Clinical Guidelines for Evaluation and Management of Amenorrhea

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
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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)
Eustrogenic Anovulatory Amenorrhea

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

High androgens
- PCOS
- Musculinizing ovarian tumor
- 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 tumor
- 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)
Imperforate hymen
Once Pregnancy and cryptomenorrhea are excluded:
The patient is a bioassy for Endocrine abnormalities
Four categoris of patients are indentified
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
AMENORRHEA
Normal secondary sex characteristics
CLINICAL GUIDELINES
FOR
EVALUATION AND MANAGEMENT OF AMENORRHEA

Dr. JEHAD YOUSEF
FICS, FRCOG
ALHAYAT ART CENTER
AMMAN – JORDAN
CLINICAL GUIDELINES
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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 hysteroscopy
• Treatment: lysis of adhesions; D&C or hysteroscopy + estrogen therapy (? ICUD or catheter)
Some will prescribe a cycle of Estrogen and Progesterone challenge Before HSG or Hysteroscopy
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<table>
<thead>
<tr>
<th>Amenorrhea</th>
<th>PRIMARY AMENORRHEA</th>
<th>SECONDARY AMENORRHEA</th>
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<tbody>
<tr>
<td></td>
<td>Ovarian failure</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Hypogonadotrophic</td>
<td>34%</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>PCOS</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Congenital lesions (other than dysgenesis)</td>
<td>4%</td>
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<tr>
<td></td>
<td>Hypopituitarism</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Hyperprolactinaemia</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Weight related</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovry syndrome</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Premature ovarian failure</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Weight related amenorrhoea</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>Hypeprolactinaemia</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Excerise related amenorrhoea</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Hypopituitarism</td>
<td>2%</td>
</tr>
</tbody>
</table>
Gonadal dysgenesis

- Chromosomally incompetent
  - Classic turner's syndrome (45X0)
  - Turner variants (45X0/46XX), (46X-abnormal X)
  - Mixed gonadal dygenesis (45X0/46XY)
- Chromosomally competent
  - 46XX (Pure gonadal dysgenesis)
  - 46XY (Swyer's syndrome)
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Gonadal dysgenesis

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Classic Turner's</th>
<th>Female</th>
<th>Streak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonad</td>
<td></td>
<td>Female</td>
<td>Streak</td>
</tr>
<tr>
<td>Height</td>
<td>Short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic stigmata</td>
<td>Classical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>XO</td>
<td></td>
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</tr>
</tbody>
</table>

Turner’s
Female
Streak
- Short
- Nil
- ±
- 46-XX (Pure)
- 46-XY (Swyer)
- XO/XY

Clinical Guidelines for Evaluation and Management of Amenorrhea
Published on Physicians Practice (http://www.physicianspractice.com)
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.
- Karotype - 80% 45, X0
- 20% mosaic forms (46XX/45X0)
- Treatment: HRT
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None-dysgenesis ovarian failure
- Steroidogenic enzyme defects (17-hydroxylase)
- Ovarian resistance syndrome
- Autoimmune oophoritis
- Postinfection (eg. Mumps)
- Postoopherectomy
- 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 does estrogen or HMG therapy resulted in ovulation
- Sometimes immunotherapy may reverse autoimmune ovarian failure
- Rarely → spont. ovulation (resistant ovaries)
- Treatment : HRT (osteoporosis, atherogenesis)
Polycystic ovary syndrome
• The most common cause of chronic anovulation
• Hyperadrogenism; ↑ 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
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Hypogonadotropic 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 amenorrhea

Anorexia Nervosa

- 1° or 2° 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 years (range 10-21 years)
- Low estradiol → risk of osteoporosis
- Bulimics less commonly have amenorrhea due to fluctuations in body weight, but any disordered eating pattern (crash diets) can cause menstrual irregularity.
- Treatment: ↑ body weight 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 amenorrhea 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 to total urine free cortisol level to confirm diagnosis
- 2 forms; adrenal tumor or ACTH hypersecretion (pituitary or ectopic site)
Utero-vaginal Agenesis
Mayer-Rokitansky-Kuster-Hauser syndrome
• 15% of 1ry amenorrhea
• Normal breasts and sexual hair development & normal female looking genitalia
• Normal female range testosterone level
• Absent uterus and upper vagina & normal ovaries
• Karotype 46-XX
• 1530% renal, skeletal and middle eear anomalies
• Treatment: STERILE ? Vaginal creation (Dilation VS Vaginoplasty)
Adrogen insensitivity
Testicular feminization syndrome
• X-linked trait
• Absent cytosol receptors
• Normal breast but no sexual hair
• Normal looking female external genitalia
• Absent uterus and upper vaginal
• Karotype 46, XY
• Male range testosterone level
• Treatment: gonadectomy after puberty + HRT
• ? Vaginal creation (dilation 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-oestrogenic amenorrhoeic women (to prevent osteoporosis; atherogenesis)
• Periodic progestogen should be taken by oestrogenic amenorrhoeic 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 endocrin 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 progestrogen to protect endometrium from unopposed estrogen.
• Frequent re-evaluation and reassurance of the patient.
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THANK YOU FOR YOUR ATTENTION
Dr. Jehad Yousef
F.I.C.S., F.R.C.O.G

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