NHS
Health Education West Midlands

Amenorrhoea

A Paediatric & Adolescent Gynaecology Approach

Glenn Davies

ST6 University Hospital of North Midlands

Principles of Obstetrics & Gynaecology ST1/ST2 Regional Teaching

Tuesday 14th February 2023

West Midlands Deanery

NHS
Health Education West Midlands

Contents

- Physiology of Menstrual Cycle
- Hypothalamic-Pituitary-Ovarian (HPO) Axis
- Puberty
- Case Studies

NHS
Health Education West Midlands

Physiology of Menstrual Cycle

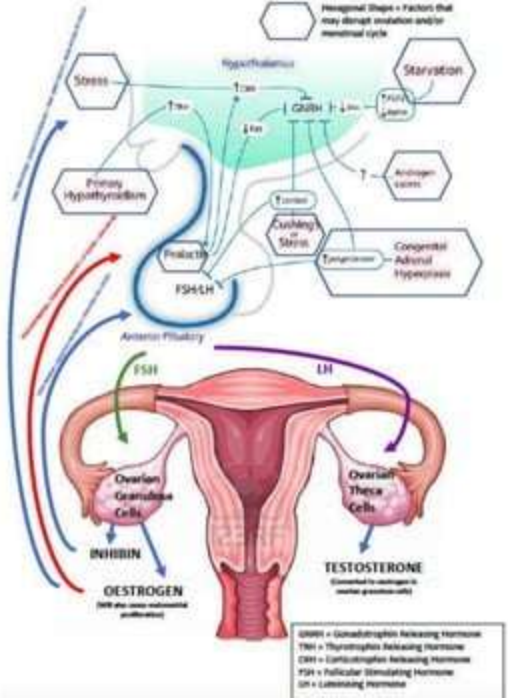
- Follicular phase – oestrogen dependent
  - Endometrial proliferation
- Follicular phase – Oestrogen surge, LH surge
  - Ovulation
  - If no LH surge, no ovulation, continue to produce oestrogen and further endometrial proliferation
- Luteal phase – progesterone dependent
  - Progesterone ONLY produced if ovulation occurred
  - This is due to corpus luteum producing progesterone
  - No ovulation? No progesterone – no endometrial stabilization, continued endometrial proliferation = irregular heavy menstrual bleeding

NHS
Health Education West Midlands

HPG Axis (HPG)

- HPO – to ovulate
  - Hypothalamus, pituitary, ovaries (+/- normal adrenals/androgens)
- But to menstruate, also need
  - Uterus (present)
  - Vagina (no outflow obstructions)

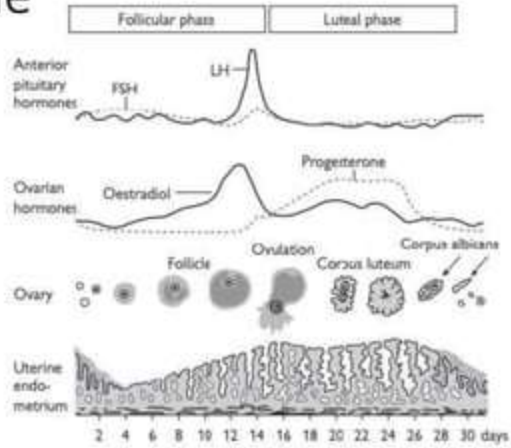
- So actually:
  - HPO(A)UV



Physiology of Menstrual Cycle

- To menstruate, you need

1. Hypothalamus
2. Pituitary Gland (Anterior)
3. Ovaries (+ normal androgens/adrenals)
4. Uterus
5. Vagina



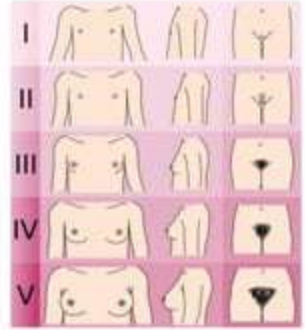
- Problems anywhere can result in primary or secondary amenorrhoea

