Definitions

**Primary amenorrhea**

Failure of menarche to occur when expected in relation to the onset of pubertal development.

- No menarche by age 16 years with signs of pubertal development.
- No onset of pubertal development by age 14 years.

**Secondary amenorrhea**

- Absence of menstruation for 3 or more months in a previously menstruating women of reproductive age.
CNS-Hypothalamus-Pituitary Ovary-uterus Interaction

Neural control
- Dopamine (-)
- Norepiniphrine (+)
- Endorphines (-)

Chemical control
- Gn-RH
- Estrogen
- Progesterone

Ovaries
- FSH, LH
- Menses

Uterus
- +
- ±

Ant. pituitary
- ±
- ?

Pituitary
- LH
- FSH

Hypothalamus

Hypothalamus 

Brain

Endometrium
Pathophysiology of Amenorrhea

- **Inadequate hormonal stimulation of the endometrium**
  - "Anovulatory amenorrhea"
    - Euestrogenic
    - Hypoestrogenic

- **Inability of endometrium to respond to hormones**
  - "Ovulatory amenorrhea"
    - Uterine absence
    - Utero-vaginal agenesis
    - XY-Females (e.g. T.F.S)
    - Damaged endometrium (e.g. Asherman’s syndrome)
## Euestrogenic Anovulatory Amenorrhea

### Normal androgens
- Hypothalamic-pituitary dysfunction (stress, weight loss or gain, exercise, pseudocyesis)
- Hyperprolactinemia
- Feminizing ovarian tumour
- Non-gonadal endocrine disease (thyroid, adrenal)
- Systemic illness

### High androgens
- PCOS
- Masculinizing ovarian tumour
- Cushing’s syndrome
- Congenital adrenal hyperplasia (late onset)
# Hypoestrogenic Anovulatory Amenorrhea

**Normal androgens**
- **Hypothalamic-pituitary failure**
  - Severe dysfunction
  - Neoplastic, destructive, infiltrative, infectious & traumatic conditions involving hypothalamus or pituitary
- **Ovarian failure**
  - Gonadal dysgenesis
  - Premature ovarian failure
  - Enzyme defect
  - Resistant ovaries
  - Radiotherapy, chemotherapy

**High androgens**
- Musculinizing ovarian tumour
- Cushing’s syndrome
- Congenital adrenal hyperplasia (late onset)
AMENORRHOEA
AN APPROACH FOR DIAGNOSIS

- HISTORY
- PHYSICAL EXAMINATION
- ULTRASOUND EXAMINATION

Exclude Pregnancy
Exclude Cryptomenorrhea
Cryptomenorrhea

Outflow obstruction to menstrual blood
- Imperforate hymen
- Transverse Vaginal septum with functioning uterus
- Isolated Vaginal agenesis with functioning uterus
- Isolated Cervical agenesis with functioning uterus

- Intermittent abdominal pain
- Possible difficulty with micturition
- Possible lower abdominal swelling
- Bulging bluish membrane at the introitus or absent vagina (only dimple)
Once Pregnancy and cryptomenorrhea are excluded:

**The patient is a bioassay for Endocrine abnormalities**

_Four categories of patients are identified_

1. Amenorrhea with absent or poor secondary sex characters
2. Amenorrhea with normal 2ry sex characters
3. Amenorrhea with signs of androgen excess
4. Amenorrhea with absent uterus and vagina
AMENORRHEA
Absent or poor secondary sex characteristics

FSH Serum level

- Low / normal
  - Hypogonadotrophic hypogonadism
- High
  - Gonadal dysgenesis
AMENORRHEA

Normal secondary sex Characteristics

- FSH, LH, Prolactin, TSH
- Provera 10 mg PO daily x 5 days

+ Bleeding
  - Prolactin
  - TSH

No bleeding

Mild hypothalamic dysfunction
- PCO (↑LH/FSH)

Further Work-up (Endocrinologist)

Review FSH result And history (next slide)
FSH

High

- Ovarian failure
  - If < 25 yrs or primary amenorrhea ⇒ karyotype
  - If < 35 yrs ⇒ R/O autoimmune disease
  - ?? Ovarian biopsy

Low / normal

- Hypothalamic-pituitary Failure
  - head CT- scan or MRI
    - Severe hypothalamic dysfunction
    - Intracranial pathology
Amenorrhea
Utero-vaginal absence

Karyotype

46-XY
- Gonadal regression
- Testicular enzyme deficiency
- Leydig cell agenesis

Absent breasts & sexual hair

46-XX
- Androgen Insensitivity (TSF syndrome)
- Mullerian Agenesis (MRKH syndrome)

Normal breasts & sexual hair
Normal FSH, LH; -ve bleeding history is suggestive of amenorrhea trumatica

