Paediatric and Adolescent Gynaecology for MRCOG part 2

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Disclosures

Name	Disclosures
Pedro Melo	No conflicts of interest to declare.

Affiliations

UNIVERSITY OF OXFORD

Oxford University Hospitals NHS Trust

Cochrane Gynaecology and Fertility

NIHR | National Institute for Health Research

The Fertility Partnership

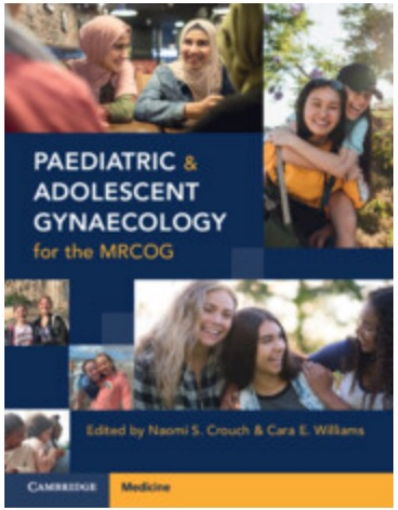
MRCOG Syllabus

Detailed knowledge requirements:

To understand the epidemiology, aetiology, biological behaviour, pathophysiology, clinical characteristics, prognostic features and management of:

- Paediatric gynaecology;
- Congenital abnormalities of the genital tract (ambiguous genitalia, imperforate hymen, vaginal septae, uterine anomalies, Mullerian duct development, gonadal dysgenesis);
- Puberty (physiology and chronology, precocious puberty, delayed puberty, excessive menstrual loss).

Sources



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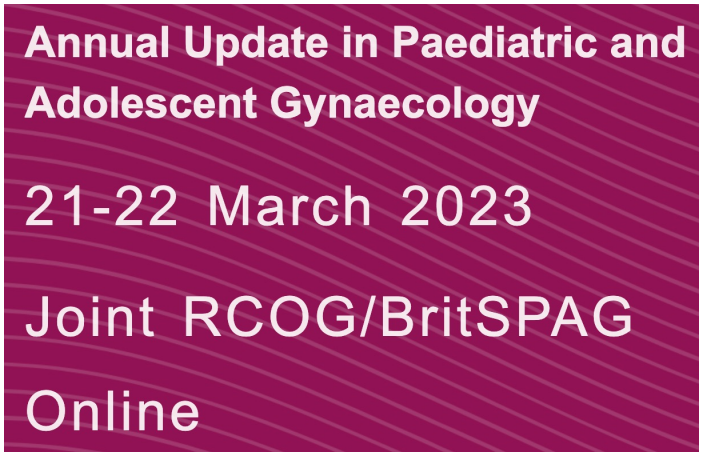


March 2023

Overview

- **Embryology**
- General considerations in PAG
- Puberty
- Common prepubertal problems in PAG
- Menstrual dysfunction
- Mullerian duct anomalies
- Primary amenorrhoea and delayed puberty
- Differences in sex development
- Legal considerations in PAG

Embryology

Internal and external genitalia: begin in the same embryological point

Week 9 of gestation: divergence (male vs female)

Internal female genitalia: development closely linked to that of the urinary tract

Embryology

Female-biasing factors: two X chromosomes, ovarian hormones

Male-biasing factors: single X chromosome; Y chromosome; testicular hormones

Embryology – male

Y chromosome:

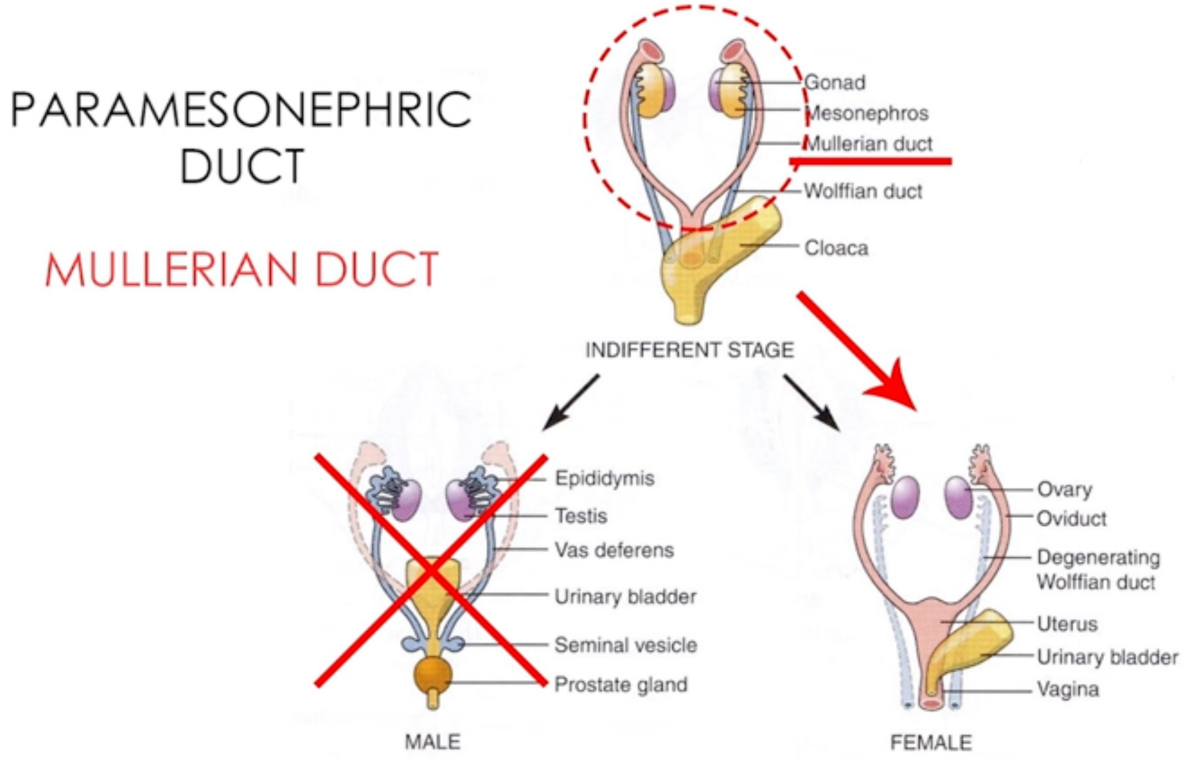
- SRY (sex-determining region on Y chromosome):
  - Transcription factor derived from the short arm of the Y chromosome (Yp11)
  - SRY initiates a cascade of downstream genes that determine the male development
  - Results in the development of testes – upregulation of steroidogenesis factor 1 (SF1) → SOX9 gene activation → differentiation of Sertoli and Leydig cells
  - Sertoli cells produce anti-Mullerian hormone → regression of the Mullerian ducts
  - Inhibits ovarian differentiation

Embryology – female

X chromosomes:

- Absent SRY
- Specific genes on X chromosome – initiate ovarian development and block testicular differentiation
  - Main genes: DAX1 and WNT4

Female reproductive tract embryology



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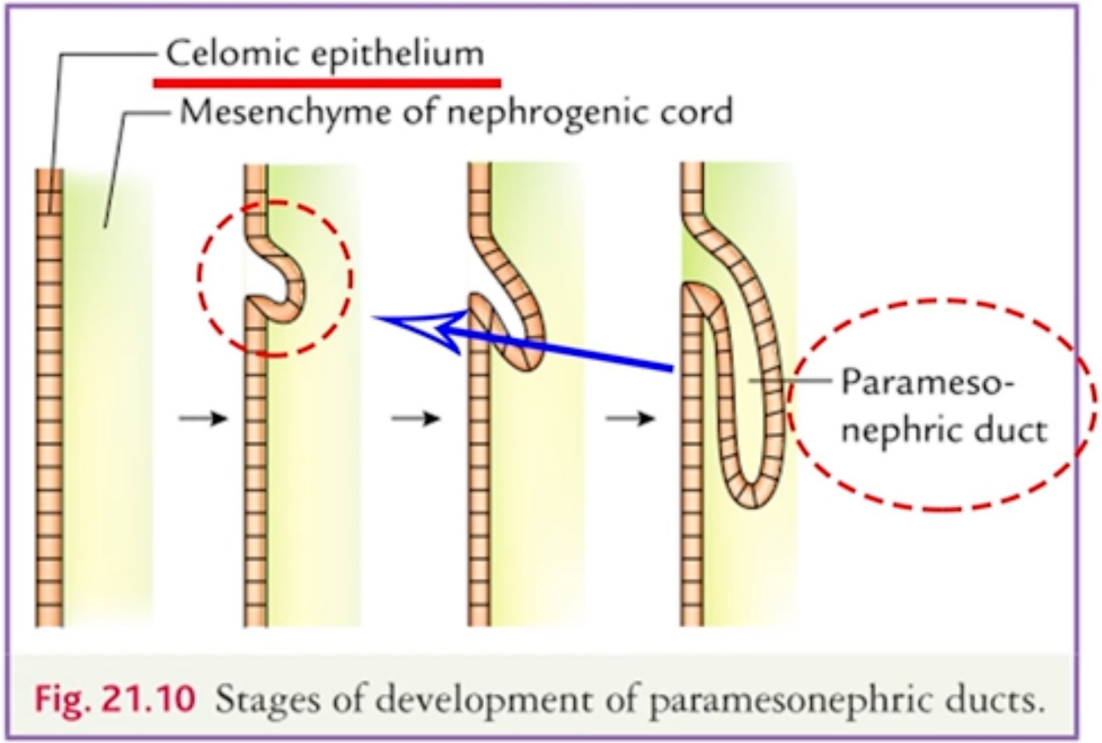
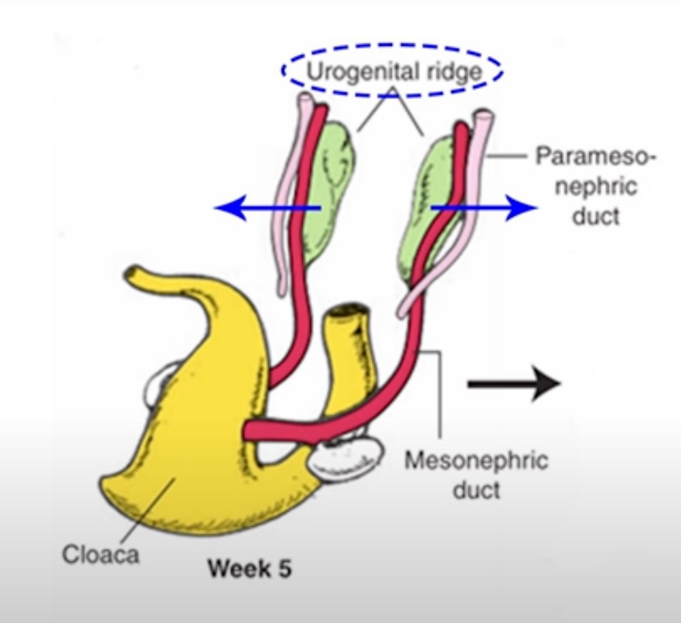


Fig. 21.10 Stages of development of paramesonephric ducts.

