

Primary & Secondary amenorrhoea

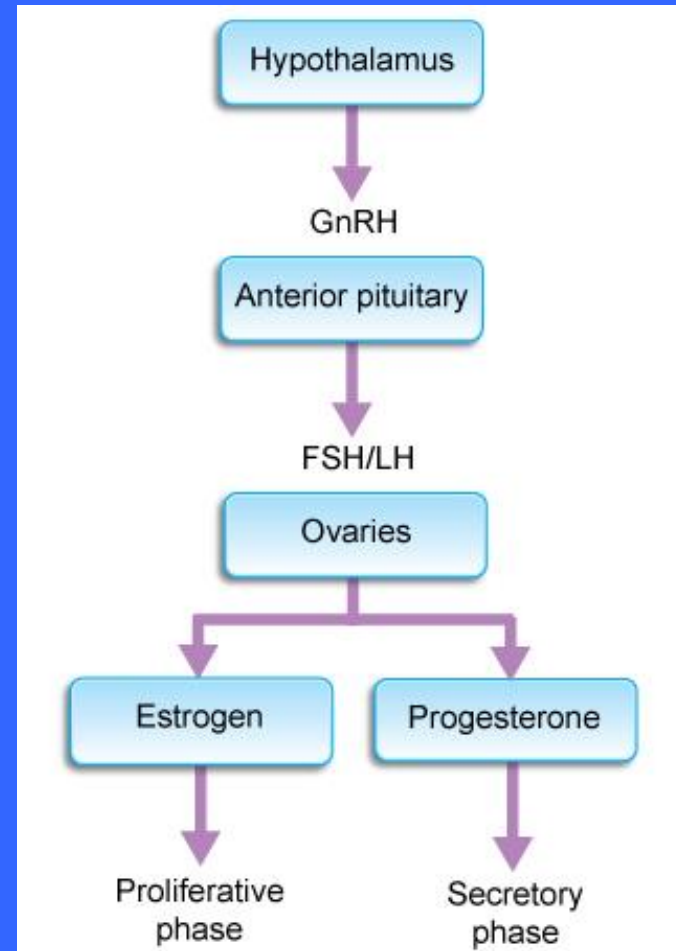
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Delayed puberty and early menopause?

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

Aetiology	
Constitutional delay	53%
Delayed, but spontaneous	19%
Hypogonadatrophic hypogonadism	12%
Hypergonadatrophic hypogonadism	13%
Unclassified	3%

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

Cause	%
Chromosomal (gonadal dysgenesis)	50
Hypothalamic hypogonadism	20
Absence of the uterus	15
Transverse septum / imperforate hymen	5
Pituitary disease	5
Other	5

Secondary amenorrhoea

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

Secondary amenorrhoea

Cause	%
Ovarian	40
Hypothalamic	35
Pituitary	19
Uterine	5
Other	1

Amenorrhoea

Cause	Primary (%)	Secondary (%)
Hypothalamic	20	35
Pituitary	5	19
Ovarian	50 (dysgenesis	40
Anatomical	20 (congenital)	5
Other	5	1

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

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

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 hirsutism 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

Idiopathic	88%
X-chromosomal	7%
Iatrogenic (chemo/DXT/surgery)	2.5%
Autoimmune	1%