Asherman’s syndrome

- History of pregnancy associated D&C
- Rarely after CS, myomectomy T.B endometritis, bilharzia
- Diagnosis: HSG or hysterescopy
- Treatment: lysis of adhesions; D&C or hysterescopy + estrogen therapy (IUCD or catheter)

Some will prescribe a cycle of Estrogen and Progesterone challenge Before HSG or Hysterescopy
Asherman’s syndrome
Amenorrhea
Signs of androgen excess

Testosterone, DHEAS, FSH, and LH

- TEST. >200 ng/dL
- DHEAS >700 mug/dL
- DHEAS 500-700 mug/dL

U/S ? MRI or CT
- Ovarian tumor
- Or adrenal tumor

↑Serum 17-OH Progesterone level
- Late CAH

Adrenal hyperfunction

Lower elevations ⇒ PCOS (High LH / FSH)
# Amenorrhea

## PRIMARY AMENORRHEA

- Ovarian failure: 36%
- Hypogonadotrophic Hypogonadism: 34%
- PCOS: 17%
- Congenital lesions (other than dysgenesis): 4%
- Hypopituitarism: 3%
- Hyperprolactinaemia: 3%
- Weight related: 3%

## SECONDARY AMENORRHEA

- Polycystic ovary syndrome: 30%
- Premature ovarian failure: 29%
- Weight related amenorrhoea: 19%
- Hyperprolactinaemia: 14%
- Exercise related amenorrhoea: 2%
- Hypopituitarism: 2%
Gonadal dysgenesis

- **Chromosomally incompetent**
  - Classic turner’s syndrome (45XO)
  - Turner variants (45XO/46XX), (46X- abnormal X)
  - Mixed gonadal dygenesis (45XO/46XY)

- **Chromosomally competent**
  - 46XX (Pure gonadal dysgeneis)
  - 46XY (Swyer’s syndrome)
## Gonadal dysgenesis

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Classic Turner’s</th>
<th>Turner Variant</th>
<th>True gonadal Dysgenesis</th>
<th>Mixed Dysgenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Ambiguous</td>
</tr>
<tr>
<td>Gonad</td>
<td>Streak</td>
<td>Streak</td>
<td>Streak</td>
<td>- Streak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Testes</td>
</tr>
<tr>
<td>Height</td>
<td>Short</td>
<td>- Short</td>
<td>Tall</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic stigmata</td>
<td>Classical</td>
<td>±</td>
<td>Nil</td>
<td>±</td>
</tr>
<tr>
<td>Karyotype</td>
<td>XO</td>
<td>XX/XO or abnormal X</td>
<td>46-XX(Pure)</td>
<td>XO/XY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46-XY (Swyer)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Turner’s syndrome

- Sexual infantilism and short stature.
- Associated abnormalities, webbed neck, coarctation of the aorta, high-arched palate, cubitus valgus, broad shield-like chest with widely spaced nipples, low hairline on the neck, short metacarpal bones and renal anomalies.
- High FSH and LH levels.
- Bilateral streaked gonads.
- Karyotype - 80 % 45, X0
  - 20% mosaic forms (46XX/45X0)
- Treatment: HRT
Ovarian dysgenesis
None-dysgenesis ovarian failure

- Steroidogenic enzyme defects (17-hydroxylase)
- Ovarian resistance syndrome
- Autoimmune oophoritis
- Postinfection (eg. Mumps)
- Postoopherectomy
- Postoopherecetomy
- Postradiation
- Postchemotherapy
Premature ovarian failure

- Serum estradiol < 50 pg/ml and FSH > 40 IU/ml on repeated occasions
- 10% of secondary amenorrhea
- Few cases reported, where high dose estrogen or HMG therapy resulted in ovulation
- Sometimes immuno therapy may reverse autoimmune ovarian failure
- Rarely → spont. ovulation (resistant ovaries)
- Treatment: HRT (*osteoporosis, atherogenesis*)
Polycystic ovary syndrome

- The most common cause of chronic anovulation
- Hyperandrogenism; ↑ LH/FSH ratio
- Insulin resistance is a major biochemical feature (↑ blood insulin level → hyperandrogenism)
- Long term risks: Obesity, hirsutism, infertility, type 2 diabetes, dyslipidemia, cardiovascular risks, endometrial hyperplasia and cancer
- Treatment depends on the needs of the patient and preventing long term health problems
Hypogonadotrophic Hypogonadism

- Normal height
- Normal external and internal genital organs (infantile)
- Low FSH and LH
- MRI to R/O intra-cranial pathology.
- 30-40% anosmia (kallmann’s syndrome)
- Sometimes constitutional delay
- Treat according to the cause (HRT), potentially fertile.
Constitutional pubertal delay