Female reproductive tract embryology



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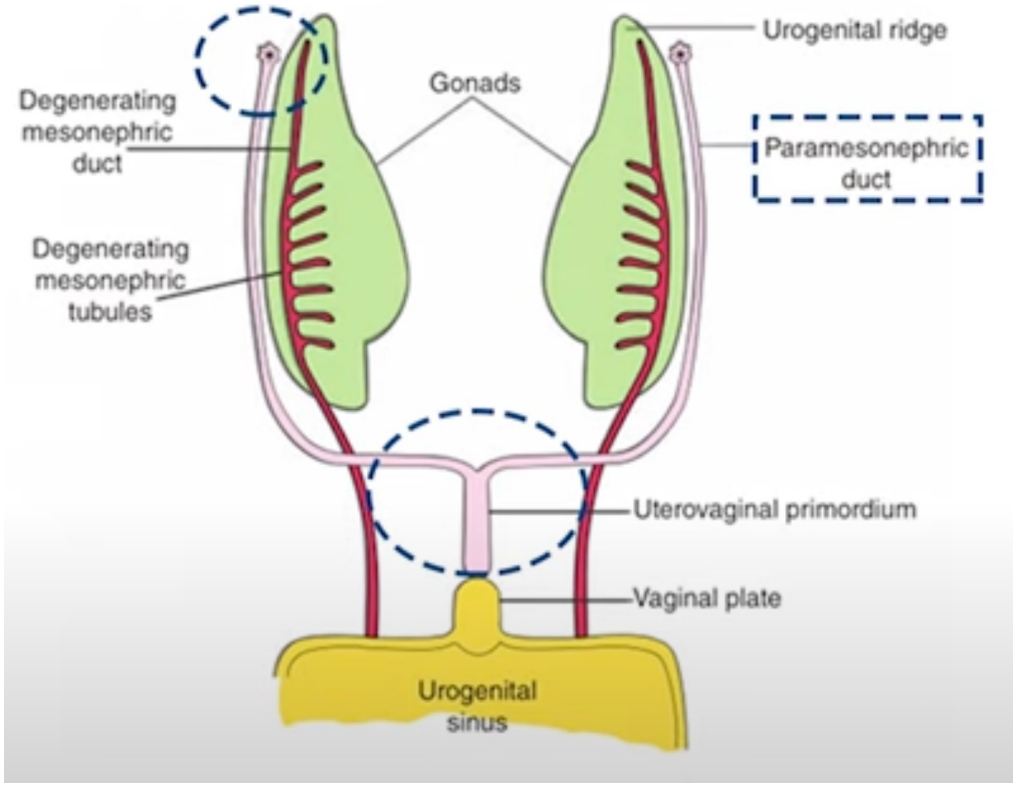

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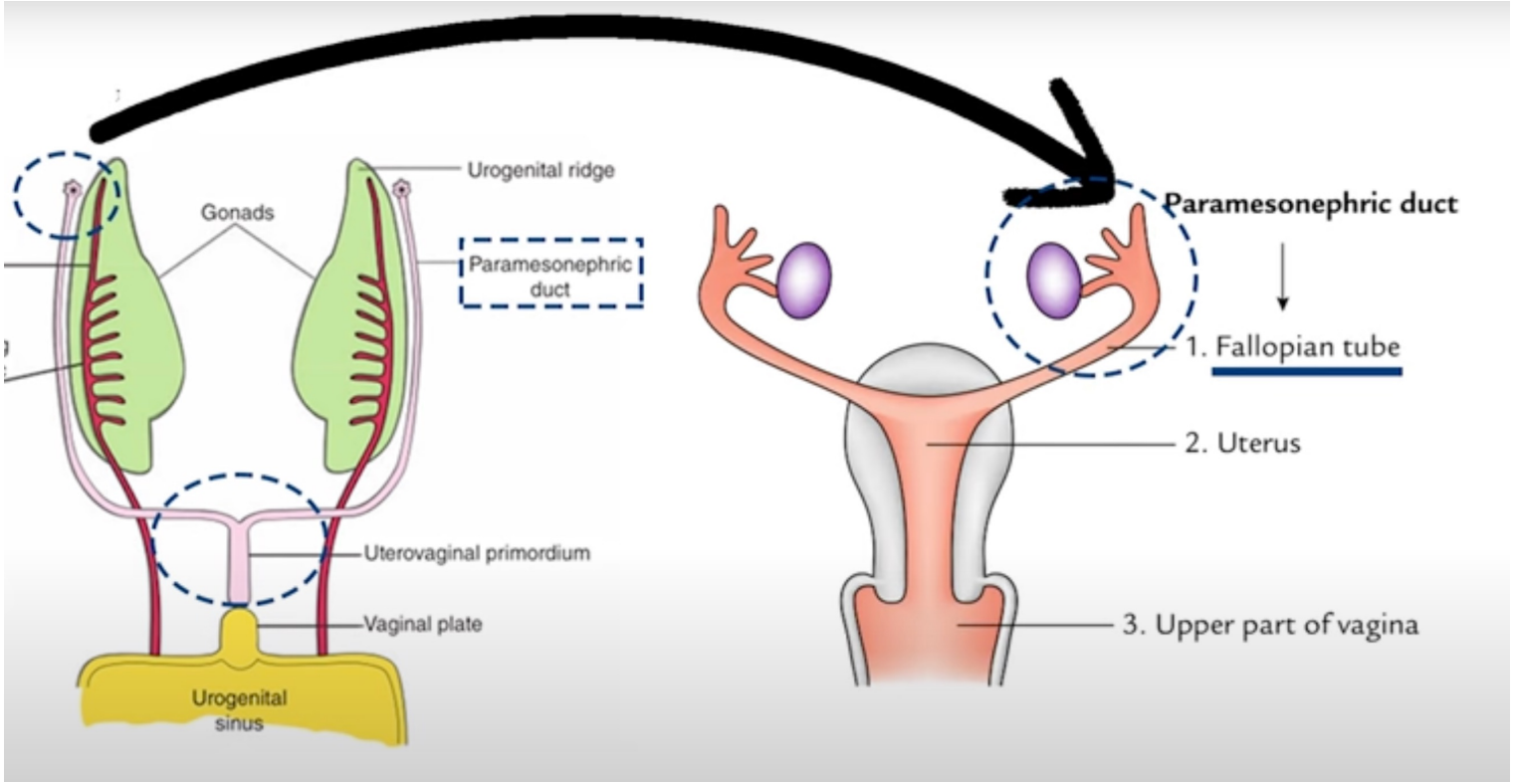

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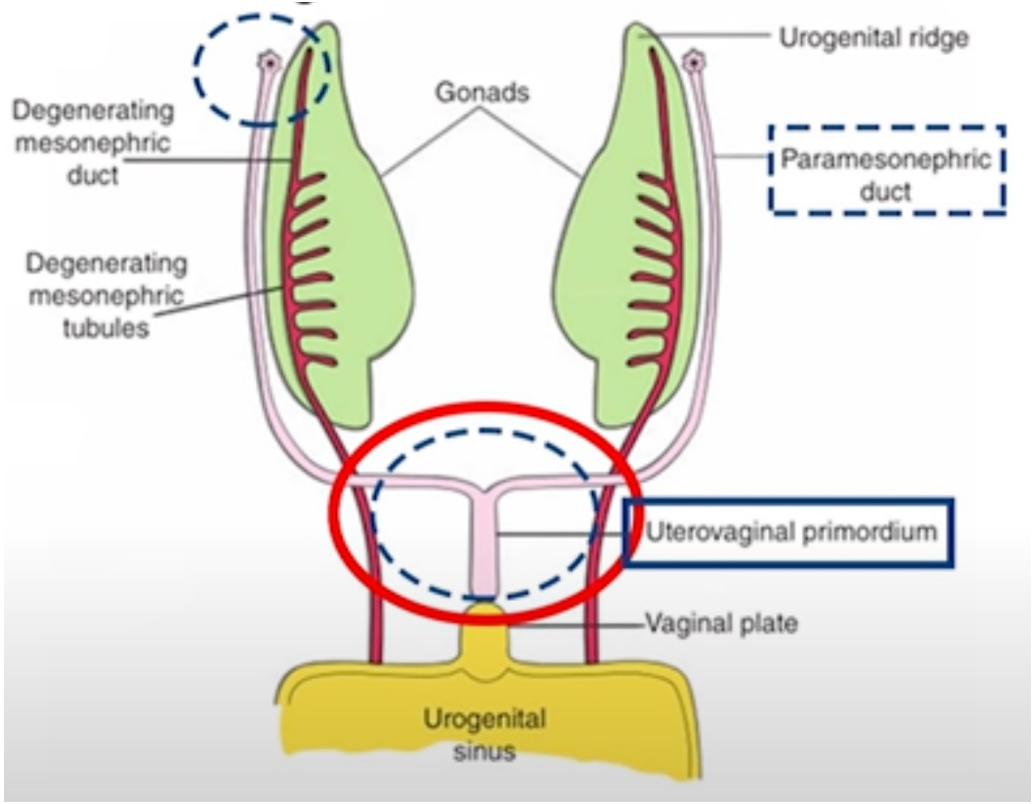

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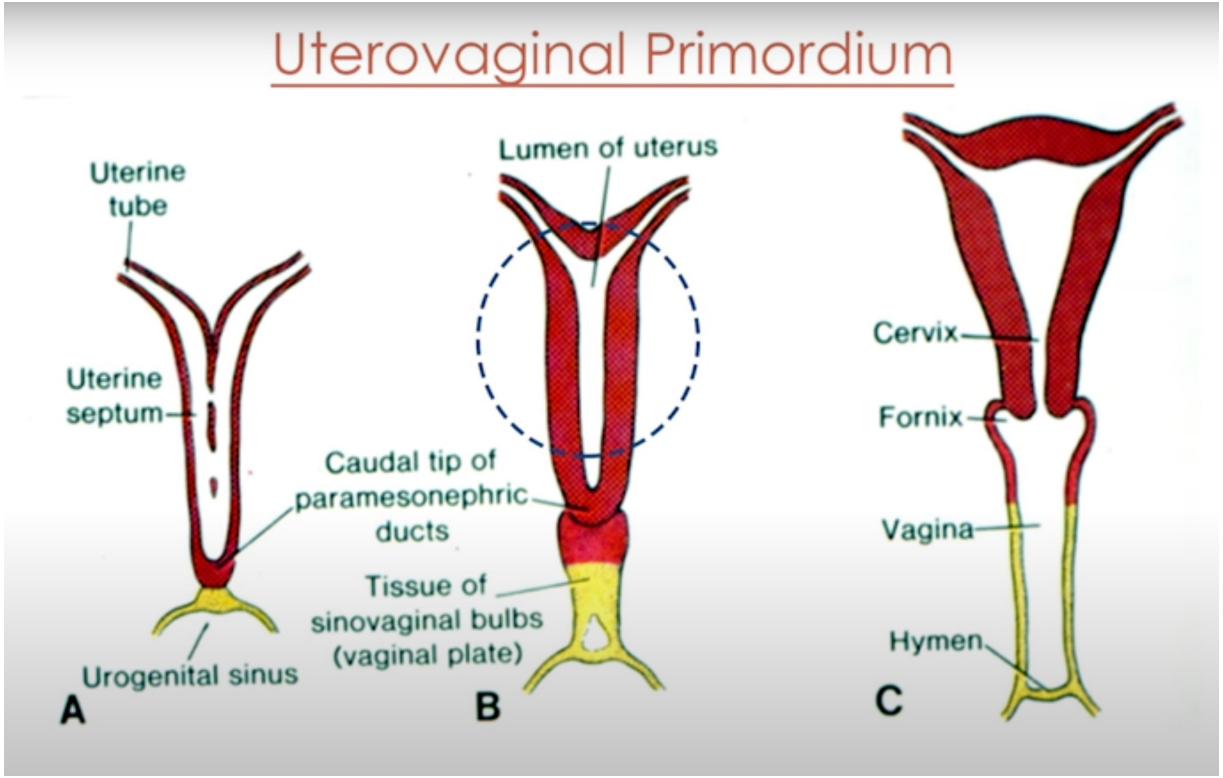

