Primary & Secondary amenorrhoea

Richard Dover
Specialist gynaecologist
Delayed puberty and early menopause?
Overview

• Outline the parameters
• Causes
• Investigations
• Management
Amenorrhoea is normal.

- Pre-pubertal
- Pregnancy
- Lactation
- Post-menopausal

- Define the end points
Puberty

- Difficult definition
- Absence of menses by age 15
- In presence of normal secondary sexual characteristics
- At age 13 if no SSC
- <13 if cyclical pelvic pain
## Delayed puberty

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional delay</td>
<td>53%</td>
</tr>
<tr>
<td>Delayed, but spontaneous</td>
<td>19%</td>
</tr>
<tr>
<td>Hypogonadatrophic hypogonadism</td>
<td>12%</td>
</tr>
<tr>
<td>Hypergonadatrophic hypogonadism</td>
<td>13%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>3%</td>
</tr>
</tbody>
</table>
Primary amenorrhoea

- Usually the result of a genetic or anatomical abnormality
- All causes of secondary amenorrhoea can present as primary (NB Sheehan’s)
Causes of primary amenorrhoea

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Chromosomal (gonadal dysgenesis)</td>
<td>50</td>
</tr>
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<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
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</table>
Secondary amenorrhoea

• Absence of menses for more than three cycles or 6 months in women who previously had menses
Secondary amenorrhoea

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Ovarian</td>
<td>40</td>
</tr>
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<tr>
<td>Uterine</td>
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</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>
# Amenorrhoea

<table>
<thead>
<tr>
<th>Cause</th>
<th>Primary (%)</th>
<th>Secondary (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamic</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Pituitary</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Ovarian</td>
<td>50 (dysgenesis)</td>
<td>40</td>
</tr>
<tr>
<td>Anatomical</td>
<td>20 (congenital)</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
Hypothalamic causes

• Congenital. Rare. With anosmia = Kallmann’s syndrome
• Tumours / meningitis / skull fractures
• Functional hypothalamic amenorrhoea
Functional hypothalamic amenorrhoea

- Excludes organic disease
- Abnormal GnRH secretion
- Low / normal LH concentrations
- Absent follicular development
- Anovulation
- FSH often normal
Causes FHA

- Eating disorders (anorexia) 10% below ideal body weight
- Stress, both emotional related to severe illness
- Excessive exercise
Pituitary

- PRL release controlled by inhibition by dopamine
- PRL suppresses hypothalamic GnRH secretion
- Effect of drugs
Medication causing hyperprolactinaemia

- Extensive list
- Antipsychotics
- Anti ulcer
- Anti-hypertensive
- Many more
- Herbal medications
Pituitary disease

• Prolactinoma cause of 20% of secondary amenorrhoea (???)

• Prolactin can be raised by stress, sleep, exercise…..repeat if elevated
# Amenorrhoea of pituitary origin

<table>
<thead>
<tr>
<th>Serum PRL</th>
<th>Interpretation</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>&lt;500 mu/l</td>
<td>Normal range</td>
<td>None</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>Consistent with stress or recent breast examination</td>
<td>Repeat</td>
</tr>
<tr>
<td>700-2500</td>
<td>Hypothyroidism / PCOS</td>
<td>Check TFT, FSH,T, SHBG</td>
</tr>
<tr>
<td>&lt;3000</td>
<td>Non-functioning macroadenoma</td>
<td>MRI or CT head will demonstrate hypothalamic tumours, micro and macro</td>
</tr>
<tr>
<td>1500-4000</td>
<td>Functioning microadenoma</td>
<td>Adenomas of the pituitary. Threshold &gt;1500 on two occasions</td>
</tr>
</tbody>
</table>
Other pituitary causes

• Sheehan’s syndrome
• Radiation / infarction
• Hypothyroidism
Hypothyroidism

- Increased TRH due to hypothyroidism can stimulate PRL secretion
Ovarian disorders

- Gonadal dysgenesis
- PCOS
- Primary ovarian insufficiency (POF)
Gonadal dysgenesis

- Single most common cause of primary amenorrhoea is ovarian failure due to gonadal dysgenesis
- Increased FSH due to absence of oocytes
- Low E2
- Turner’s syndrome 45XO most common
PCOS

• 20% of all cases of amenorrhoea
• Can be primary, but usually a normal or slightly delayed menarche followed by irregular cycles or secondary amenorrhoea
Diagnosis PCOS

• Variable
• 2 of 3 clinical features. Hyperandrogenism, oligo/amenorrhoea and polycystic ovaries
• Hyperandrogenism = acne or hirsuitism and perhaps an elevated androgen
• Diagnosis of exclusion
Premature Ovarian Failure
Mechanisms of POF