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%

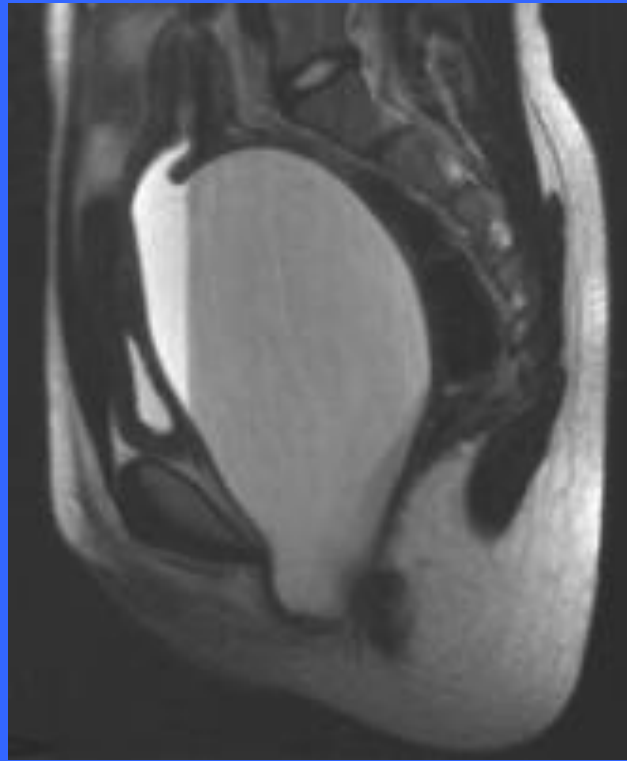
Autoimmune

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