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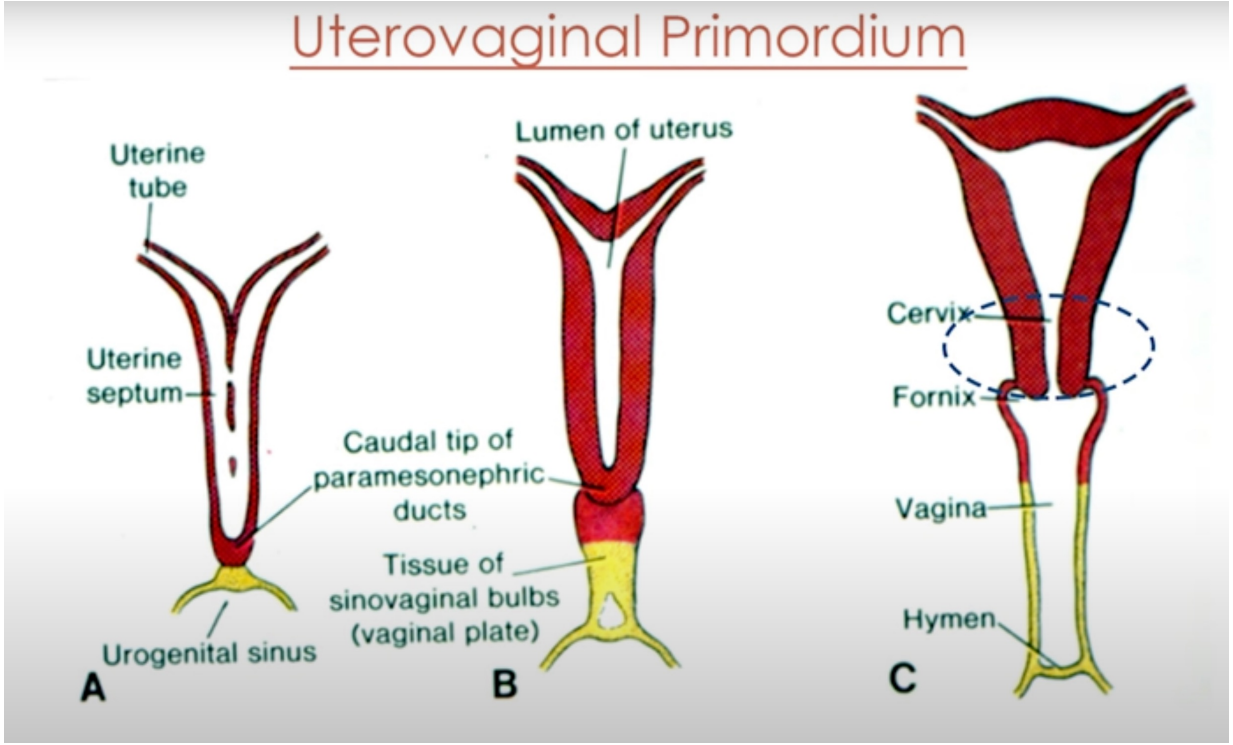

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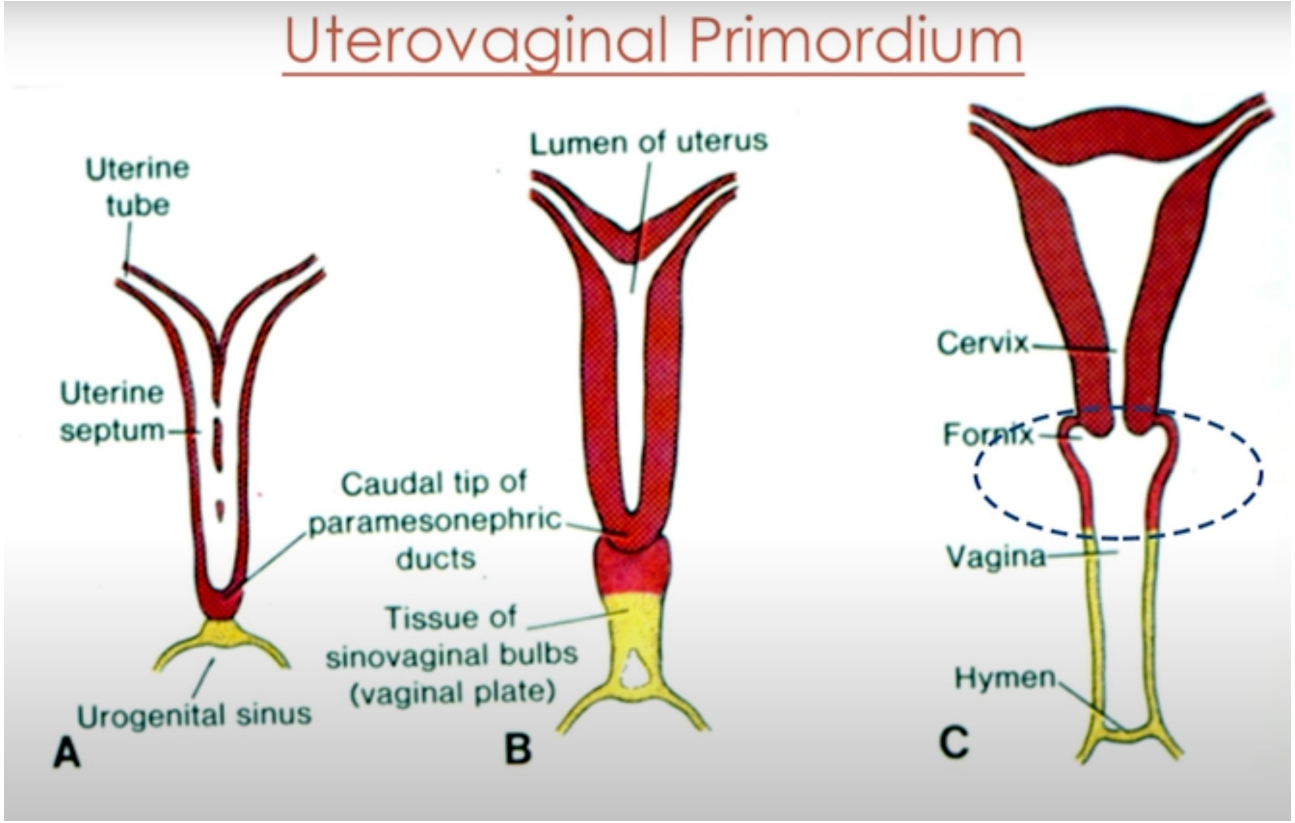

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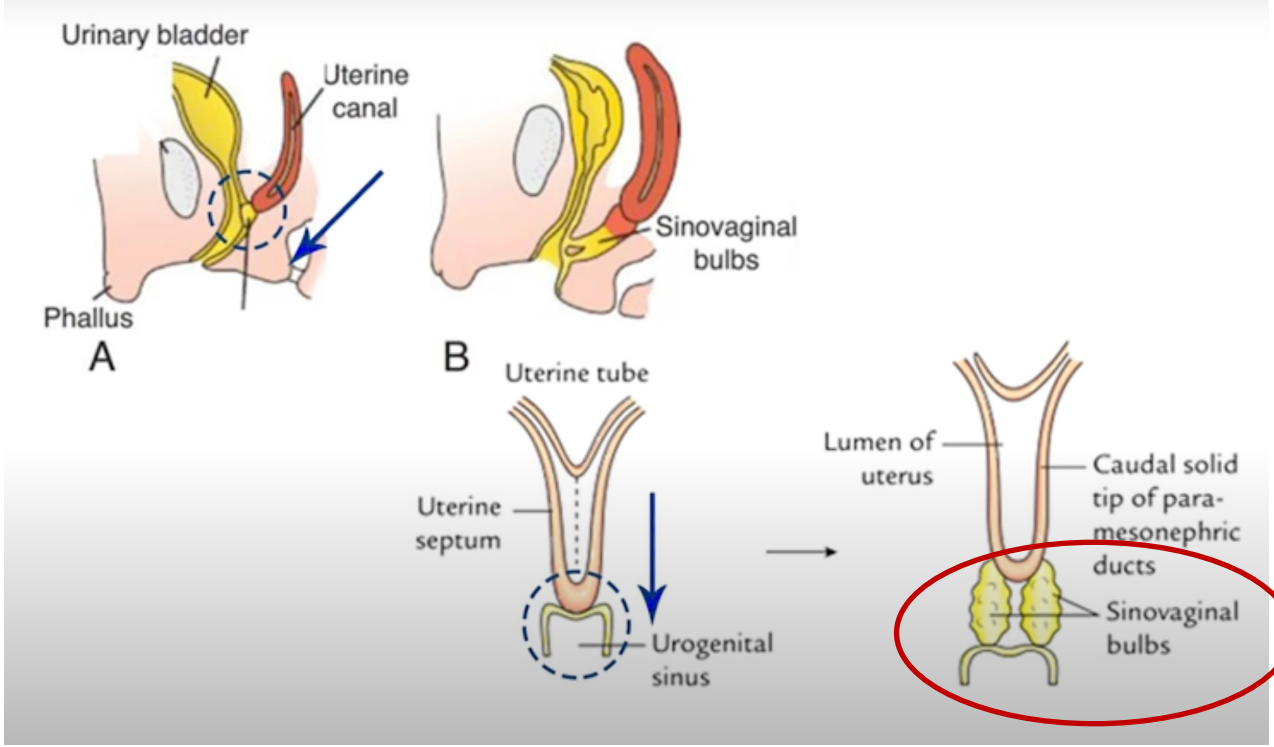

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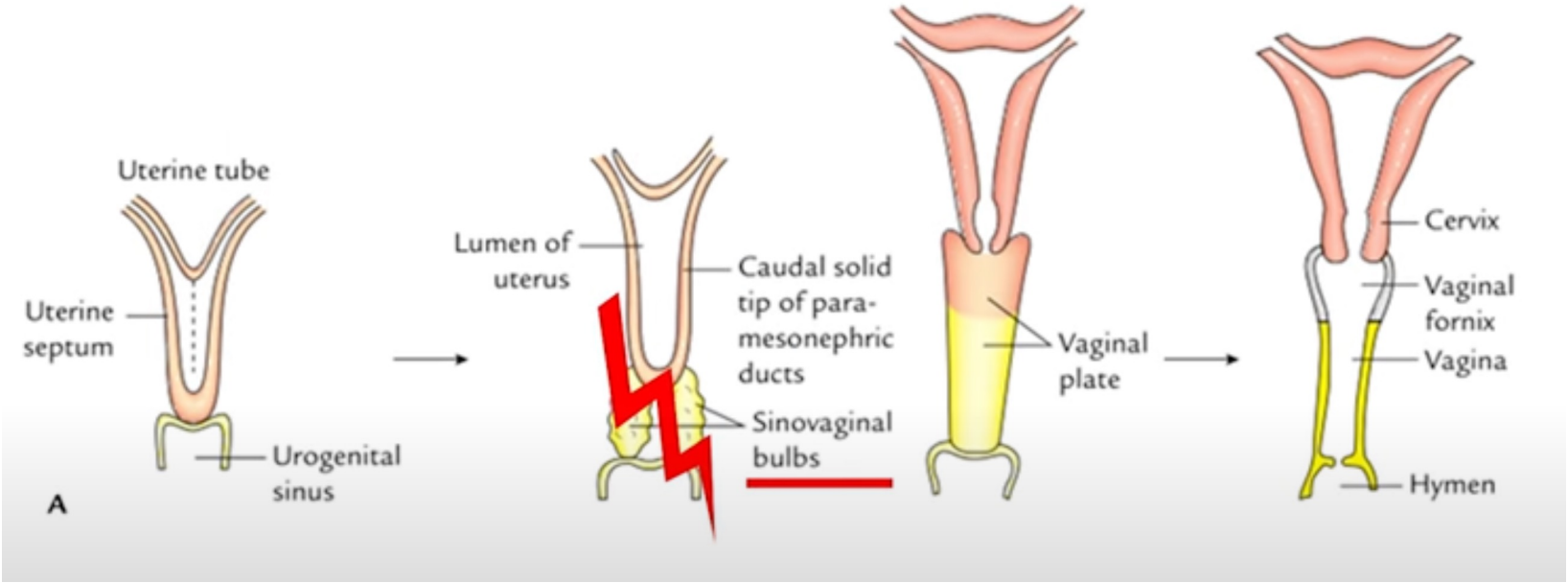