NHS
Health Education West Midlands

Puberty

- Generally occurs
1. Thelarche
2. Adrenarche
3. Growth Spurt
4. Menarche

GIRLS	AVERAGE AGE	AGE WINDOW
1. Breast start developing	10	8-13
2. Height shoots up	10	8-13
3. Pubic hair appears	10.5	8-14
4. Height growth peaks	11.7	10-13.5
5. First period	12.5	10.5-15.5
6. Breast development complete	14	10-16
7. Pubic hair growth complete	14.5	14-15
8. Reach adult size	13	10-16

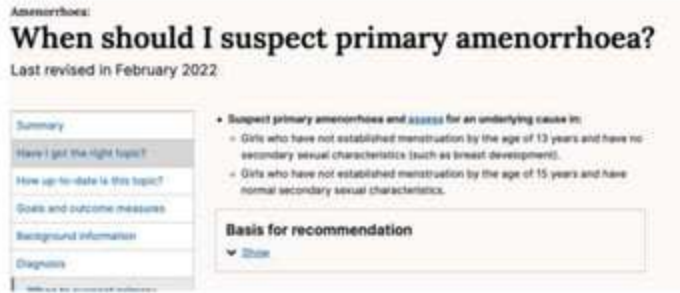


- Menarche is usually the final change to occur, with full breast changes and height changes complete after menarche
- We assess/enquire about thelarche (breast development) and adrenarche (pubic hair, axillary hair) to determine if secondary sexual characteristics are present

NHS
Health Education West Midlands

Case 1

- 16 Year Old: Amenorrhoea


Amenorrhoea:

When should I suspect primary amenorrhoea?

Last revised in February 2022

Summary
Have I got the right topic?
How up-to-date is this topic?
Goals and outcome measures
Background information
Diagnosis

- Suspect primary amenorrhoea and assess for an underlying cause in:
  - Girls who have not established menstruation by the age of 13 years and have no secondary sexual characteristics (such as breast development).
  - Girls who have not established menstruation by the age of 15 years and have normal secondary sexual characteristics.

Basis for recommendation

Show

- Primary amenorrhoea
- Signs of secondary sexual characteristics?
  - Breast development noted, wears bra
  - Axillary and pubic hair
  - 50th centile height, 90th centile weight (BMI 28)
- Neonatal history? Born at 27 weeks
- No ongoing medical issues
- Examination – no evidence of imperforate hymen

NHS
Health Education West Midlands

Case 1 - Investigations

- Bloods:
  - LH 0.1 IU/L (LOW)
  - FSH 0.4 IU/L (LOW)
  - TSH 4.61 mU/L (NAD)
  - PRL 78 mIU/L (NAD)
  - OESTRADIOL 43 pmol/L(LOW)
  - TESTOSTERONE 0.6 nmol/L (NAD)
- Imaging:
  - TAUSS: Prepubertal uterus, ovaries not clearly visualized
  - MRI Pelvis: Uterus present, small ovaries noted ?Premature ovarian insufficiency

NHS
Health Education West Midlands

Case 1 - Diagnosis

- Idiopathic Hypogondatrophic Hypogonadism
- A type of hypothalamic amenorrhoea
  - Therefore low levels of FSH, LH and oestradiol
- Management
  - COCP will provide oestrogen and menstruation (can use transdermal HRT)
  - Gonadotrophins required for fertility
- Bone X-Ray
  - Performed by endocrine team
  - Compares bone age with patient age
    - 15.7 years X-ray (17.7 years chronological age)

Hypothalamic Amenorrhoea	Signs/Symptoms/ Investigations
Constitutional Delay	Family History
Chronic Illness	Co-morbidities
Weight loss/exercise/eating disorders	BMI <19
Space occupying lesions (compression on hypothalamus/pituitary)	Headache +/- vision changes CT/MRI +/- other pituitary hormone changes
Kallmann Syndrome (rare)	Anosmia Colour blindness

NHS
Health Education West Midlands

Case 2

- 15 Year Old, Amenorrhoea

- Secondary Amenorrhoea
  - Menarche 11YO, amenorrhoea 2 years
- Secondary sexual characteristics?
  - Normal breast development
  - Normal pubic and axillary hair
  - Height 157cm, weight 67.6kg, BMI 27
- Neonatal history – term vaginal delivery
- No other medical issues
- Associated headache, no change in visual fields
- No galactorrhoea