- Common cause (20%)
- Under stature and delayed bone age (X-ray Wrist joint)
- Positive family history
- Diagnosis by exclusion and follow up
- Prognosis is good (late developer)
- No drug therapy is required – Reassurance (? HRT)
Sheehan’s syndrome

- Pituitary inability to secrete gonadotropins
- Pituitary necrosis following massive obstetric hemorrhage is most common cause in women
- Diagnosis: History and ↓ E2, FSH, LH + other pituitary deficiencies (MPS test)
- Treatment: Replacement of deficient hormones
Weight-related amenorrhoea

Anorexia Nervosa

- 1º or 2º Amenorrhea is often first sign
- A body mass index (BMI) <17 kg/m² → menstrual irregularity and amenorrhea
- Hypothalamic suppression
- Abnormal body image, intense fear of weight gain, often strenuous exercise
- Mean age onset 13-14 yrs (range 10-21 yrs)
- Low estradiol → risk of osteoporosis
- Bulemics less commonly have amenorrhea due to fluctuations in body wt, but any disordered eating pattern (crash diets) can cause menstrual irregularity.
- Treatment: ↑ body wt. (Psychiatrist referral)
Exercise-associated amenorrhoea

- Common in women who participate in sports (e.g. competitive athletes, ballet dancers)
- Eating disorders have a higher prevalence in female athletes than non-athletes
- Hypothalamic disorder caused by abnormal gonadotrophin-releasing hormone pulsatility, resulting in impaired gonadotrophin levels, particularly LH, and subsequently low oestrogen levels
Contraception related amenorrhea

- Post-pill amenorrhea is not an entity
- Depot medroxyprogesterone acetate
  Up to 80% of women will have amenorrhea after 1 year of use. It is reversible (oestrogen deficiency)
- A minority of women taking the progestogen-only pill may have reversible long term amenorrhoa due to complete suppression of ovulation
Late onset congenital adrenal hyperplasia

- Autosomal recessive trait
- Most common form is due to 21-hydroxylase deficiency
- Mild forms closely resemble PCO
- Severe forms show signs of severe androgen excess
- High 17-OH-progesterone blood level
- Treatment: cortisol replacement and corrective surgery
Cushing’s syndrome

- Clinical suspicion: Hirsutism, truncal obesity, purple striae, ↑ BP
- If Suspicion is high:
dexamethasone suppression test (1 mg PO 11 pm) and obtain serum cortisol level at 8 am:
  < 5 µg/dl excludes Cushing’s
- 24 hours total urine free cortisol level to confirm diagnosis
- 2 forms; adrenal tumour or ACTH hypersecretion (pituitary or ectopic site)
Utero-vaginal Agenesis
Mayer-Rokitansky-Kuster-Hauser syndrome

- 15% of primary amenorrhea
- Normal breasts and sexual hair development & Normal looking external female genitalia
- Normal female range testosterone level
- Absent uterus and upper vagina & Normal ovaries
- Karyotype 46-XX
- 15-30% renal, skeletal and middle ear anomalies
- Treatment: STERILE? Vaginal creation (Dilatation VS Vaginoplasty)
Androgen insensitivity

Testicular feminization syndrome

- X-linked trait
- Absent cytosol receptors
- Normal breasts but no sexual hair
- Normal looking female external genitalia
- Absent uterus and upper vagina
- Karyotype 46, XY
- Male range testosterone level
- Treatment: gonadectomy after puberty + HRT
- ? Vaginal creation (dilatation VS Vaginoplasty)
General Principles of management of Amenorrhea

- Attempts to restore ovulatory function
- If this is not possible HRT (oestrogen and progesterone) is given to hypo-estrogenic amenorrheic women (to prevent osteoporosis; atherogenesis)
- Periodic progestogen should be taken by euestrogenic amenorrheic women (to avoid endometrial cancer)
- If Y chromosome is present gonadectomy is indicated
- Many cases require frequent re-evaluation
Hormonal treatment
Primary Amenorrhea with absent secondary sexual characteristics

To achieve pubertal development

Premarin 5mg D1-D25 + provera 10mg D15-D25 X 3 months; ↓ 2.5mg premarin X 3 months and ↓ 1.25mg premarin X 3 months

Maintenance therapy

0.625mg premarin + provera OR ready HRT preparation OR 30µg oral contraceptive pill
Summary

- Although the work-up of amenorrhea may seem to be complex, a carefully conducted physical examination with the history, and looking to the patient as a bioassay for endocrine abnormalities, should permit the clinician to narrow the diagnostic possibilities and an accurate diagnosis can be obtained quickly.
- Management aims at restoring ovulatory cycles if possible, replacing estrogen when deficient and Progestosterone to protect endometrium from unopposed estrogen.
- Frequent re-evaluation and reassurance of the patient.
THANK YOU FOR YOUR ATTENTION