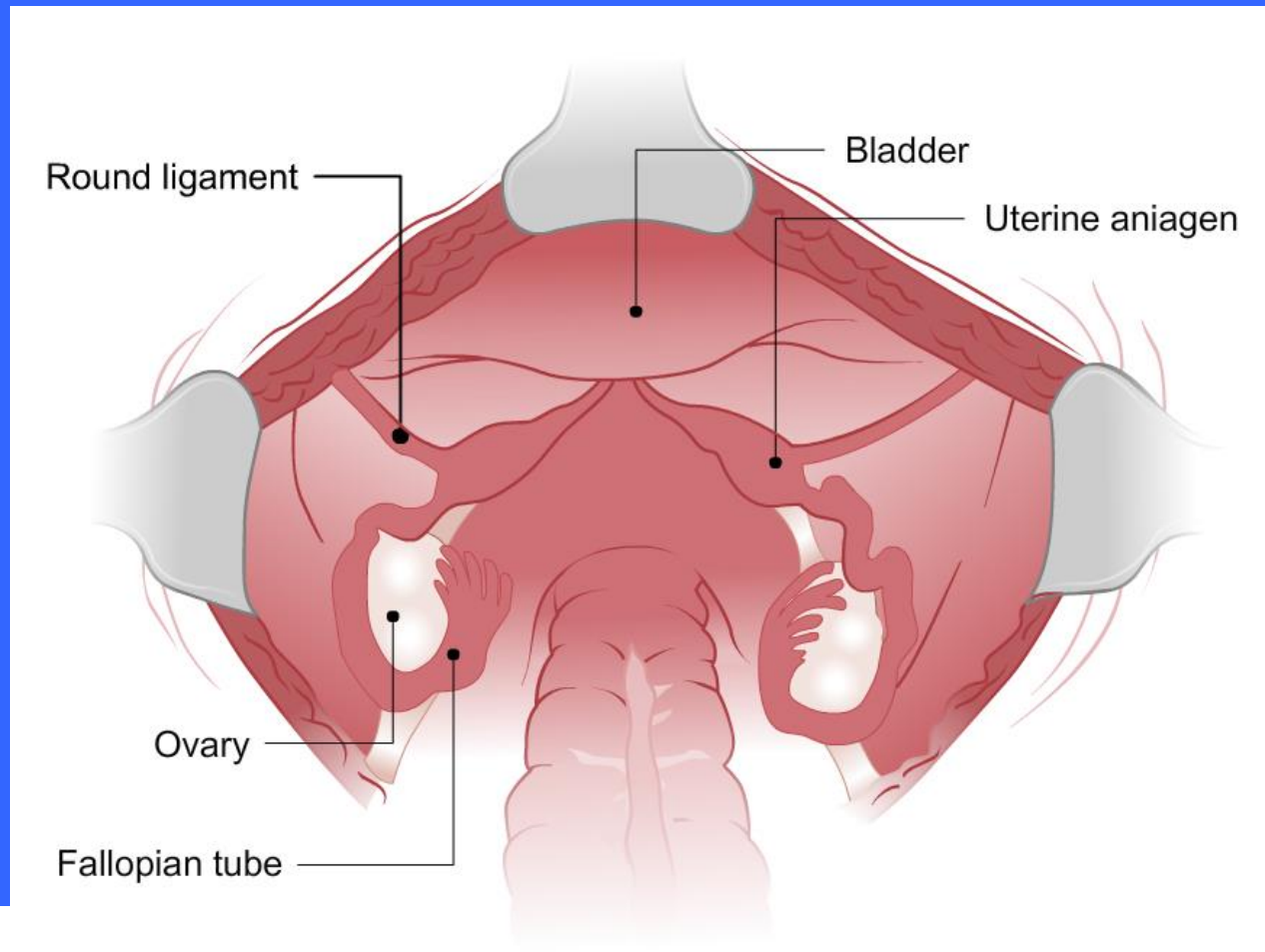
Anatomical causes

- Congenital causes = primary
- Acquired = secondary

