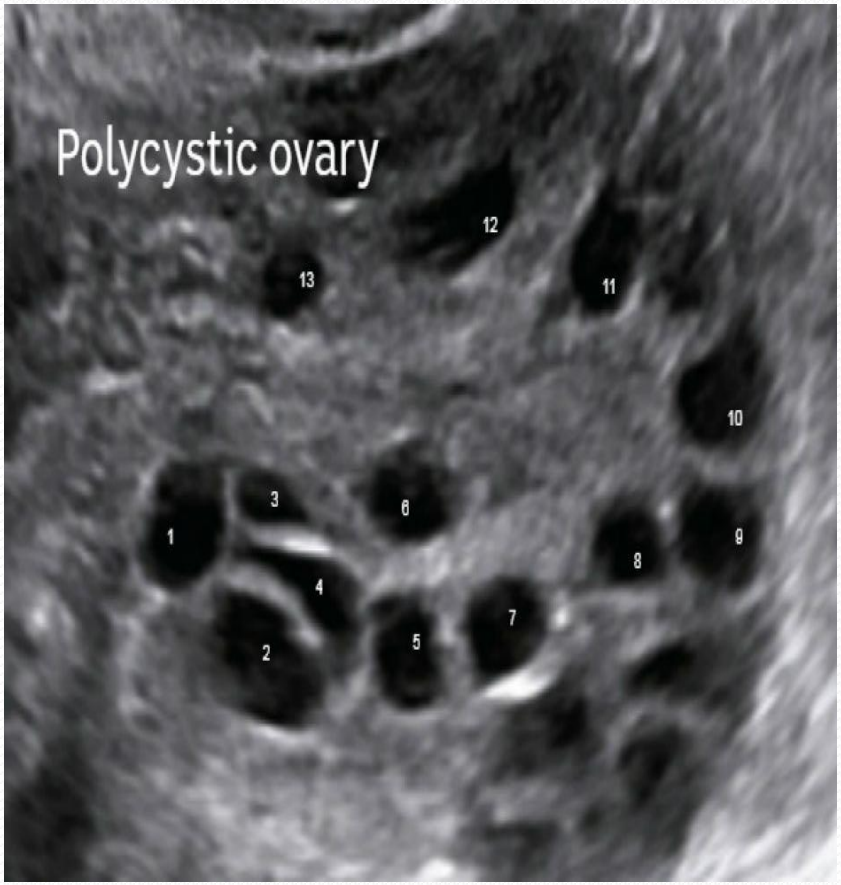
Acanthosis nigricans

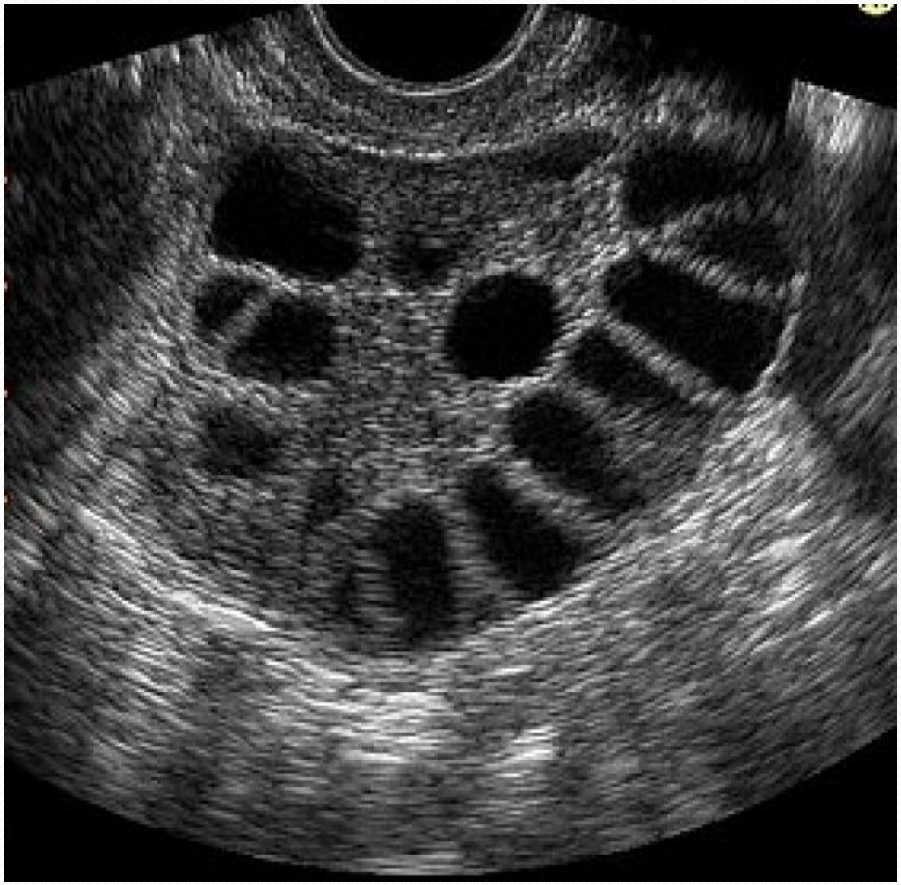


Diagnosis

- Patients must have **two out of the three** features below:
- • Amenorrhoea/oligomenorrhoea.
- • Clinical or biochemical hyperandrogenism.
- • Polycystic ovaries on ultrasound. The ultrasound criteria for the diagnosis of a polycystic ovary are eight or more subcapsular follicular cysts <10 mm in diameter and increased ovarian stroma. While these findings support a diagnosis of PCOS, they are not by themselves sufficient to identify the syndrome.

POLYCYSTIC OVARIES





Serum endocrinology

- Increased Fasting insulin (not routinely measured; insulin resistance or impaired glucose tolerance assessed by GTT)
- Increased Androgens (testosterone and androstenedione)
- Increased or normal LH, normal FSH
- Decreased SHBG, results in elevated free androgen index