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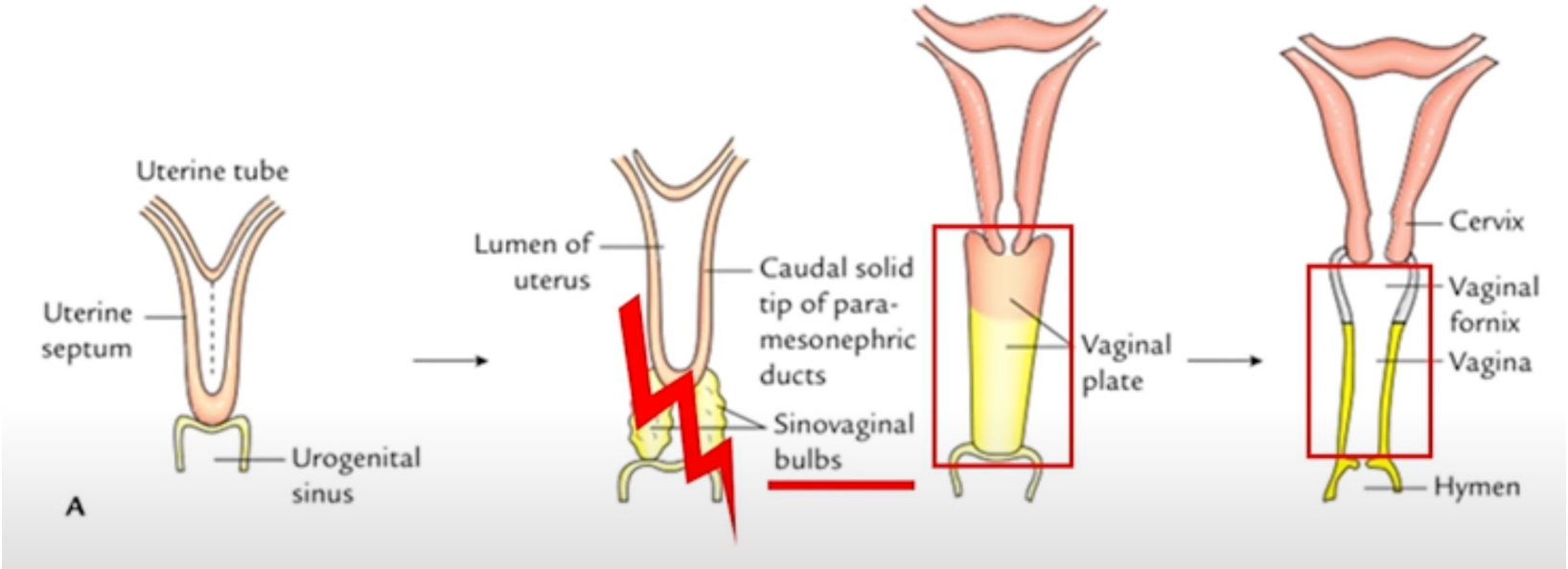

Female reproductive tract embryology – summary

Mesoderm → Mullerian (paramesonephric) ducts → uterus, cervix, upper 1/3 of vagina

Mesoderm → Wolffian (mesonephric) ducts → regress

Mesoderm → urogenital sinus → inferior 2/3 of vagina and hymen

Overview

Embryology

General considerations in PAG

Puberty

Common prepubertal problems in PAG

Menstrual dysfunction

Mullerian duct anomalies

Primary amenorrhoea and delayed puberty

Differences in sex development

Legal considerations in PAG

PAG setting

Child: young person who lacks the understanding or maturity to make important decisions for themselves

Consultation anxieties:

- Normal puberty - range of phenotypes which may be mistaken as disease
- Parent / caregiver may assume speculum will be part of the consultation
- Limited experience of gynaecologist with children / young people

Possible consequences: lifelong trauma and health consequences

PAG setting

Acute reviews: paediatric emergency department

Outpatient setting:

- Consultant PAG
- Specialist / appropriately trained nursing staff
- Toys / seating area
- Consultation room – privacy and comfort; avoid stirrups / speculum display
- Telephone / video calls – ensure child or young person present

History

Identify who has attended with the child / young person and relationship

Preferred name and pronouns

Avoid assumptions – use gender neutral language, pick up on queues

Direct, open, non-judgemental questions rather than assuming

Adolescents: signpost at the beginning that you will ask the parent or caregiver to step outside at one point (to exercise autonomy and allow privacy)

History

Adaptive consultation model – modulated to YP's age and development

2–5 years old: centre of their world, objects are alive/enjoys pretend play
6–11 years old: concrete thinking, aware of the feelings of others
12+: seeking autonomy as an individual

Remain flexible to who relays the history (older children will contribute more)

Ask younger children direct questions with parents' help

Be mindful of shyness

Presenting complaint

Ask general questions to establish rapport / what is the reason for the referral

Take time to explore issues and how they affect child / young person / family

Establish timeline of events

Clarify terminology – commonly used terms for “private parts”

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Normal and Precocious Puberty

Normal puberty starts between 8-13 years

Decline in age of puberty onset since the beginning of the 20th century (especially in affluent countries)

Investigate any girls <8 years of age with signs of puberty

Normal Puberty – physical changes

First outward sign: breast development (thelarche)

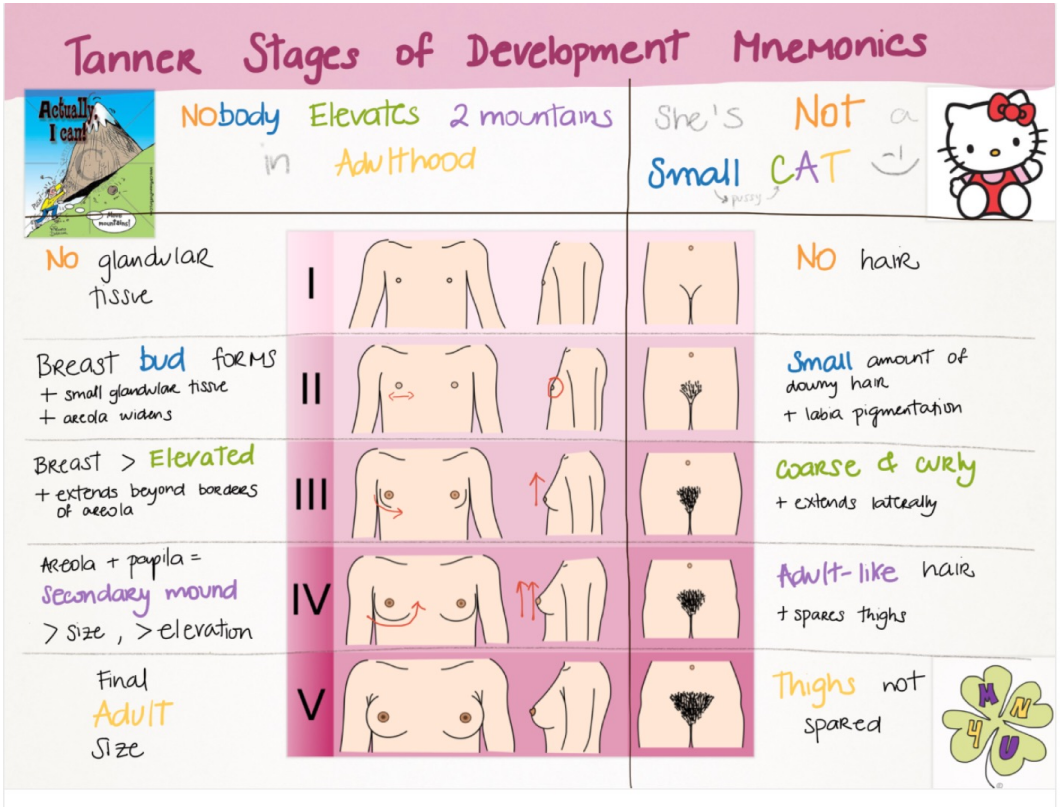
Overweight / obesity – difficult to distinguish between adipose tissue and breast tissue → ultrasound of uterus / ovaries OR ”bone age” in xray

Pubic/axillary hair growth first sign in 15% of girls (especially Black ethnicity)

Menarche (first menstrual bleed): 2-2.5 years after first signs of puberty

- First few periods can be heavy/irregular up to 18 months (anovulatory)

Normal Puberty – Tanner stages



Menarche usually occurs around Tanner stage 4 (~12 years old)

Normal Puberty – Uterine development

Prepubertal uterus: cylindrical in shape, volume 0.8-1.6 ml; endometrium not visualised on ultrasound

Puberty:

- Uterus descends into the pelvis and increases in size; pubertal uterus ≥4 cm in length
- Endometrium: increases in thickness; menarche imminent once ET 6-8 mm
- Oestrogen: stimulates growth of the fundus more than the cervix

Normal Puberty – Ovarian development

Prepubertal ovaries: increase (from <1 ml to 1.2-2.3 ml) throughout childhood but few follicles on US (relatively constant)

Puberty:

- ovaries descend deeper into the pelvis
- FSH stimulates follicle growth and E2 secretion
- Ovaries increase in volume → premenarche ovary 2-4 ml in volume

Post-puberty:

- Ovarian volume 4-9.5 ml on average

Precocious puberty – presentation

Precocious puberty: evidence of puberty <8 years

Early puberty: 8-9 years

Signs:

- Premature pubic hair growth
- Isolated vaginal bleeding
- Premature breast development
- Evidence of androgen exposure (premature adrenarche, most common in Black girls, obesity)
    - Tall, modestly advanced skeletal maturity (but not extreme)
    - Adult body odour
    - Greasy hair and skin
    - Pubic and axillary hair growth
    - **Unlikely clitoromegaly**

Precocious puberty – investigations

Investigation	Purpose
Hand and wrist bone age X-ray	To determine degree of advance of skeletal maturity
Thyroid function tests and prolactin	To exclude primary hypothyroidism and hyperprolactinaemia
Pelvic ultrasound	To assess oestrogen stimulation of uterine and endometrial growth and development To determine gonadotropin stimulation of the ovaries To identify ovarian cysts To identify ovarian tumours
GnRH stimulation test	To determine whether gonadotropins are in the pubertal range (CPP) or suppressed (PPP)
MRI brain with pituitary views in patients with confirmed CPP	To determine whether there is a structural lesion of the hypothalamic–pituitary pathway

Precocious puberty – treatment

Directed at the underlying pathology

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Isolated vaginal bleeding

May occur more than once in prepubertal years

Likely benign in the absence of other symptoms

Investigations:

- Hormone profile (normal: low FSH and LH)
- TA ultrasound (normal: prepubertal uterus)

Differentials:

- Trauma, sexual assault, foreign body
- Urethral prolapse
- Infection (group A strep)
- Vaginal rhabdomyosarcoma, juvenile granulosa tumour
- Exogenous oestrogen exposure
- Profound hypothyroidism

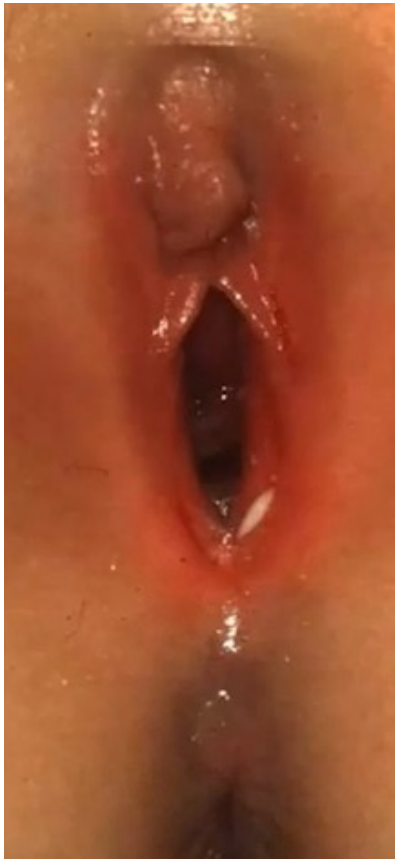
Vulvovaginitis

- Most common presentation in ages 2-7 years
  - Poor hygiene
  - Sitting on the ground, sand pits
- Vulval anatomy in prepubertal girl predisposes to nonspecific infection/irritation
  - Lack of pubic hair and vaginal oestrogen (→ more alkaline pH)
  - Open introitus because:
    - Labia minora are underdeveloped
    - Labia majora have minimal adipose tissue – flattened appearance
  - Open introitus more susceptible to infection (especially due to proximity to the anus)