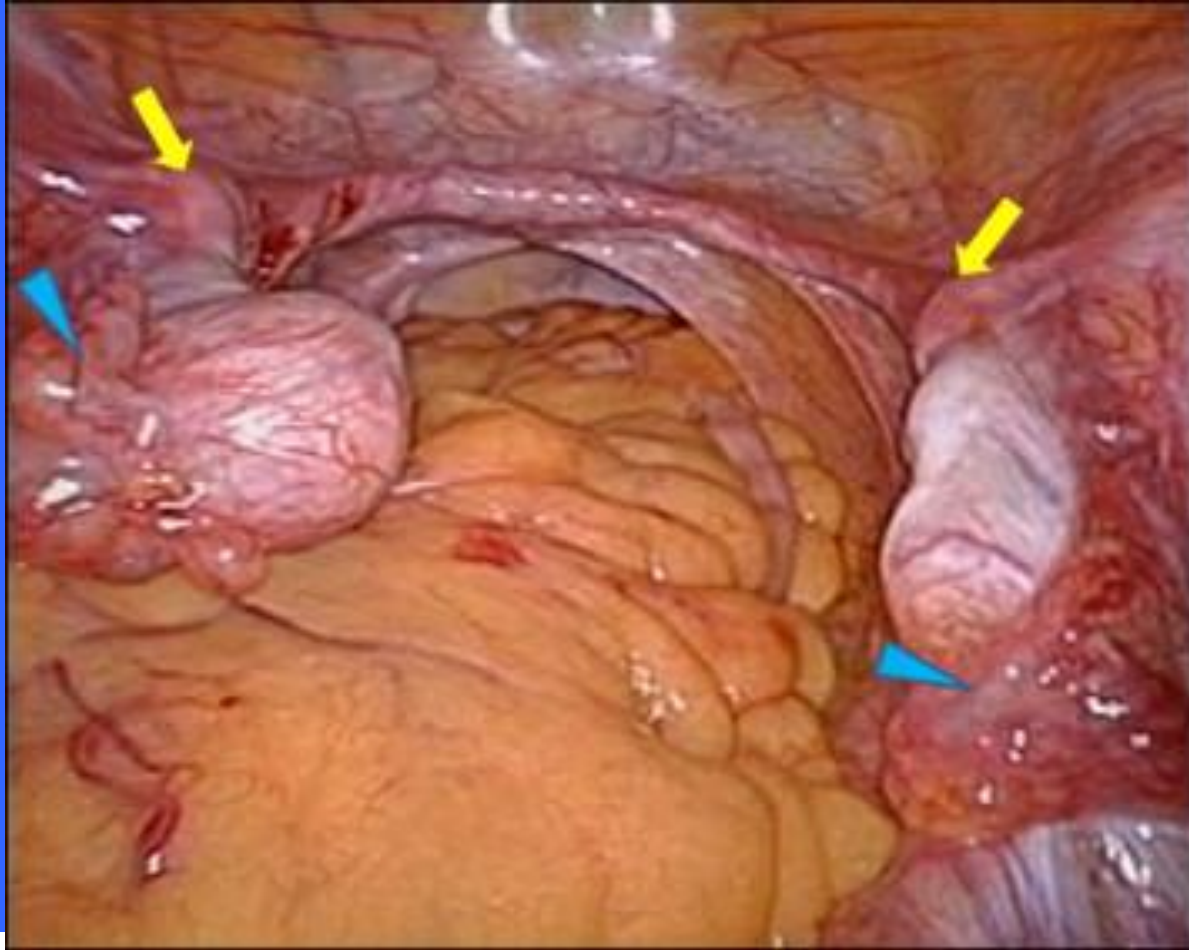
Imperforate hymen



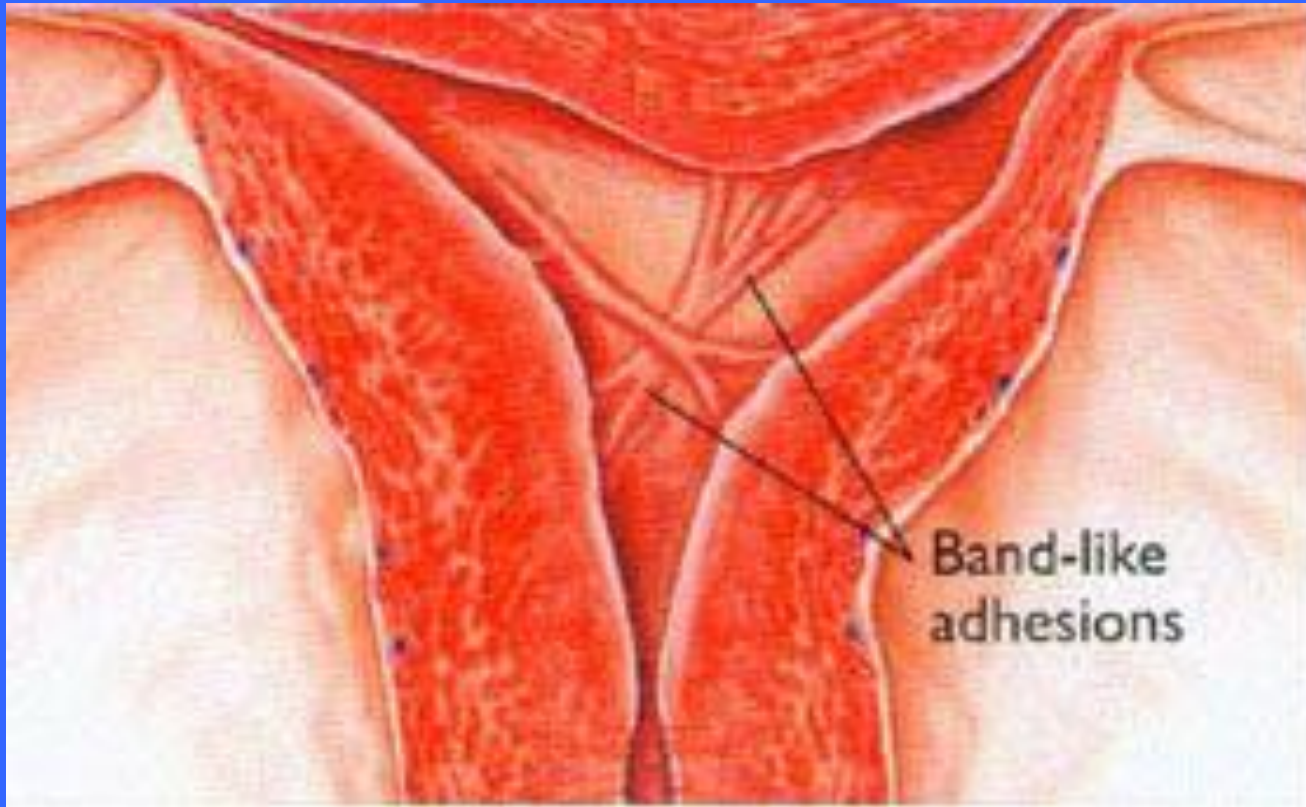
MRKH



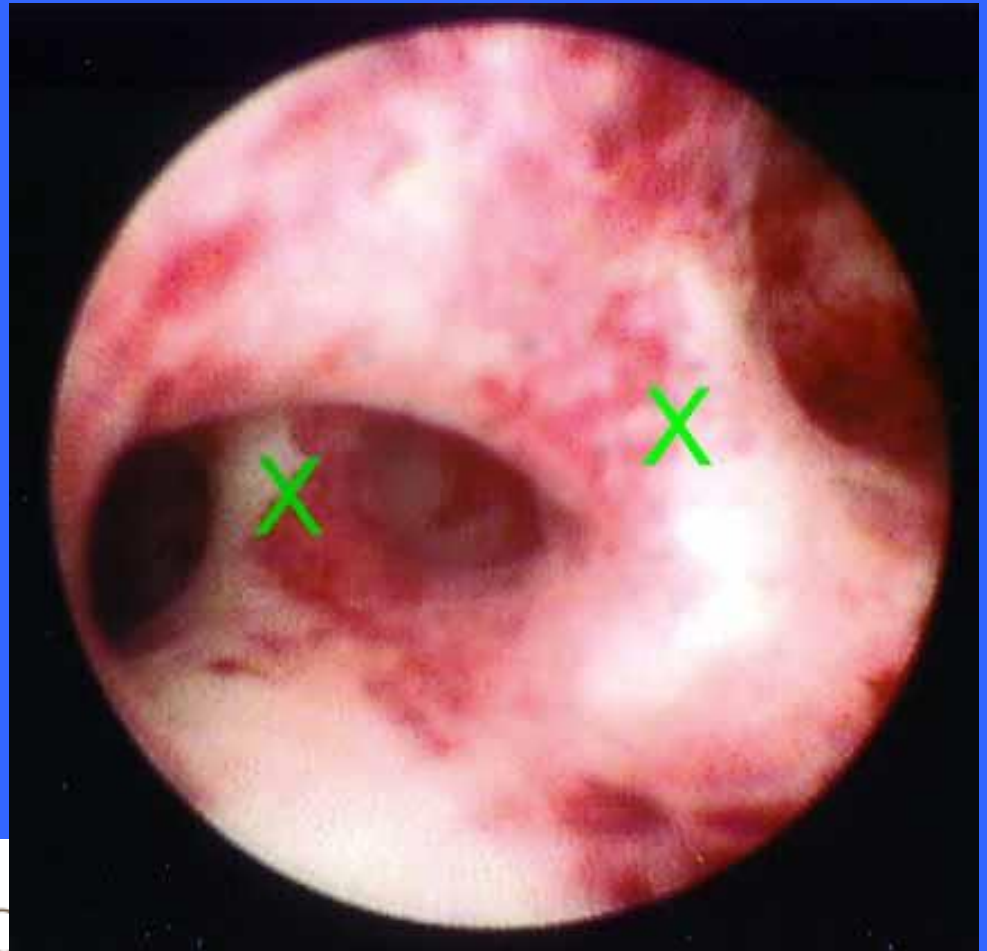