- Increased Estradiol, estrone (neither measured routinely as very wide range of values)
- Increased Prolactin

Management

- Management of PCOS involves the following:
- • Lifestyle advice: dietary modification and exercise is appropriate in these patients as they are at an increased risk of developing diabetes and cardiovascular disease later in life. Aerobic exercise has been shown to improve insulin resistance.
- • Weight reduction: It is sensible to keep carbohydrate content down and to avoid fatty foods. It is often helpful to refer to a dietitian. Bariatric surgery (either gastric banding or gastric bypass procedures)
- Menstrual irregularities:

1• Combined oral contraceptive pill (COCP) to regulate menstruation. This also increases sex hormone binding globulin, which will help reduce androgenic symptoms.

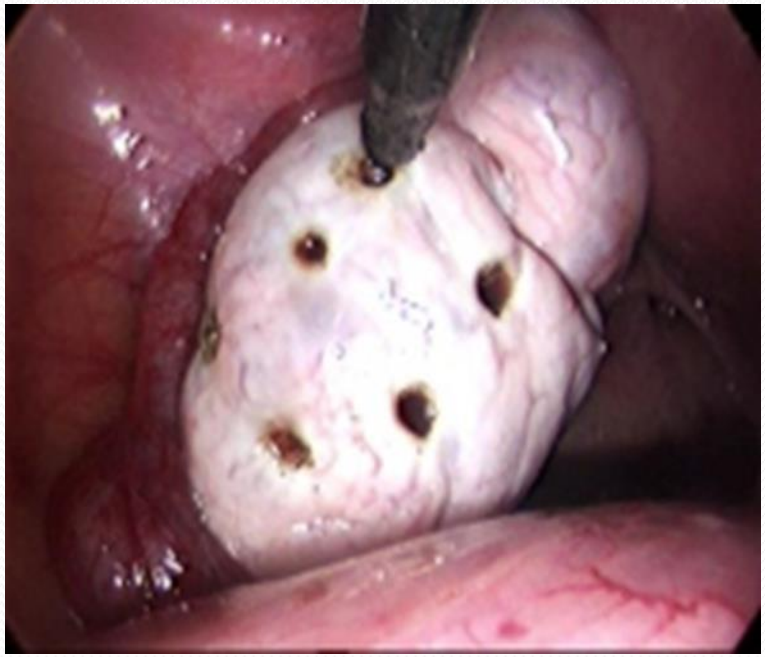
2• Cyclical oral progesterone: used to regulate a withdrawal bleed.