Case 2 - Investigations

- Bloods
  - LH 0.6 (LOW)
  - FSH 0.8 (LOW)
  - TSH 1.9 (NAD)
  - PRL 15000 (HIGH)
  - Testosterone 1.6 (NAD)
- Imaging
  - MRI Pituitary: Pituitary macroadenoma (16x13x15mm) in right pituitary lobe

NHS
Health Education West Midlands

Case 2 – Prolactinoma

- A type of pituitary amenorrhoea (rare)
- High levels of PRL inhibit GnRH secretion
  - Low LH/FSH levels
  - If prolactinoma large enough, may cause compression on pituitary gland and pan hypopituitarism
- Management
  - Endocrine input
  - Dopamine agonists (cabergoline)
  - Consider surgery if resistant to medication or mass effect

Pituitary Amenorrhoea	Signs/Symptoms/ Investigations
Empty sellar syndrome	History of pituitary surgery/radiotherapy
Sheehan syndrome	Secondary to PPH (infarction)
Trauma/surgery/ radiotherapy	History
Infection	TB (rare)
Idiopathic/ congenital	Likely pan hypopituitarism

NHS
Health Education West Midlands

Case 3

- 16 Year Old – Amenorrhoea

- Primary amenorrhoea
- Signs of secondary sexual characteristics?
  - No pubic or axillary hair
  - Minimal breast development
  - 91st centile height, 99th centile weight
- Neonatal history? Term vaginal delivery
- No ongoing medical issues
- No evidence of imperforate hymen

NHS
Health Education West Midlands

Case 3 - Investigations

- Bloods
  - LH 28.3 (HIGH)
  - FSH 88.1 (HIGH)
  - Oestradiol 127 (LOW/NORMAL)
  - Testosterone 0.5 (NAD)
  - TSH 2.59 (NAD)
  - Prolactin 178 (NAD)
- Imaging
  - TAUSS – Small pretubular uterus present, difficult to visualize ovaries
  - MRI Pelvis – Normal uterus, small bilateral ovaries ?ovarian dygenesis

NHS
Health Education West Midlands

Case 3 - Diagnosis

- Premature Ovarian Insufficiency
  - Hypergonadotrophic Hypogonadism
- A type of ovarian amenorrhoea
- Management
  - Karyotype
    - To rule out 45XO, 46XY
  - Puberty induction
    - Usually transdermal oestrogen patches (see British Society Paediatric Endocrinology for regime/guideline)
  - Menstruation with COCP/HRT
  - Psychological support (Daisy Network)
  - May have autoimmune associations (DM, hypothyroid, Addison's)
- Bone X-ray
  - Bone age = 13YO (Chronological age 15Y 9M)

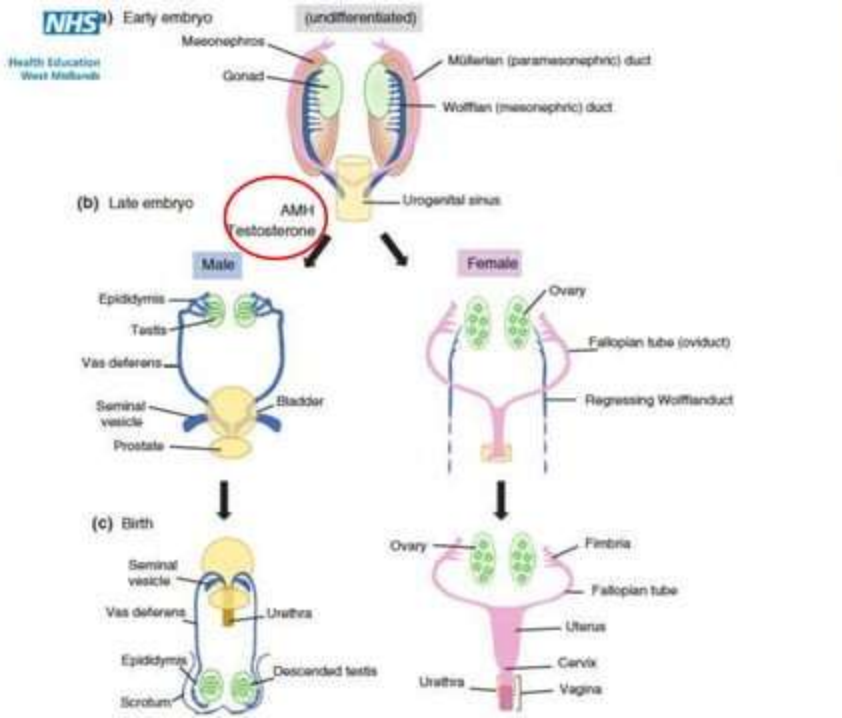
Ovarian Amenorrhoea	Signs/Symptoms/Investigations
POI (46XX)	Raised FSH Minimal breast development
45XO (Turners)	Raised FSH Minimal breast development
46XY (Swyer Syndrome) ***1. Mutation in SRY gene = no testosterone OR AMH*** ***2. No AMH = Mullerian ducts develop (uterus/tubes/cervix/upper vagina)*** ***3. No testosterone = urogenital sinus develops female external genitalia (lower vagina, introitus, labia)*** ***4. Rudimental gonadal tissue (undifferentiated gonads)***	Raised FSH Minimal breast development May have scanty pubic hair (adrenal testosterone)