• Accelerated atresia (genetic)

• Dysfunction of follicular maturation
Menopause

- Gradual cessation of ovarian function
- Oestrogen deficiency
- Reduction in fertility
- Rise in gonadatrophin levels

- Mean 50 +/- 4
Premature menopause

• Prior to age 40 (~1%)
• 4/12 amenorrhoea
• FSH x 2 >30 iu/ml

• With improving cancer cure rates in children and young women, incidence will increase
## Aetiology

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<th>Type</th>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>X-chromosomal</td>
<td>7%</td>
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<tr>
<td>Iatrogenic (chemo/DXT/surgery)</td>
<td>2.5%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>1%</td>
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More specifically

• Surgery/DXT/Chemotherapy
• Autoimmune (Addison’s/hypothyroid)
• Family history of POF (15-30%)
Genetic

- Turner’s syndrome.
- Usually primary amenorrhoea
- Mosaic, atresia rate lower. Secondary amenorrhoea
Iatrogenic

• Usually cancer related therapy
• Incidence dependent on age and regimes/dosages used
• ~8% of all childhood cancer survivors
• But 30-40% if DXT and alkylating agents
• Women <40 with Ca breast ~17%
Autoimmune

- Frequent associations
- Hypothyroidism 17%
- IDDM 1.7%
- Parietal cell antibodies 3.7%
- Myasthenia gravis 2.7%
Anatomical causes

- Congenital causes = primary
- Acquired = secondary
Imperforate hymen
Asherman’s
Asherman’s
Assessment - Primary

- History. Breasts, hair growth (Tanner)
- Family
- Weight
- Health
- Phenotype
- NO VE / PR
# Causes of primary amenorrhoea

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Assessment - Options

- FSH / LH / TFT’s
- E2
- USS
Assessment - Primary

• Presence or absence of breast development
• Oestrogen (and therefore ovarian) dependent
• If no breast development and FSH is elevated, then gonadal dysgenesis is likely
• Check karyotype
Primary continued

- USS = absent uterus and normal FSH then Mullerian agenesis (or androgen insensitivity) is likely
- If breasts, normal FSH and uterus then focus on causes of secondary amenorrhoea
Assessment - Secondary

- hCG
- FSH / LH / E2
- PRL
- TFT’s
- T, SHBG, DHEA, 17-OH prog
Secondary amenorrhoea

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Secondary - cont

- If PRL elevated
- Drug history
- Repeat
- MRI
- TFT’s
Secondary - cont

- Increased FSH
- Repeat
- AMH / TVS for follicular count?
- POF
- Karyotype
Secondary - cont

- Previous uterine instrumentation, Asherman’s

- High androgens (rapid onset of virilisation and possibly glucocorticoid excess)
Second-line investigations

- Timing of referral???

- Karyotyping and FMR-1 premutation analysis

- Screen for auto-immune disease (diagnostic, but also other at-risk conditions)

- AMH to assess ovarian reserve

- DEXA scan. POF= 50% chance of osteopenia

[Oxford Clinic logo]
Treatment

• Depends on the diagnosis

• Irrespective of the diagnosis

• 46XO, POF etc

• Many common issues related to permanent loss of “ovarian” function
Problems

• Fertility issues
• HRT
Management

• Education, counselling and support
• Treatment of oestrogen deficiency
• Fertility management
Psychological support

• “Menopausal” “Infertile”
• Counsellors
• Psychologists
• Geneticist
• Endocrinologist
HRT

• Young women with POF have an increased risk of osteoporosis, CHD. . . .
• Exogenous oestrogen helps
• Unless contraindicated, use until 50 and then review
What to use?

• WHI data does not apply to pre-menopausal women
• There is no clear data to guide decision making
• Should be individualised according to choice and risk factors
Progesterone

• Needed if uterus still present
• Can be oral or uterine
• Sequential or continuous
Oestrogen

- May need higher doses (2mg/100mcg)
Testosterone

- Loss of ovarian function can reduce androgens by 50%, even with normal adrenal function.
- Profound changes in general and sexual wellbeing
General measures

- Exercise
- Vitamin D
- Calcium
- Smoking / alcohol
Conclusion

• Causes of primary and secondary amenorrhoea can overlap
• Think “from the top – down”
• Common things are common!
Conclusion II

- Whilst possibly confusing, the diagnosis is probably the easy part
- Hormonal replacement
- Counselling+++
ENDINGS
Not everything can end well.