Vulvovaginitis

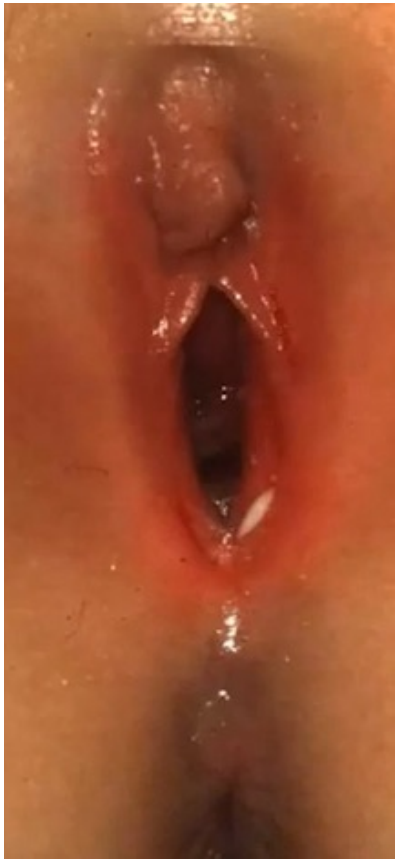
- **Symptoms:**
  - Discharge (green, yellow, foul smelling)
  - Itching
  - Pain
  - Dysuria

- **Examination:**
  - Erythema around vulva and anus
  - Excoriated
  - Dry skin
  - Discharge
  - Associated labial adhesions



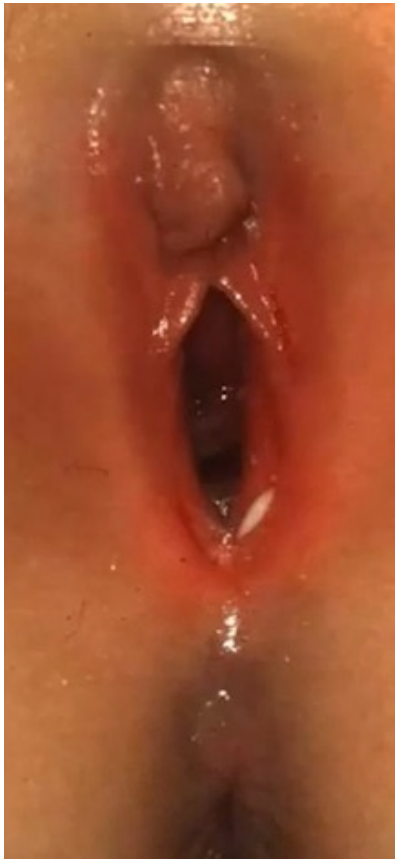
Vulvovaginitis

- **Investigations:**
  - Low vaginal swab
    - Pathogens:
      - Thrush unlikely as vaginal pH too alkaline
      - Group A strep, Haem influenza, staph aureus, strep pneumoniae
      - Chlamydia / Gonorrhoea / Trichomonas indicate sexual abuse



Vulvovaginitis

- **Management**
  - Hygiene (wiping front to back)
  - Emollients (dermol cream / hydromol ointment)
  - Avoidance of soaps/shower gel/bubble baths
  - Cotton underwear
  - Non-bio laundry detergent
  - Avoid constipation
  - No antifungal creams unless found on culture
  - Night time symptoms – think threadworm (Mebendazole)
  - Reassurance



Labial adhesions

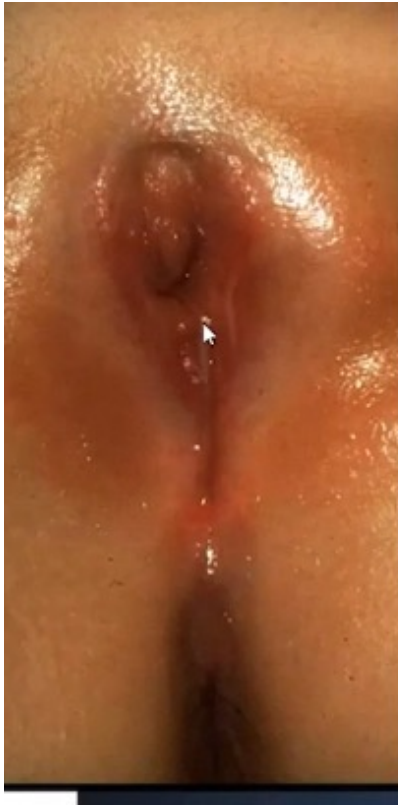
- 2% of prepubertal girls
- 3 months to 8 years (typically present age 2 years)
- Uncommon before age 1 year – NOT PRESENT AT BIRTH

- Mostly asymptomatic
- Possible associated vulvovaginitis / skin irritants
- **Urinary symptoms:** post-void dribbling, UTI, vulval irritation

- Management:
  - 80% resolve without treatment
  - Most resolve by puberty with endogenous oestradiol exposure

Labial adhesions - examination

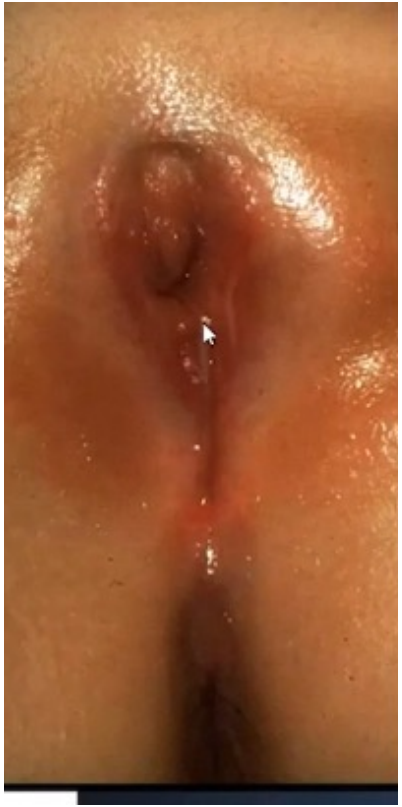
- Fusion of labial skin from posterior vaginal introitus toward urethra
- Complete or partial
- May only be pinhole opening
- Thin membranous line (translucent) in the midline



Labial adhesions - management

- Reassurance
- Emollients
- Topical oestrogen only if symptomatic (e.g. urinary sx):
  - Estriol 0.01% or Ovestin 1 mg
  - Small amount twice daily up to 6 weeks
  - Recurrence common (34%)
  - Systemic effects of oestrogen: breast budding, vulval pigmentation, vaginal bleeding

- Surgery: severe cases may require surgical separation of adhesions under GA, bur recurrence is common



Lichen sclerosus

- Lymphocyte-mediated dermatosis
- Auto-immune pathogenesis
- Pre-pubertal and post-menopausal but can occur at any age
- Can run in families
- 0.1% of prepubertal girls (15% have a family history)

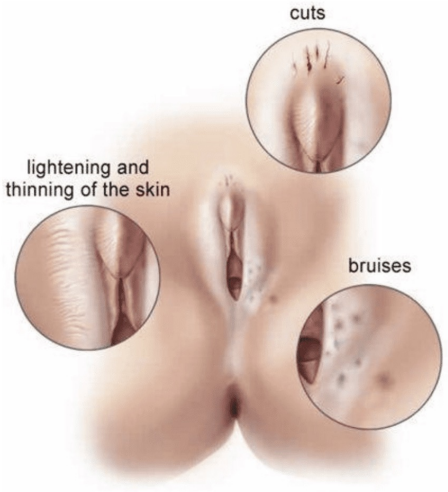


Illustration by Lisa Clark

Lichen sclerosus - symptoms

- Itching
- Pain
- Dysuria
- Bleeding from erosions or fissures
- Pain on defecation / constipation

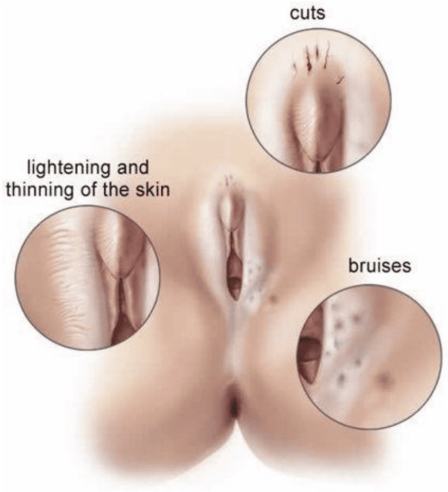


Illustration by Lisa Clark

Lichen sclerosus - examination

- Hypopigmented skin
- Figure of 8 – vulval and perianal
- Ecchymoses / fissures / erosions
- Scarring / fusion / introital narrowing (less common)
- Can be confused with sexual abuse

- Low malignancy risk
- Most resolve at puberty (75%)

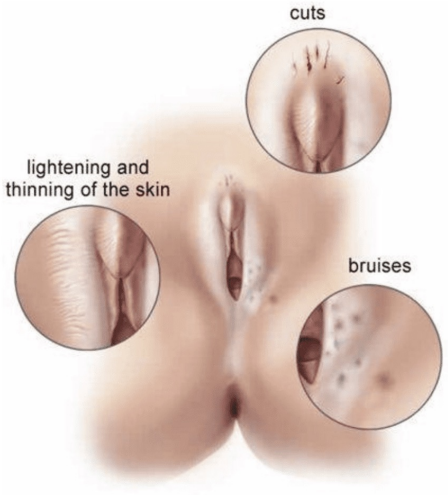


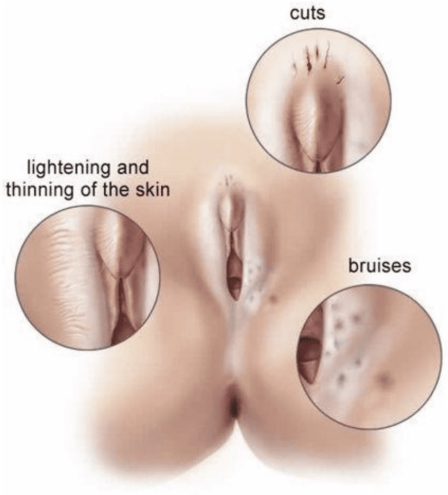
Illustration by Lisa Clark

Lichen sclerosus - management

- 0.05% clobetasol propionate ointment (Dermovate)
  - One a night for 4 weeks
  - Alternate nights for 4 weeks
  - Twice weekly for 4 weeks

- Ointments preferred as less preservative
- Emollients (dermol cream / hydromol ointment)
- Antihistamine at night

- If recurring frequently → consider calcineurin inhibitors (tacrolimus 0.1%) if steroid resistant



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Adolescent menstrual dysfunction

- Irregular, heavy or painful periods
- Most common cause is immaturity of the HPO axis leading to **anovulatory cycles**

- 50% of cycles are anovulatory in the first 2 years after menarche

Multiple follicles→ no oestradiol surge → no LH surge → no ovulation → no progesterone → unopposed oestradiol → thicker endometrium → heavier periods

Parameter	Normal	Abnormal
Cycle length	21–45 days	Frequent: <21 days Infrequent: >45 days
Duration of menses	<8 days	Prolonged: >8 days
Amount of bleeding	Usually 30–40 mL, i.e. ~3–6 soaked tampons or pads each day	Heavy: >80 mL or any excessive loss that interferes with physical, social, emotional and/or material quality of life
Painful periods	Anovulatory cycles likely to be painless Likely painful cramps when cycles become ovulatory, but usually respond to simple analgesia	Persistent pain not responding to simple medical treatment may have an underlying pelvic pathology, such as endometriosis or Müllerian anomaly