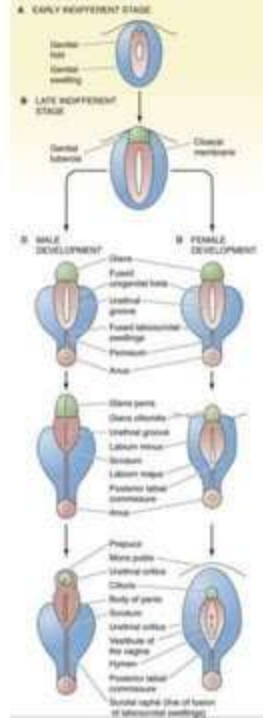
REPORT

KARYOTYPE: 46,XX

Apparently normal female karyotype

daisy network


NHS
Health Education West Midlands
(a) Early embryo
(undifferentiated)
Mesonephros
Gonad
Müllerian (paramesonephric) duct
Wolffian (mesonephric) duct
Urogenital sinus
(b) Late embryo
AMH
Testosterone
Male
Female
Epididymis
Testis
Vas deferens
Seminal vesicle
Prostate
Bladder
Ovary
Fallopian tube (oviduct)
Regressing Wolffianduct
(c) Birth
Seminal vesicle
Vas deferens
Epididymis
Scrotum
Urethra
Descended testis
Ovary
Fimbria
Fallopian tube
Uterus
Cervix
Urethra
Vagina


A EARLY INDIFFERENT STAGE
B LATE INDIFFERENT STAGE
C MALE DEVELOPMENT
D FEMALE DEVELOPMENT

NHS
Health Education West Midlands

Case 4

- 17 Year Old – Amenorrhoea

- Secondary
- Irregular heavy menstrual bleeding every 3/12 for 3Y
- Menarche 12YO
- Secondary sexual characteristics
  - Normal breast development
  - Normal axillary and pubic hair
  - Height 155cm, weight 84kg, BMI 35
- Additional symptoms
  - Hyperandrogenaemia – hirsutism and acne
- Neonatal history: Term vaginal delivery

NHS
Health Education West Midlands

Case 4 - Investigations

- Bloods
  - LH 12.7 (HIGH)
  - FSH 7.4 (NAD)
  - TSH 1.29 (NAD)
  - Prolactin 160 (NAD)
  - Testosterone 2.7 (NAD)
- Imaging
  - TAUSS – normal uterus, normal ovaries
  - ***Beware of PCO findings on USS in paediatric/adolescent gynaecology setting***
    - ***Common finding in the first 8 years post menarche (base diagnosis on symptoms and investigations)***

NHS
Health Education West Midlands

Case 4 – Diagnosis

- Polycystic Ovarian Syndrome
- A type of ovarian/androgenic amenorrhoea
  - Raised androgen levels affect LH surge = anovulation
  - Very high cortisol and/or androgen levels can also affect GnRH secretion
- Rotterdam criteria, 2 out of:
  - Oligomenorrhoea/amenorrhoea
  - Clinical and/or biochemical hyperandrogenaemia
  - Ultrasound suggestive of PCO
- Management
  - Weight loss
  - Progesterone to induce withdrawal bleed (or COCP)
  - COCP to regulate oestrogen and induce withdrawal bleed
  - Metformin – some evidence at reducing hyperandrogen symptoms +/- fertility
  - Fertility? Ovulation induction with clomiphene +/- metformin +/- gonadotrophins +/- ovarian drilling +/- IVF

