1) **Secondary Amenorrhea - Dr. Hanaa**

**Amenorrhea:** Is the absence or abnormal cessation of the menses. It is of two types:

- **Physiological Amenorrhea** (Pre-puberty, pregnancy-related, menopause)
- **Pathological Amenorrhea** (primary, secondary)

**Control of Menstrual Cycle**

- Hypothalamus → pituitary → endocrine → ovarian → outflow tract axis

**Pathological Amenorrhea**

- A patient is diagnosed with *primary* amenorrhea if she has not reached menarche by age 16 with normal secondary sexual characteristics.
- *Secondary* amenorrhea is established if menses have ceased for longer than 6 months without any physiological reasons.
- **Physiological:** The most common cause of secondary amenorrhea in reproductive age women is pregnancy and this should always be excluded by physical exam and laboratory testing for the pregnancy hormone - HCG.

**Etiology**

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Ovarian</th>
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<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Premature ovarian failure</td>
</tr>
<tr>
<td>Cushing’s</td>
<td>PCOS</td>
</tr>
<tr>
<td>Adrenal tumour</td>
<td>Surgical removal</td>
</tr>
<tr>
<td>Ovarian tumour (androgen)</td>
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<tr>
<td>Hypothalamic dysfunction</td>
<td></td>
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<tr>
<td>Pituitary tumour</td>
<td></td>
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<tr>
<td>Sheehan’s syndrome</td>
<td></td>
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<tr>
<td>Hypothalamic dysfunction</td>
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</table>

**Hypothalamus-Pituitary**

| Pituitary tumour                              |                                              |
| Sheehan’s syndrome                            |                                              |
| Hypothalamic dysfunction                      |                                              |

**Most common etiologies:**

- Ovarian disease – 40%
- Hypothalamic dysfunction – 35%
- Pituitary disease – 19%
- Uterine disease – 5%
- Other – 1%
- Pregnancy
- Thyroid disease
- Hyperprolactinemia
  - Prolactinoma
  - Breastfeeding, Breast stimulation
  - Medication (i.e. Antipsychotics, Antidepressants)
- Hypergonadotropic hypogonadism
  - Postmenopausal ovarian failure
  - Premature ovarian failure
- Hypogonadotropic hypogonadism
  - Functional hypothalamic amenorrhea (i.e. Anorexia or Bulimia nervosa)
  - CNS tumor (i.e. Craniopharyngioma)
  - Sheehan’s syndrome
  - Chronic illness

<table>
<thead>
<tr>
<th>Outflow tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asherman’s syndrome</td>
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<tr>
<td>Hysterectomy</td>
</tr>
</tbody>
</table>
• Normogonadotropic
  o Outflow tract obstruction (i.e. Asherman’s syndrome, Cervical stenosis)
  o Hyperandrogenic anovulation (i.e. PCOS, Cushing’s disease, CAH)

Hypothalamic Causes
• Hypothalamic dysfunction is a common cause (30%).
• It is more often seen as a result of stress, weight loss and eating disorders
• It may be due to tumour, infarction, thrombosis or inflammation.

Pituitary Causes
• Pituitary failure - It is usually the acquired type as the result of trauma, treatment of pituitary tumour or infarction after massive blood loss (Sheehan’s syndrome)
• Pituitary tumour → hyperprolactinaemia which cause secondary amenorrhea.

Endocrine Causes
• Thyroid disorder and Cushing’s disease interfere with the normal functioning of the hypothalamic-pituitary - ovarian axis → present with amenorrhea.
• High level of thyroxine inhibit FSH release.
• Androgen – secreting tumours of the ovaries → cause secondary amenorrhea.