MRKH



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

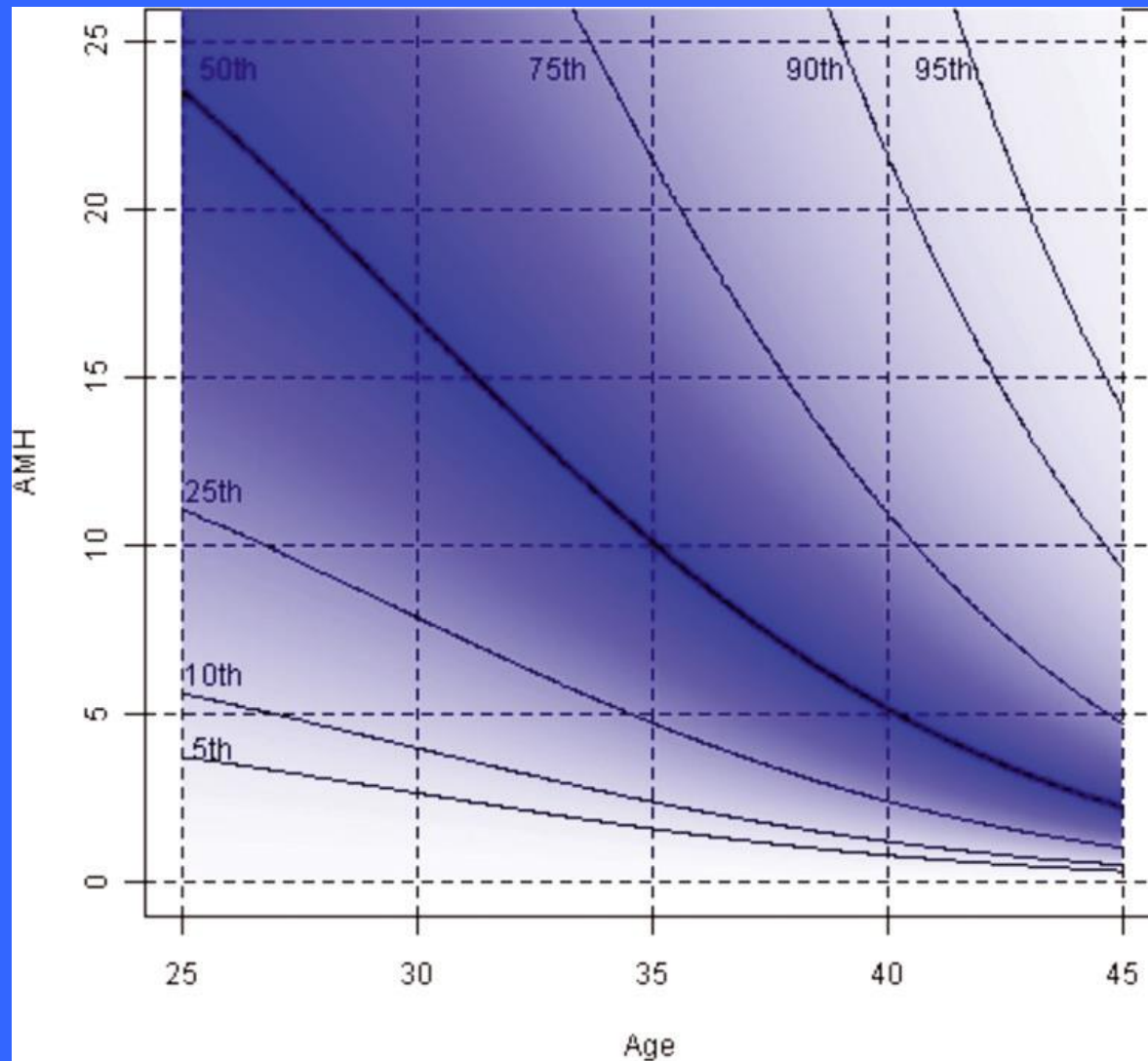
- Increased FSH
- Repeat
- AMH / TVS for follicular count?
- POF
- Karyotype

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



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.