Androgenic Amenorrhoea	Signs/Symptoms/Investigations
PCOS	Raised LH, hirsutism Borderline raised testosterone
Congenital Adrenal Hyperplasia (Non classical 21 hydroxylase deficiency)	May be associated with **hypertension** Raised testosterone Raised 17 hydroxyprogesterone levels
Androgen secreting tumours (adrenal or ovarian)	Frank virilization and rapid onset Raised testosterone Raised DHEAs indicates adrenal source
Rarer causes	1. Cushing's Syndrome (ACTH dependent e.g. pituitary adenoma [Cushing's Disease] or ectopic ACTH producing tumour [bronchial]) 2. Cushing's Syndrome (ACTH independent e.g. exogenous steroid use, pseuo-Cushings, adrenal/ovarian tumours)

NHS
Health Education West Midlands

Case 5

- 16 Year Old, Amenorrhoea

- Primary amenorrhoea
- Presence of secondary sexual characteristics?
  - Normal breast development
  - Normal pubic and axillary hair
  - Height 167cm, weight 49kg, BMI 17.6
- Neonatal history? Term vaginal delivery
- No other medical problems
- Perineal inspection – no evidence of imperforate hymen

NHS
Health Education West Midlands

Case 5 - Investigations

- Bloods
  - LH 4.5 (NAD)
  - FSH 6 (NAD)
  - Oestradiol 305 (NAD)
  - TSH 1.7 (NAD)
  - Testosterone 0.8 (NAD)
  - PRL 88 (NAD)
- Imaging
  - TAUSS – Uterine agenesis, ?small ovaries noted bilaterally
  - MRI Pelvis – Absence of uterus noted, ovaries normal bilaterally

NHS
Health Education West Midlands

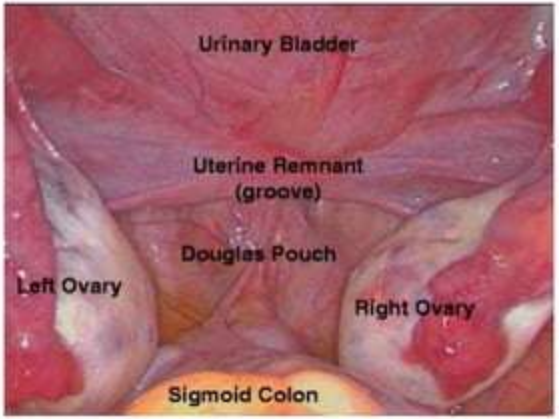
Case 5 – Diagnosis

- Mullerian agenesis
  - AKA Mayer-Rokitansky-Kuster-Hauser syndrome
- A type of uterine amenorrhoea
- Absent uterus +/- hypoplasia of vagina (upper 2/3 = Mullerian duct)
- Management
  - Psychological support
  - Renal USS/MRI (associated anomalies)
  - May need creation of neovagina to allow/improve sexual function
  - Fertility? Ovaries still functioning, would need surrogate

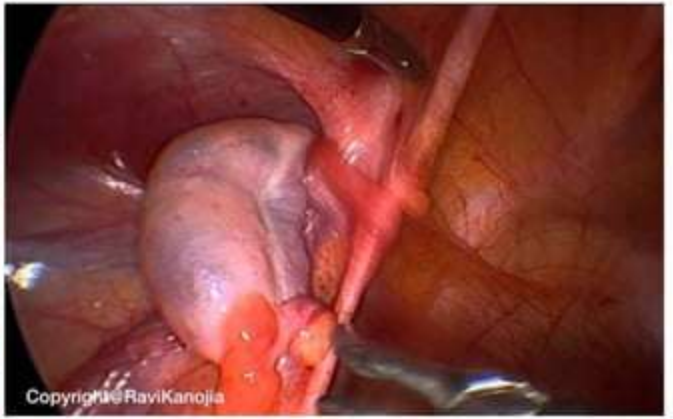
Uterine Amenorrhoea	Signs/Symptoms/Investigations
Mullerian agenesis	Normal hormonal profile Normal secondary sexual characteristics Absent uterus on USS/MRI
Complete Androgen Insensitivity Syndrome ***(body will not respond to testosterone, but will respond to AMH)*** ***1. AMH = no uterus develops*** ***2. Lack of testosterone = urogenital sinus develops into female external genital*** ***3. Testosterone aromatized = some breast development***	Primary amenorrhoea Breast development (peripheral aromatisation) **Lack of axillary or pubic hair** Normal LH/FSH High testosterone Karyotype (46 XY)