Heavy menstrual bleeding – History

- Menarche
- Cycle length, duration and amount of bleeding
- Symptoms of anaemia
- Symptoms of easy bruising, nose bleeds
- Period camps / pelvic pain
- Symptoms of hypothyroidism / hyperprolactinaemia
- History of acute weight loss / gain
- Acne, hirsutism, scalp hair loss
- Medical/surgical history
- Family history of bleeding disorders
- Sexual history
- Social history
- Medication including hormonal contraception

Heavy menstrual bleeding – Examination

- BMI
- Signs of hyperandrogenism
- Pelvic examination in sexually active patients only if indicated

Heavy menstrual bleeding – Investigations

- FBC
- Serum ferritin (50% will have iron deficiency)
- Coagulation profile
- Von Willebrand factor screen
- Hormone profile: FSH, LH, oestradiol, testosterone, SHBG. If indicated: TFTs, prolactin
- Consider genital swabs if infected suspected:
    - Culture and sensitivity
    - PCR testing for chlamydia and gonorrhoea

- Pelvic ultrasound scan (transabdominal) – more for reassurance
- MRI if Mullerian anomalies suspected

Heavy menstrual bleeding – Management

1. Non-hormonal

A. Tranexamic acid 1 g TDS up to 4 days during periods (↓ blood flow by 50%)

B. Mefenamic acid 500 mg TDS, initiate before period starts (↓ blood flow by 25%)

Heavy menstrual bleeding – Management

2. Hormonal

A. FIRST LINE: Combined hormonal contraception (COCP / patch)

I. Advantages: better cycle control, reduced bleeding; can take continuously (4-day breaks) if breakthrough bleeding

II. Disadvantages: interactions (enzyme-inducing antiepileptic drugs, lamotrigine – increased seizure frequency); VTE risk (dose-related)

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B. Progesterone only pill

I. Desogestrel 75 mcg OD → fewer medical contraindications but not as effective for cycle control; can cause irregular bleeding; double dose (150 mcg) possible, more likely to achieve amenorrhoea, but off-license

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I. Medroxyprogesterone acetate 10 mg BD → TDS (preferred to NTE as safer)

II. Norethisterone acetate 5 mg BD → TDS (↑ VTE, ↑ androgenic side effects)

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D. Mirena coil
   I. Good option when COCP/POP haven't worked; less progesterone sensitivity in PMS
   II. Irregular bleeding for first 6 months
   III. Do under GA if not sexually active
   IV. Risks: perforation (1%), expulsion (5%), PID (<1%)

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   I. Desogestrel 75 mcg OD → fewer medical contraindications but not as effective for cycle control; can cause irregular bleeding; double dose (150 mcg) possible, more likely to achieve amenorrhoea, but off-license

C. Oral progestogens (NOT CONTRACEPTIVE) cyclically or continuously
   I. Medroxyprogesterone acetate 10 mg BD → TDS (preferred to NTE as safer)
   II. Norethisterone acetate 5 mg BD → TDS (↑ VTE, ↑ androgenic side effects)

D. Mirena coil
   I. Good option when COCP/POP haven't worked; less progesterone sensitivity in PMS
   II. Irregular bleeding for first 6 months
   III. Do under GA if not sexually active
   IV. Risks: perforation (1%), expulsion (5%), PID (<1%)

E. Intramuscular medroxyprogesterone depot injection every 12 weeks
   A. Good for amenorrhoea, but avoid due to concerns with bone mineral density

Heavy menstrual bleeding – Management

2. Hormonal

A. FIRST LINE: Combined hormonal contraception (COCP / patch)
   I. Advantages: better cycle control, reduced bleeding; can take continuously (4-day breaks) if breakthrough bleeding
   II. Disadvantages: interactions (enzyme-inducing antiepileptic drugs, lamotrigine – increased seizure frequency); VTE risk (dose-related)

B. Progesterone only pill
   I. Desogestrel 75 mcg OD → fewer medical contraindications but not as effective for cycle control; can cause irregular bleeding; double dose (150 mcg) possible, more likely to achieve amenorrhoea, but off-license

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F. GnRH agonists – only with MDT input (paeds, haematology, GP); reduced BMD

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Mullerian duct anomalies

Congenital Mullerian anomalies occur in 5% of females

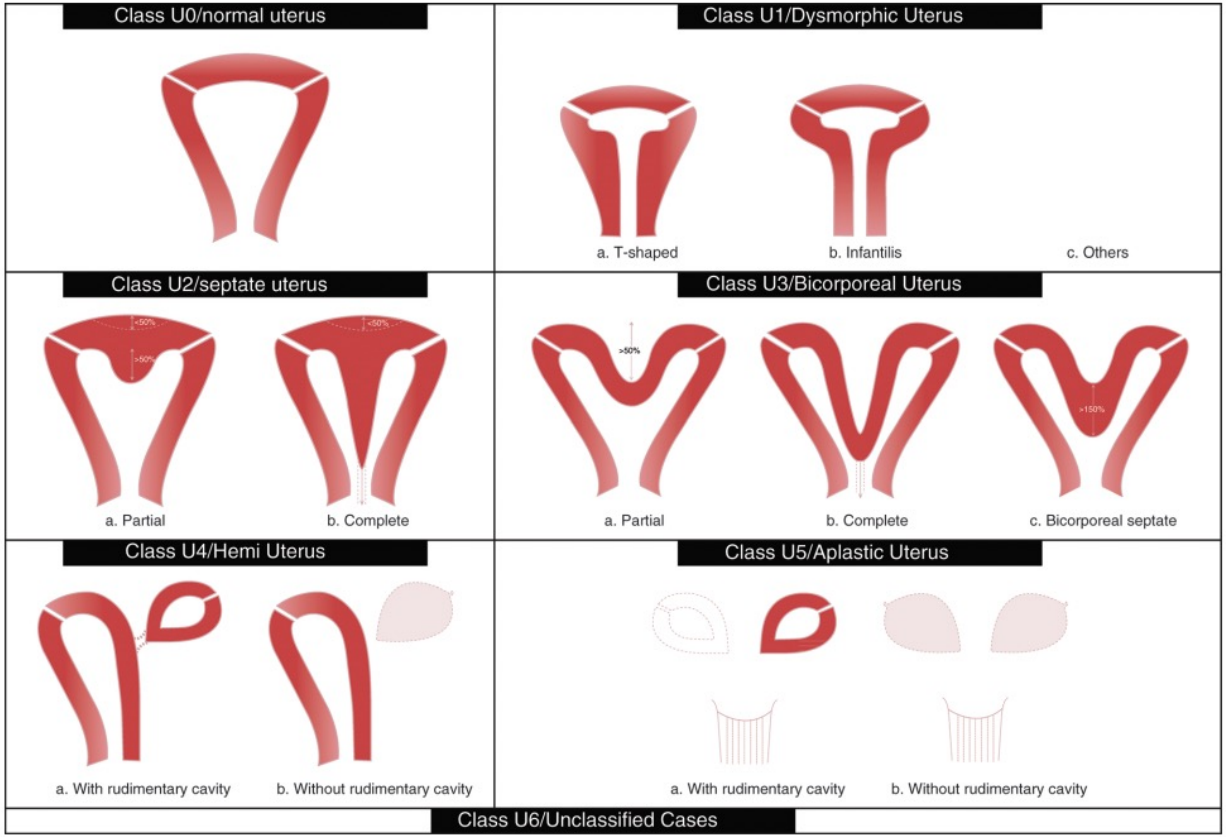
Present in many ways, most commonly:
- Primary amenorrhoea
- Obstructed menstruation
- Dysmenorrhoea
- Dyspareunia
- Difficulty with tampons
- Infertility
- Recurrent miscarriage

Diagnosis:
- Clinical assessment
- Pelvic ultrasound (preferably with 3D)
- MRI

- Commonly associated with renal anomalies – always perform US KUB

Mullerian duct anomalies - classifications

ESHRE/ESGE 2015



Mullerian duct anomalies - classifications

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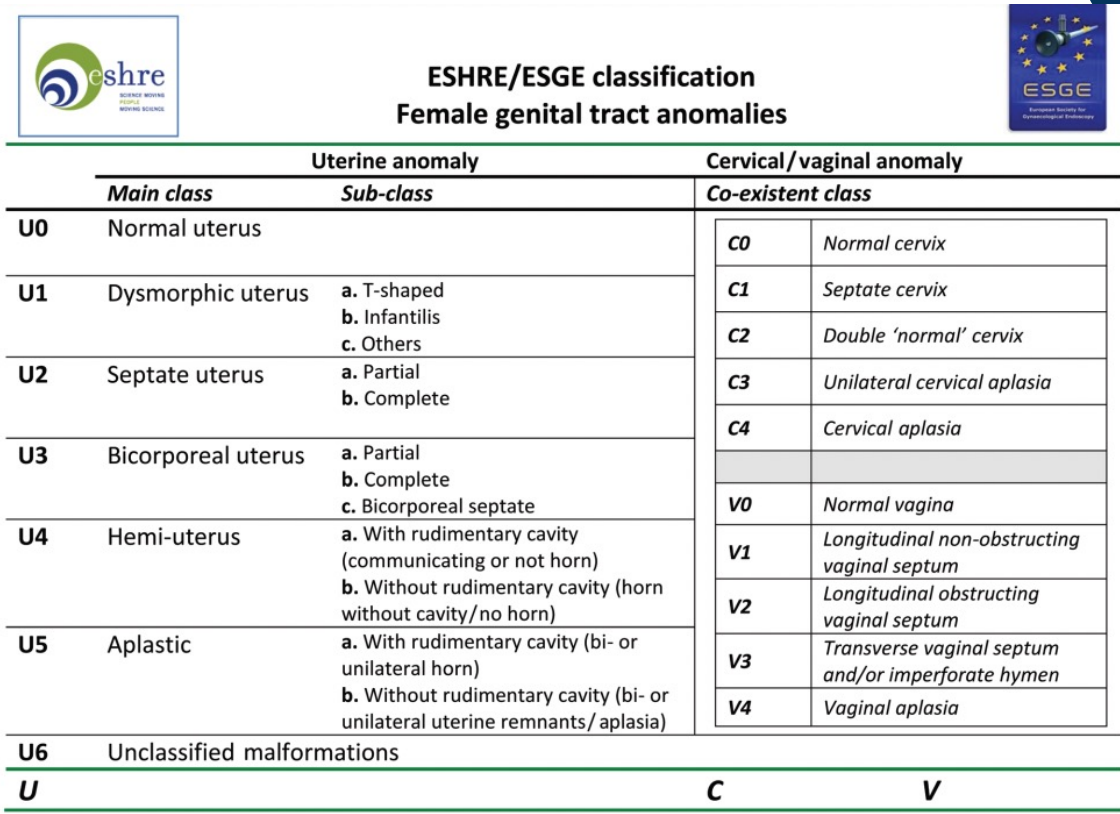
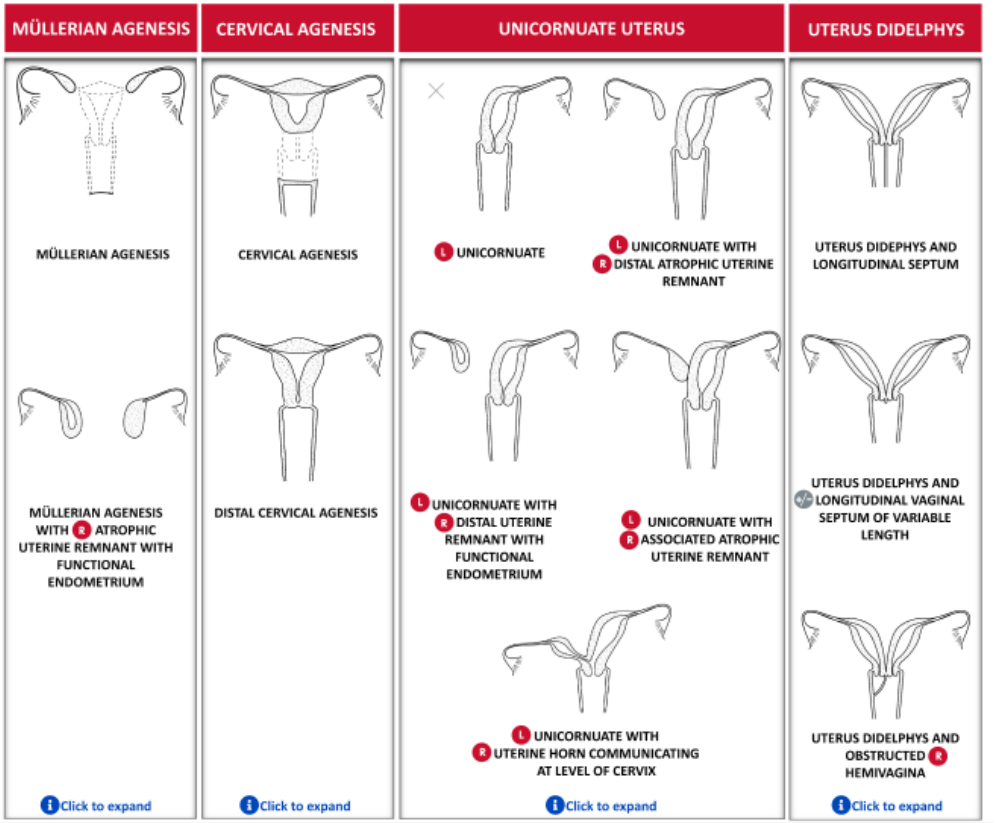