Infertility

- Strategies to induce ovulation include weight loss, oral antioestrogens (principally clomifene citrate or tamoxifen), parenteral gonadotrophin therapy and laparoscopic ovarian surgery.
- Clomifene is the traditional first-line therapy and can be continued for 6–12 cycles of treatment if the patient is ovulating with normal endocrinology.((50–100 mg) taken from days 2–6 of a natural or artificially induced bleed).
- For those who do not ovulate, the options include daily injections of either recombinant FSH, human menopausal gonadotrophins (hMGs, which contain both FSH and LH activity) or laparoscopic ovarian diathermy.
- Risks of ovulation induction:multiple pregnancy and ovarian hyperstimulation syndrome.
- • Ovarian drilling, a laparoscopic procedure to destroy some of the ovarian stroma that may prompt ovulatory cycles.

- • Treatment of hirsutism/androgenic symptoms:
- Electrolysis, Laser and photothermolysis techniques,
- • eflornithine cream applied topically;
- • cyproterone acetate (an antiandrogen contained in the Dianette™ contraceptive pill, sometimes used alone);
- spironolactone, a weak diuretic with anti-androgenic properties, may be used at a daily
- dose of 25–100 mg.
- Other anti-androgens such as ketoconazole, finasteride
- and flutamide

Laproscopic ovarian drilling



Insulin-sensitizing agents and metformin

- Metformin: this is beneficial in a subset of patients with PCOS, those with hyperinsulinaemia and cardiovascular risk factors. It improves parameters of insulin resistance, hyperandrogenaemia, anovulation and acne in PCOS, and may aid weight loss. It is less effective than clomiphene for ovulation induction and does not improve pregnancy outcome;
- This biguanide inhibits the production of hepatic glucose and enhances the sensitivity of peripheral tissue to insulin, thereby decreasing insulin secretion.
- Because metformin may ameliorate hyperandrogenism and abnormalities of gonadotrophin secretion in some women with PCOS, and therefore it was suggested that it might restore menstrual cyclicity and fertility.

- Metformin appears to be less effective in those who are significantly obese (BMI >35 kg/m2).

- *Possible late sequelae*
- Diabetes mellitus
- Dyslipidaemia
- Hypertension, cardiovascular disease
- Endometrial carcinoma