NHS
Health Education West Midlands

Mullerian Agenesis = Normal Ovaries



Androgen Insensitivity Syndrome = Undifferentiated Gonads



Case 6

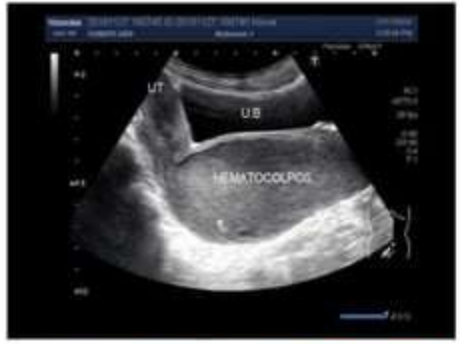
- 14 Year Old, Amenorrhoea

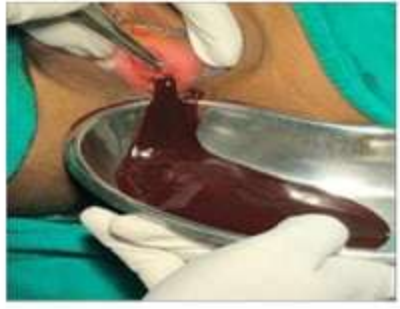
- Primary amenorrhoea
- Cyclical pelvic and perineal pain
- Presence of secondary sexual characteristics
- Neonatal history – vaginal term delivery
- No other medical issues
- Perineal inspection – blue bulging mass at introitus

NHS
Health Education West Midlands

Case 6 – Imperforate Hymen

- Investigations not necessarily needed – can be clinical diagnosis
- Imaging
  - Ultrasound may show haematocolpos +/- haematometra
- Management
  - Usually seen as an emergency admission
  - Incision and drainage under general anaesthetic
- A type of outflow tract (vaginal) amenorrhoea
  - ***Transverse vaginal septum (low/mid/high)***
    - ***More complex, laparoscopic excision***
  - Other types include Ashermann's (uterine adhesions), cervical stenosis or radiotherapy to pelvis (fibrosis/adhesions)





NHS
Health Education West Midlands

Conclusions…

- Stepwise approach
- Always consider
  - **Height/weight/BMI**
  - **BP (as you may consider using the COCP)**
  - **Asking about secondary sexual characteristics +/- examination**
  - Hormonal profile (FSH, LH, PRL, TSH, Testosterone, Oestradiol)
  - Imaging (TAUSS [virgo intact] to visualize uterus +/- large masses, MRI to assess ovaries if limited TAUSS views)
  - Multidisciplinary approach – paediatric team, endocrinology team, radiology input
  - Don't forget other causes! (pregnancy, hormonal contraception, medications)

Hypothalamic	Pituitary	Ovarian	Androgenic	Uterine	Vaginal/ Outflow tract
Low LH/FSH	**Low LH/FSH**	**High LH/FSH**	**High or normal LH/Normal FSH**	**Normal LH/FSH**	**Normal LH/FSH**
Low Oestradiol	**Low Oestradiol**	**Low/normal oestradiol**	**Normal/low oestradiol**	**Normal oestradiol**	**Normal oestradiol**
Headache/ Vision changes	**Raised PRL +/- abnormal TSH**	Minimal breast development	**Normal/high testosterone**	May have high testosterone	Normal oestradiol
BMI <19	Galactorrhoea +/- vision changes	USS/MRI = uterus present, small ovaries	**BP check (CAH)**	**USS = absent uterus**	Typically amenorrhoea and pelvic pain
Stress	Sheehan (rare)	Karyotype!	Cushing Syndrome	Mullerian agenesis = pubic hair	Haematocolpos = clinical diagnosis
Chronic illness	Pituitary surgery/trauma/ radiotherapy		**Check testosterone! (+/- 17OHP, +/- DHEAS)**	If CAIS = no pubic or axillary hair	Ashermanns/ Cervical stenosis/ adhesions = hysteroscopy