ESHRE/ESGE classification
Female genital tract anomalies

	Uterine anomaly		Cervical/vaginal anomaly	
	Main class	***Sub-class***	***Co-existent class***	
U0	Normal uterus		***C0***	*Normal cervix*
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	***C1***	*Septate cervix*
U2	Septate uterus	**a.** Partial **b.** Complete	***C2***	*Double 'normal' cervix*
			C3	*Unilateral cervical aplasia*
			C4	*Cervical aplasia*
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate		
			V0	*Normal vagina*
U4	Hemi-uterus	**a.** With rudimentary cavity (communicating or not horn) **b.** Without rudimentary cavity (horn without cavity/no horn)	***V1***	*Longitudinal non-obstructing vaginal septum*
			V2	*Longitudinal obstructing vaginal septum*
U5	Aplastic	**a.** With rudimentary cavity (bi- or unilateral horn) **b.** Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	***V3***	*Transverse vaginal septum and/or imperforate hymen*
			V4	*Vaginal aplasia*
U6	Unclassified malformations			
U			***C***	***V***

Mullerian duct anomalies - classifications

ASRM MAC 2021



Mullerian duct anomalies – imperforate hymen

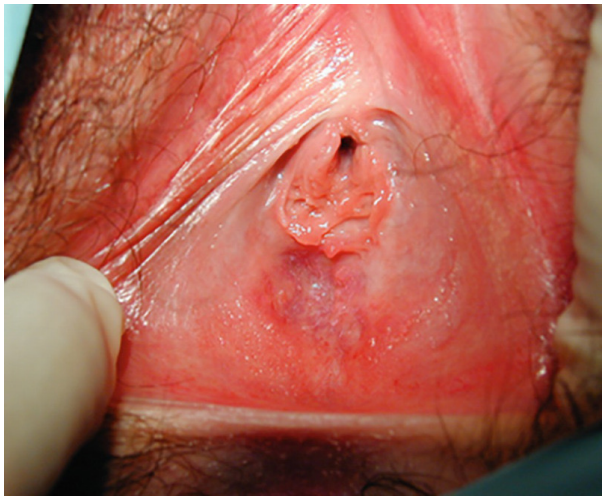
Hymen usually becomes perforate before or shortly after birth

Incidence 1:1000 live female births
NOT associated with other Mullerian duct or renal abnormalities

Presentation:
- Increasing cyclical pain in the absence of menstruation in adolescence

Examination:
- Possible palpable pelvic mass
- Gentle parting of the labia:
    - Visible bulging membrane, with a bluish coloration (blood)

Treatment:
- Incision, drainage of haematocolpos and hymen resection (otherwise risk of reobstruction)



Mullerian duct anomalies – transverse vaginal septum

Rare (1 in 2100 to 1 in 72000)

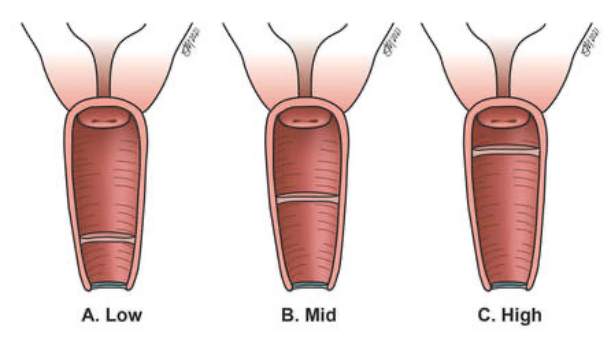
Failure of canalisation of the vaginal plate at the point where the urogenital sinus meets the Mullerian duct

Varying thickness and location in the vagina

Can be:
- Perforate (normal menses; difficulties with intercourse / tampons)
- Imperforate (present in adolescence)

Classification:
- Low (<3 cm from introitus)
- Mid (3-6 cm from introitus)
- High (>6 cm from introitus)

Assessment:
- Clinical
- USS
- MRI



Mullerian duct anomalies – transverse vaginal septum

Treatment:

- Surgical resection (vaginally, laparoscopically or abdomino-perineal approach)

- Low, thin (<1 cm) and perforate: vaginal operation
- Mid, high (<2 cm): laparoscopic resection, good longterm reproductive outcomes
- Mid, high (>2 cm) and imperforate: abdomino-perineal approach (bowel segment may be required for bridging), poorer longterm prognosis

- Vaginal dilation recommended following all laparoscopic and abdomino-perineal vaginoplasties

Mullerian duct anomalies – longitudinal vaginal septum

Failure of canalisation of the vaginal plate during embryogenesis

Can be:
- Complete (from cervix to introitus)
- Partial (involving any part of the vagina)

Presentation:
- Dyspareunia
- Difficulties inserting tampons
- Occasional obstruction of one hemivagina → regular menstruation with gradually worsening pelvic pain

Examination:
- Unilateral vaginal wall swelling secondary to haematocolpos

Imaging:
- MRI is the modality of choice
- In most cases there is an associated uterine anomaly (complete uterine septum or uterus didelphys)

Treatment:
- Surgical resection (vaginally – low complication rates, good long-term outcomes)
- Dilation rarely required post-operatively

Mullerian duct anomalies – uterine anomalies

Arcuate uterus:

- Mild indentation of the endometrium at the fundus (<1 cm)
- Normal fundal contour
- Variant of normal (but increases risk of second-trimester miscarriage)

Mullerian duct anomalies – uterine anomalies

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Septate uterus:
- Most common congenital uterine anomaly (35%)
- Incomplete resorption of the septum following Mullerian duct fusion
- Can be complete (fundus to cervix) or partial (any length)
- Associated with pregnancy loss, infertility, preterm birth, fetal malpresentation
- BUT unclear whether resection accrues any benefit

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Bicornuate uterus:
- 25% of uterine anomalies
- Increased risk of miscarriage, preterm birth, malpresentation

Mullerian duct anomalies – uterine anomalies

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- Increased risk of miscarriage, preterm birth, malpresentation

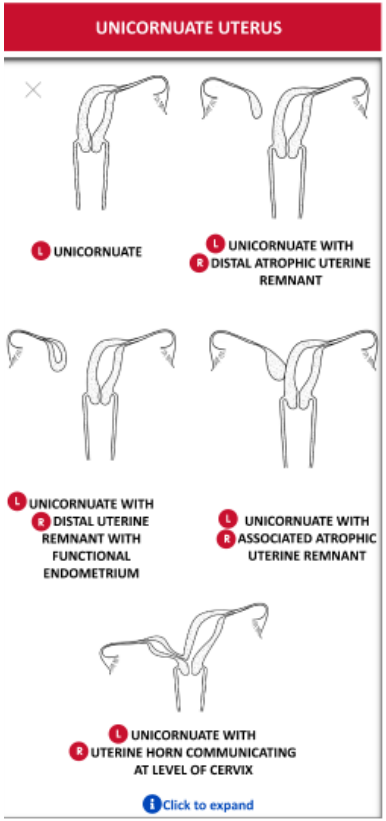
Uterus didelphys:
- 10% of uterine anomalies
- Associated with longitudinal septa
- Surgery not recommended in the absence of septum
- Strong association with renal tract anomalies

Mullerian duct anomalies – uterine anomalies

Unicornuate uterus:

- Only one of the Mullerian ducts differentiates fully
- Increased risk of miscarriage, preterm labour and malpresentation

- Rudimentary horn may be present
  - Communicating or non-communicating
  - If non-communicating with functional endometrium → increasing dysmenorrhoea
  - Pregnancy can occur in rudimentary horns (cornual ectopic), hence removal of rudimentary horns should be considered



Mullerian duct anomalies – cervical agenesis

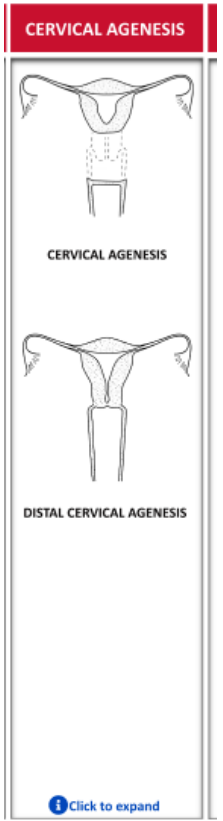
Cervical agenesis:

- Congenital absence of the cervix
- Rare (1:80,000 to 1:100,000) births

- Presentation: primary amenorrhoea and worsening lower abdominal pain secondary to haematometra

- Associated with vaginal agenesis in 40% of cases

- Treatment:
    - 1st line – laparoscopic uterovaginal anastomosis



Mullerian duct anomalies – MRKH

Mayer-Rokitansky-Kuster-Hauser syndrome
- 1 in 4500 female births
- interrupted embryonic development and failure of fusion of the Mullerian ducts
- hypoplasia of the uterus and upper 1/3 of vagina

Normal ovarian function (normal karyotype)

Presentation:
- primary amenorrhoea
- normal pubertal development and secondary sexual characteristics

Diagnosis:
- clinical assessment
  : vaginal length can vary from a small dimple to over 6 cm (but most will be <2 cm)
- pelvic ultrasound
  : >90% will have rudimentary uterine buds (but small and undifferentiated)
  : sometimes rudimentary uterus will have functional endometrium – cyclical pain, necessitate laparoscopic resection
- MRI may be required
- US KUB to rule out urinary tract anomalies (40%)

Mullerian duct anomalies – MRKH

Mayer-Rokitansky-Kuster-Hauser syndrome

Treatment:
- vaginal dilation (1st line – dedicated programmes have >85% success rates)
- creation of a functional vagina (laparoscopic Vecchietti procedure)
- fertility: adoption / surrogacy
- uterine transplantation remains experimental
- psychological input

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Primary amenorrhoea and delayed puberty

Pubertal transition requires:
- an intact HPO axis
- functional reproductive organs

Some numbers:
- female puberty requires ~3 years for completion (starting in 95% of cases between 8.5 and 13 years)
- puberty begins with HPO axis maturation
- puberty is mostly driven by high oestradiol concentrations

First sign: breast budding (thelarche), will begin in most girls by age 11.3 years
- menses usually occurs 2 years after thelarche
- by age 14.5 years, 95% of girls will have had periods

Primary amenorrhoea and delayed puberty

Primary amenorrhoea: 0.3% of females

Delayed puberty:
- primary amenorrhoea with no secondary sexual characteristics by age 13
OR
- primary amenorrhoea by 15 years old in the presence of secondary sexual characteristics (implies normal oestrogenisation, thus likely anatomical cause rather than hormonal)