Anatomical Causes
• Usually due to previous surgery. Commonest example:
  o Hysterectomy
  o Endometrial ablation
  o Asherman’s syndrome (damage to the endometrium with adhesion formation)
  o Stenosis of the cervix following cone biopsy

1) Uterine defect
• Asherman’s syndrome
• This is intrauterine synechiae
• withdrawal beeding after hormonal test is negative
• history of D&C after delivery or termination of pregnancy other cause TB or schistosomiasis
• normal ovulatory cycle & premenstrual symptoms
• Patients with Asherman’s syndrome may evaluated by HSG & transvaginal US
• Treatment
  o Hysteroscopic treatment with excision of synechiae
  o Mainaining of seperation of uterine walls by insertion of a large inert IUCD such as a Lippes loop
  o Result of treatment are often disappointing in term of subsequent fertility

Premature Ovarian Failure
• Premature ovarian failure occurs in about 1% before the age of 40.
• Premature ovarian failure may be due to:
  • Chemotherapy and radiotherapy.
  • Autoimmune disease following viral infection
  • Following surgery for conditions such as endometriosis
2) Premature ovarian failure

- Ovarian failure before 40 years
- Ovarian failure before 30 years may be due to chromosomal disorders. Karyotyping is done to check for mosaicism (some cells have Y chromosome) gonadectomy is indicated to prevent malignant transformation
- Other causes of premature ovarian failure
  - Ovarian injury from surgery, radiation or chemotherapy, galactocaemia & autoimmunity
- When premature ovarian failure is secondary to autoimmunity other endocrine organs could be affected
- Investigations
  - FBS for diabetes
  - Free thyroxine, TSH for hypothyroidism
  - Serum calcium for hypoparathyroidism
  - Fasting morning cortisol
- Treatment of premature ovarian failure
  - By hormone therapy (estrogen & progesterone)

Drugs Causing Hyperprolactinaemia

- Hyperprolactinaemia accounts for 20% of cases of amenorrhea.
- Prolactin inhibits GnRH release from the hypothalamus
- Drugs may cause hyperprolactinaemia

3) Amenorrhea with Hyperprolactinaemia

- Galactorrhea is the most frequently observed abnormalities associated with hyperprolactinemia
- Hyperprolactinemia that is severe or associated with menstrual disturbances or galactorrhea should be confirmed by a second test, TSH should be tested for hypothyroidism
- If clinically significant hyperprolactinaemia is not explained by hypothyroidism or drug use a CT or MRI scan of sella turcica should be performed
- Drugs that may cause hyperprolactinaemia includes
  1. tranquilizers
  2. antidepressants
  3. antihypertensives
  4. narcotics
  5. metaclopramide
- Mechanisms that produce ↑ Prolactin
  1. Normally dopamine suppresses prolactin production. If a mass compresses the stalk of the pituitary, the dopamine feedback pathway is interrupted and it can no longer inhibit prolactin → ↑ prolactin levels. Also, GnRH will not be able to pass through and there will be ↓ LH and ↓ FSH. If there is ↑ prolactin and ↓ LH & FSH there may be ↓ E2 (Estradiol) levels - consider hormone replacement therapy.
  2. Hyperprolactinemia may also be caused by psychoactive drugs which suppress dopamine. Even so, you will still see ↓ FSH & LH levels.
  3. Prolactin secreting adenomas produce excess prolactin → ↑ levels
Two types of prolactin-secreting adenomas

<table>
<thead>
<tr>
<th>Microadenomas</th>
<th>Macroadenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs.</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>&gt; 10 mm</td>
</tr>
<tr>
<td>MRI</td>
<td>diagnosed on</td>
</tr>
<tr>
<td>important to</td>
<td></td>
</tr>
<tr>
<td>do</td>
<td></td>
</tr>
<tr>
<td>visual</td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td></td>
</tr>
<tr>
<td>Very benign</td>
<td></td>
</tr>
<tr>
<td>and headaches</td>
<td></td>
</tr>
<tr>
<td>Treat symptoms only – amenorrhea</td>
<td>Must be treated</td>
</tr>
</tbody>
</table>

Follow up MRIs every 1-2 yrs to check surgical treatment

Bromocriptine agonist – may shrink adenoma for additional growth

Radiation - works well but may cause panhypopituitarism.

Treatment of Hyperprolactinemia

- Dopamine agonist therapy - (Cabegolin, Bromocriptine) - most common. This should induce ovulation and shrink the adenoma. With drug induced hyperprolactinemia, bromocriptine may counter the effects of the anti-depressent medications.
- If it is a macroadenoma, transphenoidal resection may be done. This will result in resumption of ovulation for 40% of patients. Only 10-50% will have a long tercure with the surgery.
- Response to radiation can be very slow.
- If a patient has a microadenoma or other causes of hyperprolactinemia, birth control pills may be used to bring on regular periods and to correct the galactorrhea. If a woman wants to try and have a baby you can try ovulation induction.
- Goals of Treatment: regulate menses, prevent endometrial hyperplasia, induce ovulation for pregnancy, and improve hirsutism (excessive body hair in a masculine pattern of distribution due to hereditary or hormonal factors.)