Hyperprolactinaemia

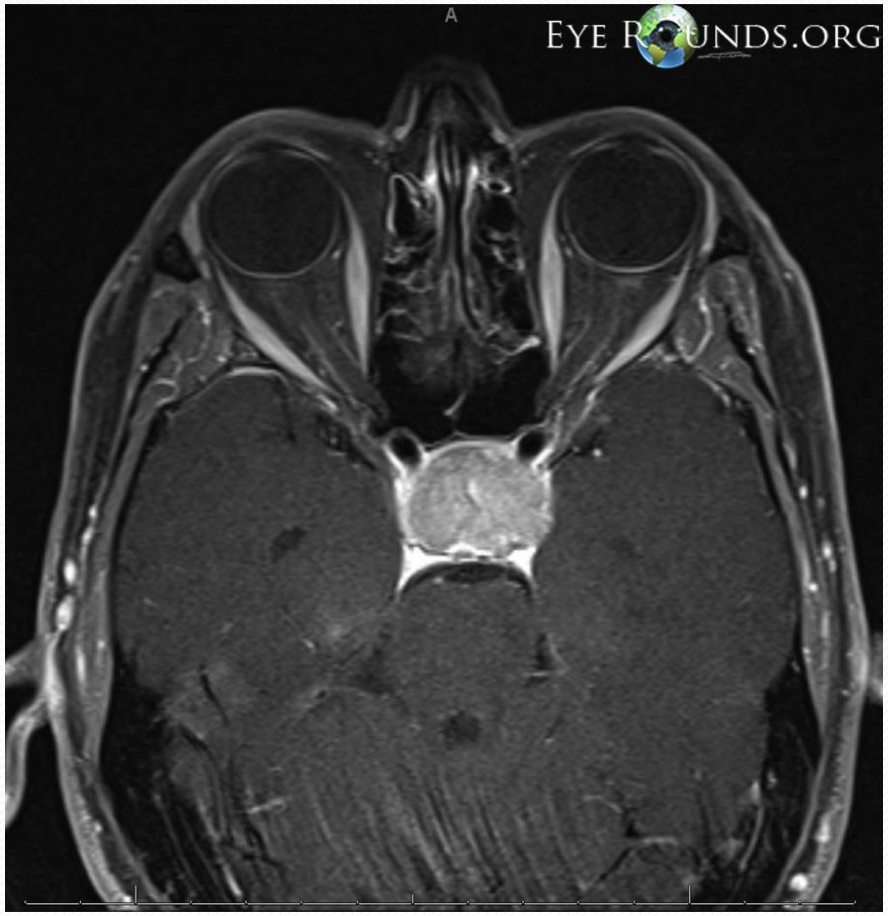
- Hyperprolactinaemia is the commonest pituitary cause of amenorrhoea.
- There are many causes of a mildly elevated serum prolactin concentration, including stress, and a recent physical or breast examination.
- If the prolactin concentration is greater than 1000 mIU/L then the test should be repeated, and if still elevated it is necessary to image the pituitary fossa (with CT or MRI).
- Hyperprolactinaemia may result from a prolactin-secreting pituitary adenoma or from a non-functioning 'disconnection' tumour in the region of the hypothalamus or pituitary, which disrupts the inhibitory influence of dopamine on prolactin secretion.

- Other causes include:
- hypothyroidism, PCOS (up to 2500 mIU/L) and several drugs (e.g. the dopaminergic antagonists phenothiazines, domperidone and metoclopramide).

- In women with amenorrhoea associated with hyperprolactinaemia, the main symptoms are usually those of **oestrogen deficiency**.
- In contrast, when hyperprolactinaemia is associated with PCOS, the syndrome is characterized by adequate oestrogenization, polycystic ovaries on ultrasound scan and a withdrawal bleed in response to a progestogen challenge test.
- **Galactorrhoea** may be found in up to one-third of patients with hyperprolactinaemia, although its appearance is correlated neither with prolactin levels nor with the presence of a tumour.
- Approximately 5% of patients present with **visual field defects**.

- Typical radiological changes on skull x-ray: an asymmetrically enlarged pituitary fossa with a double contour to its floor and erosion of the clinoid processes.
- Skull X-rays are rarely performed these days as CT and MRI scans now allow detailed examination of the extent of the tumour and, in particular, identification of suprasellar extension and compression of the optic chiasma or invasion of the cavernous sinuses.

Brain MRI, axial view, showing a pituitary adenoma with compression of the optic chiasm



Management

- The management of hyperprolactinaemia centres around the use of a dopamine agonist, of which bromocriptine and cabergoline are the most widely used. Of course, if the hyperprolactinaemia is drug induced, stopping the relevant preparation should be commended.

- However, this may not be appropriate if the cause is a psychotropic medication, for example a phenothiazine being used to treat schizophrenia. In these cases it is reasonable to continue the drug and prescribe a low-dose combined oral contraceptive preparation in order to counteract the symptoms of oestrogen deficiency.

- Serum prolactin concentrations must then be carefully monitored to ensure that they do not rise further. Most patients show a fall in prolactin levels within a few days of commencing bromocriptine therapy and a reduction in tumour volume within 6 weeks.

- Surgery, in the form of trans-sphenoidal adenectomy, is reserved for
- Cases of drug resistance
- Failure to shrink a macroadenoma or
- There are intolerable side effects of the drugs (the most common indication).
- Non-functioning tumours should be removed surgically


Thank
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