Causes:

Absence of secondary sexual characteristics	Presence of secondary sexual characteristics
Constitutional delay	Uterine outlet obstruction
Chronic illness	Mayer–Rokitansky–Küster–Hauser
Hypothalamic amenorrhoea	Polycystic ovary syndrome
Hypogonadotrophic hypogonadism	Hyperprolactinaemia and other endocrinopathies
Hypopituitarism	Complete androgen insensitivity syndrome
Premature ovarian Insufficiency	Pregnancy
Turner syndrome	
Swyer syndrome	

Primary amenorrhoea and delayed puberty

Investigations

Investigations for all	Additional investigations (on a case-by-case basis)
Gonadotrophins (FSH and LH) and oestradiol	Karyotype
Testosterone, SHBG, androstendione	FRAXA screening
Renal profile	Autoantibodies
Prolactin and TFTs	MRI pituitary
Pregnancy test	MRI pelvis
Pelvic US	DEXA
	Tumour markers

Primary amenorrhoea and delayed puberty

Management – absence of secondary sexual characteristics

Cause	Considerations	Management
Constitutional delay (14%)	Variant of normal. All aspects of puberty will be delayed, including growth. Common in family clusters. No other concerning factors. Bloods: low FSH/oestradiol	Reassurance and follow-up Sometimes pubertal induction
Chronic illness	Physical or psychological. Cystic fibrosis, chronic cardiac problems, coeliac disease, emotional/physical abuse.	Specialist input (MDT)
Hypothalamic amenorrhoea	Usually because of excessive exercise, stress, calorific restriction. Onset of menses requires BMI 19 kg/m2 and 22% body fat May be permanent	Weight restoration, psychological support May require HRT longterm
Hypogonadotrophic hypogonadism	Any loss of GnRH / FSH / LH secretion E.g. Kallman syndrome (1 in 50,000) – colour blindness and anosmia + hypogonadism E.g. Pituitary tumours – craniopharyngiomas Sometimes idiopathic – more likely to be irreversible (80-90%)	According to pathology (e.g. surgical resection of pituitary tumour, radiotherapy)
Premature ovarian insufficiency	1% of all women aged <40 years 0.01% of women aged <20 years, therefore rare in PAG	MDT (bone, cardiovascular health, fertility, psychological input)
Turner syndrome	Complete or partial (mosaic) loss of one X chromosome Hastened ovarian follicle atresia 5-20% will enter spontaneous puberty, but most will experience primary amenorrhoea	MDT (growth optimization, cardiac health)

Primary amenorrhoea and delayed puberty

Management – presence of secondary sexual characteristics

Cause	Considerations	Management
MRKH (10-15%)	Intact HPO, the problem is purely anatomical (absent uterus and upper 2/3 of vagina) Most cases are sporadic in nature Unlikely cyclical pain unless there is rudimentary uterus with functioning endometrium	Specialist PAG input
Imperforate hymen (1 in 1000), transverse vaginal septum (1 in 80,000) , vaginal/cervical agenesis	Primary amenorrhoea with cyclical pain because of outflow blockage Haematocolpos (blood-filled vagina) / haematometra (blood-filled uterus)	Specialist PAG input
PCOS	Do not diagnose until at least 8 years after menarche US not recommended in adolescents as high incidence of multifollicular appearance	As per RCOG PCOS guideline
Hyperprolactinaemia	Prolactin exerts negative feedback on the hypothalamus / pituitary → loss of FSH/LH Look out for headaches / visual disturbances secondary to space occupying lesions Galactorrhoea may result simply from hyperprolactinaemia (without prolactinoma)	Medical (e.g. cabergoline, bromocriptine) or surgical treatment
Hypothyroidism	Results in high TSH → stimulates prolactin release	Correction of hypothyroidism
Differences of sex development	“atypical development of chromosomal, gonadal and anatomic sex”	Specialist PAG input

Primary amenorrhoea and delayed puberty

Hormone replacement (pubertal induction) considerations

Royal College of Obstetricians & Gynaecologists

Sex Steroid Treatment for Pubertal Induction and Replacement in the Adolescent Girl

Scientific Impact Paper No. 40
June 2013

Table 1. Common conditions requiring sex steroid replacement

Constitutional delay of puberty
Gonadal dysgenesis – 45X, 46XX, 46 XY
Premature ovarian insufficiency
Surgical hypogonadism
Hypopituitarism
Hypogonadotrophic hypogonadism
Hypothalamic amenorrhoea
Disorders of sexual development

Primary amenorrhoea and delayed puberty

Hormone replacement (pubertal induction) considerations

- **Aim**: to imitate spontaneous puberty over several years, with gradual exposure to oestrogen

- Unopposed low-dose oestrogen should be commenced ideally between the ages of 11-12 years

- Titration of dose to full adult replacement over a 2-3 year period

- Progesterone:
  add to induce menarche (withdrawal bleed) after 2 years of unopposed oestrogen
  OR
  to provide cycle regularity in those who have experienced withdrawal bleed

- Premature progesterone initiation could lead to arrest of uterine and breast development

- Regular bleeds: essential for endometrial protection

Primary amenorrhoea and delayed puberty

Hormone replacement (pubertal induction) considerations

- Common regimens

Table 2. Published examples of induction of puberty regimens

Age	Ethinylestradiol[2,6]	Oestradiol[6]	Oestradiol[5]
		Oral	Patch
	mcg	mcg/kg	mcg/24hrs
8	2		
9	4		
10	6		
11	8		
12	10	5.0	3.1–6.25
13	15	7.5	6.25–12.5
14	20	10.0	12.5–18.8

Progestogen is introduced only after a suitable duration of unopposed oestrogen or if break through unscheduled bleeding occurs. Progestogen is usually given as part of a pre–packed cyclical regimen with oestradiol using one of the preparations formulated for post–menopausal women. Progestogens can also be prescribed separately if a particular one is favoured because of side effects. Northisterone, the most potent progestogen, may be considered excessive in this situation and fewer side effects may be experienced with medroxyprogesterone acetate or micronized progesterone prescribed for 12–14 days each cycle. It is also possible to administer the progestogen every 2–3 months to reduce the frequency of withdrawal bleeding. Progestogen cover can also be achieved using the oral contraceptive pill.

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Differences of sex development

Umbrella term – difference in observed and expected sex development (based on karyotype, gonadal tissue or genital appearance)

Individual conditions should be referred to by their genetic basis (e.g. 46,XY DSD)

Previously used terms:
- intersex
- pseudo-hermaphrodite
- testicular feminisation

Prevalence: 1 in 1000 live births, more common in consanguinity

Genetics: many are autosomal recessive, so family history may be present (ask about other female family members who were unable to have children)

All DSD should have MDT management in a specialised DSD centre (paeds endocrine, psychologist, paediatric urologist, specialist nurses, geneticists, biochemists, radiologists, gynaecologists)

Differences of sex development

Initial investigations

External female genital appearance	Karyotype	Androgens	Internal gonads and structures	Condition
Atypical	46, XX	Raised (>2)	Ovaries, uterus, tubes and upper vagina	Congenital adrenal hyperplasia (CAH)
Typical	46, XY	Raised for female	Testes	Complete androgen insensitivity syndrome (cAIS)
Typical	46, XY	Normal for female	Dysgenic testes (gonads), uterus, tubes and upper vagina	Pure gonadal dysgenesis (Swyer syndrome)

Differences of sex development

Congenital adrenal hyperplasia (CAH)

- Karyotype: 46,XX DSD

- Autosomal recessive
- 1 in 14,000 births

- Commonest type: lack of 21 hydroxylase

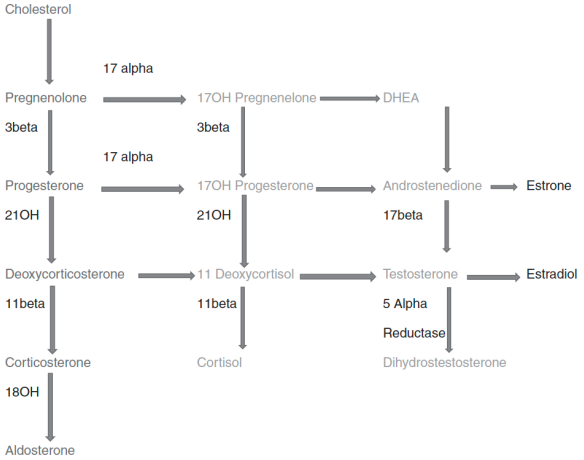

Figure 11.1 Testosterone and steroid biosynthetic pathway with enzymes shown.

- Excess of androgens in utero → androgenisation / "virilisation" of the female fetus
- O/E:
  :enlarged clitoris, urethra opening near the glans
  :labia majora – rugose appearance, may be fused

- Can cause life-threatening salt-wasting crisis because of lack of cortisol (carry hydrocortisone injection)
- Life-long endocrine team input
- Clitoral reduction surgery possible but remains cosmetic (may damage nerves / cause sexual dysfunction – 25% experience anorgasmia after surgery) **DO NOT PERFORM SURGERY UNTIL OLD ENOUGH TO CONSENT**

Differences of sex development

Complete Androgen Insensitivity Syndrome

- **Karyotype**: 46,XY DSD
- **Prevalence**: 1 in 40,000 births
- **Autosomal recessive** – mutation in androgen receptor genes
- Rarely recognised at birth because external genitalia are typically female

Mechanism:
- normal functioning testes BUT DYSFUNCTIONAL PERIPHERAL ANDROGEN RECEPTORS
- normal anti-Mullerian hormone → Mullerian ducts do not develop, so no uterus/ no cervix/ no upper vagina

Lower vagina is shortened and blind-ending

Presentation:
- early: girl with hernia in childhood (testes prolapsing into the labia)
- late:
  :primary amenorrhoea in adolescence;
  :tall girl (height determined by Y chromosome);
  :sparse pubic and axillary hair (lack of androgenisation);
  :BUT normal breasts (peripheral conversion of androgens to oestrogen)

Gonadectomy:
- intraabdominal testes carry a 5% risk of cancer – offer removal FROM THE ONSET OF PUBERTY
- **HRT** required until the age of the menopause

Differences of sex development

Gonadal dysgenesis (Swyer syndrome)

- Karyotype: 46,XY DSD
- Testes do not express AMH → normal uterus and vagina
- Normal external genitalia (female)

Presentation:
- primary amenorrhoea WITHOUT secondary sexual characteristics
- tall (because of Y chromosome)

Gonadectomy:
- intraabdominal testes carry a 30-40% risk of cancer
- offer removal FROM THE TIME OF DIAGNOSIS
- **HRT** required to induce puberty, with addition of progesterone once periods have established

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Legal considerations in PAG

Consent

Law:
- any competent young person in the UK can consent to medical treatment, including contraception
- 16 years old and above: presumed competent unless otherwise stated
- <16 years: competence to consent has to be demonstrated; if competence demonstrated and procedure deemed to be in the best interest of the child, parents cannot override consent by withdrawing it

Sexual activity:
- Age of consent in the UK: 16 years
- Mutually agreed sexual activity between two people <16 years: unlawful, but rarely prosecuted
- Sexual Offences Act 2003: girl <13 years not considered capable of consenting
- Any sexual activity with male or female child <13 years is rape

Treatment refusal in people with capacity:
- Age <16 years: cannot refuse treatment
- Age 16-17 years: refusal can be overridden by parents or court
- Age 18 years and above: can refuse treatment

Legal considerations in PAG

Consent

Young people without capacity:
- only person with parental responsibility or court can give consent
- consent from one parent usually sufficient
- if parental disputes → seek legal advice

Fraser guidelines / criteria:
- apply to people <16 years old seeking contraception
- include:
    1. the young person understands the professional's advice
    2. the young person cannot be persuaded to inform their parents
    3. the young person is likely to begin, or continue having, sexual intercourse
    4. the young person's health is likely to suffer unless they receive contraception
    5. the young person's best interests require them to receive contraceptive advice / treatment

Questions?