POLYCYSTIC OVARIAN SYNDROME (PCOS)

- PCOS accounts for 90% of cases of oligoamenorrhea
- Also known as Stein-Leventhal syndrome
- The etiology is probably related to insulin resistance, with a failure of normal follicular development and ovulation
- The classical picture – Amenorrhea, Obese, Subinfertility & Hirsuitism

The Assessment

- History
- Examination
- Investigations

The most common cause of secondary amenorrhea in reproductive age women is pregnancy and this should always be excluded by physical exam and laboratory testing for the pregnancy hormone - HCG.
History

- A good history can reveal the etiologic diagnosis in up to 85% of cases of amenorrhea.

- Ask About
  - Menstrual cycle → age of menarche and previous menstrual history
  - Previous pregnancies - severe PPH (Sheehan’s syndrome)
  - Weight change → A large amount of weight loss (anorexia nervosa)
  - Hot flashes, decreased libido → premature menopause
  - Certain medications
  - Contraception
  - Associate symptoms - Cushing's disease, hypothyroidism
  - Previous gynaecological surgery
  - Chronic illness

Examination

- Check for
  - Body mass index (BMI) → weight loss-related amenorrhea
  - Blood pressure → elevated in cushing and pcos
  - Androgen excess → hirsuitism (PCOS) – virilization (tumour)
  - Secondary sexual characteristic
  - Breast examination → may revealed galactorrhea,
  - Abdominal (haemato mera) and pelvic masses (ovarian tumour)
  - Inspection of genitalia → cervical stenosis

INVESTIGATIONS

- If the history and physical exam are suggestive of a certain etiology → the workup can sometimes be more directed → some patients will not demonstrate any obvious etiology for their amenorrhea on history and physical examination → these patients can be worked up in a logical manner using a stepwise approach.

- Once pregnancy has been excluded
  - Progesterone challenge test
  - TSH (thyroid stimulating hormone)
  - FSH, LH
  - Prolactin level

Progestin challenge test

- Medroxyprogesterone acetate 10 mg daily for 10 days
- IF withdrawal bleed occurs – Not outflow tract obstruction
- IF no withdrawal bleed occurs – Estrogen/Progestin challenge test

Estrogen/Progestin challenge test

- Oral conjugated estrogen 0.625 – 2.5 mg daily for 35 days
- Medroxyprogesterone acetate 10 mg daily for 26-35 days
- IF no withdrawal bleed occurs – Endometrial scarring
- Hysterosalpingogram or Hysteroscopy to evaluate endometrial cavity
Investigating Secondary Amenorrhea

Evaluation of hyperandrogenism

- Symptoms: hirsutism, acne, alopecia, masculinization, and virilization
- Differential diagnosis:
  - Adrenal disorders: Atypical congenital adrenal hyperplasia (CAH), Cushing’s syndrome, Adrenal neoplasm
  - Ovarian disorders: PCOS, Ovarian neoplasms
  - Lab: Testosterone, DHEA-S, 17α-hydroxyprogesterone

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Level</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>&lt; 200 ng/dL</td>
<td>PCOS</td>
</tr>
<tr>
<td></td>
<td>&gt; 200 ng/dL</td>
<td>Evaluate for adrenal or ovarian tumor</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>&lt; 700 ng/dL</td>
<td>PCOS</td>
</tr>
<tr>
<td></td>
<td>&gt; 700 ng/dL</td>
<td>Evaluate for adrenal or ovarian tumor</td>
</tr>
<tr>
<td>17α-hydroxyprogesterone</td>
<td>&gt; 4 ng/mL</td>
<td>Consider ACTH stimulation test to diagnose CAH</td>
</tr>
</tbody>
</table>

Ovarian Failure (premature menopause)

- Chromosomal abnormalities → if the woman is under 30, a karyotype should be performed to rule out any mosaicism involving a Y chromosome. If a Y chromosome is found the gonads should be surgically excised.
- Autoimmune diseases → it is prudent to screen for thyroid, parathyroid, and adrenal dysfunction. Lab evidence of autoimmune phenomenon is much more prevalent than clinically significant disease

Hypothalamic-pituitary failure

- Patients who do not bleed after the progestin challenge
- But do bleed after estrogen/progestin and
- Have normal or low FSH and LH levels
Investigations

<table>
<thead>
<tr>
<th>Site Of Disorder</th>
<th>Diagnosis</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>Hypothalamic – Failure Weight-Related Amenorrhea</td>
<td>FSH, LH and Estradiol – Low</td>
</tr>
<tr>
<td></td>
<td>Sheehan Syndrome</td>
<td>Prolactin – High FSH, LH and Estradiol – Low FSH, LL and Estrogen – Low</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism</td>
<td>TSH – Raised; T4 – Low or N</td>
</tr>
<tr>
<td>Ovary</td>
<td>Premature Menopause PCos</td>
<td>FSH, LH – High; E₂ – Low FSH – Normal; LH – High</td>
</tr>
<tr>
<td>Mullerian Tract</td>
<td>Asherman’s Syndrome</td>
<td>EPCT – Negative HSG / Hystereoscopy</td>
</tr>
</tbody>
</table>

Treatment of Amenorrhea

- The need for treatment depends on
  - Underlying causes
  - Need for regular periods
  - Trying to conceive (fertility)
  - Need for contraception
- Trying to Conceive
  - The prognosis for women with confirmed ovarian failure is poor.
  - *Anovulation* → response well with ovulation induction treatment
  - *PCOS* → ovulation may resume with weight reduction – fertility drugs - use of gonadotrophins or ovarian drilling.
  - *Hyperprolactinaemia* → respond to treatment with dopamine agonist.
  - *Hypothalamic Dysfunction* → maintenance of normal weight and change of lifestyle
  - *Asherman’s syndrome* → breaking down adhesion + insert IUCD
- Want Regular Period
  - The use of
    1. Combined Oral Contraceptive
    2. HRT
- Need Contraception
  - Confirmed ovarian failure will not require contraception
  - Women requiring contraception → oral contraceptives are method of choice

Amenorrhea/Oligomenorrhea: Management

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian insufficiency</td>
<td>Hormone replacement therapy (HRT)</td>
</tr>
<tr>
<td>• Premature ovarian failure</td>
<td></td>
</tr>
<tr>
<td>• Postmenopausal ovarian failure</td>
<td></td>
</tr>
<tr>
<td><em>Congenital anatomic lesions</em>*</td>
<td>Surgical correction</td>
</tr>
<tr>
<td>*Presence of Y chromosome (i.e. AIs)</td>
<td>Gonadectomy</td>
</tr>
<tr>
<td>*Gonadal dysgenesis (i.e. Turner syndrome)</td>
<td>Estrogen + progestin, growth hormone IVF (IF pregnancy desired)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Dopamine agonist (Bromocriptine, Cabergoline)</td>
</tr>
<tr>
<td>Functional hypothalamic amenorrhea</td>
<td>Increase caloric intake &gt; energy expenditure</td>
</tr>
<tr>
<td>Hypothalamic or pituitary dysfunction</td>
<td>OCP’s, pulsatile GnRH or exogenous gonadotropins</td>
</tr>
<tr>
<td>(non-reversible)</td>
<td></td>
</tr>
<tr>
<td>CNS tumor</td>
<td>Surgical resection</td>
</tr>
<tr>
<td>• Craniopharyngioma</td>
<td>Microadenoma (&lt;10mm) – Dopamine agonist</td>
</tr>
<tr>
<td>• Prolactinoma</td>
<td>Macroadenoma (&gt;10mm) – Trans-sphenoidal resection</td>
</tr>
<tr>
<td>PCOS</td>
<td>OCP’s, weight loss, and metformin</td>
</tr>
<tr>
<td>Asherman’s syndrome</td>
<td>Hysteroscopic lysis of adhesions</td>
</tr>
</tbody>
</table>

Treatment goals of amenorrhea and oligomenorrhea include prevention of complications such as osteoporosis, endometrial hyperplasia and heart disease; preservation of fertility; and in primary amenorrhea, progression of normal pubertal development.