Embryology and physiology

All 4 major chromosomal abnormalities a/w urogenital abnormality:

<table>
<thead>
<tr>
<th>Chromosome defect or syndrome</th>
<th>Frequency (%)</th>
<th>Genitourinary anomalies</th>
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<tbody>
<tr>
<td>Turner's syndrome 45X0</td>
<td>60–80</td>
<td>Horseshoe kidney</td>
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<td>Duplication</td>
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<td>Trisomy 18 (Edwards' syndrome)</td>
<td>70</td>
<td>Horseshoe kidney</td>
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<td>Renal ectopia</td>
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<td>Duplication</td>
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<td>Trisomy 13 (Patau syndrome)</td>
<td>60–80</td>
<td>Cystic kidney</td>
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<td></td>
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<td>Hydronephrosis</td>
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<tr>
<td>4p (Wolf–Hirschorn syndrome)</td>
<td>33</td>
<td>Hypospadias</td>
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<tr>
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<td>Cystic kidney</td>
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<tr>
<td>Trisomy 21 (Down's syndrome)</td>
<td>3–7</td>
<td>Renal agenesis</td>
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<td>Horseshoe kidney</td>
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Upper urinary tract
From intermediate mesoderm
Arises at 4th week of gestation
3 sequential stages;
pronephros segmented, vestigial, recedes
mesonephros unsegmented, briefly functional, develops into gonads, drains via mesonephric duct
metanephros arises in 5th week (28 days on); Bowman’s capsule to DCT arise from metanephric blastema, collecting ducts to ureter from ureteric bud. Interaction of ureteric bud with blastema stimulates productions of nephrons – reciprocal induction (Mackie and Stevens) ascent up abdominal wall completed by 10th week, appearance of urine (and bladder) week 10-12; continued production of nephrons until wk 36 (ante or post-natal)

Genes involved in renal development
WT-1 Formation of ureteric bud
Pax-2 Crucial control gene
GDNF Expressed in metanephric mesenchyme Ligand for RET receptor on ureteric bud – important for bud/mesenchyme interaction

Renal agenesis
Intrinsic defect of embryonic mesenchyme; Failed induction of nephrogenesis; or involution of multicystic dysplastic kidney
Bilateral renal agenesis fatal, but as placenta does job in utero, may survive till term. Lack of urine = 90% reduction in liquor –
leads to pulmonary hypoplasia and molding abnormalities (hypognathism etc.)
Risk of second child with bilateral renal agenesis ~ 3.5%
Unilateral renal agenesis 1:1500 live births

Renal dysplasia
Defective interaction of ureteric bud with blastema

Abnormalities of ascent
- Horseshoe: 1:400 live births
- Pelvic kidney: 1:100 – 1:500

Ureter initially solid. Recanalisation mediated by angiotensin/AT2 receptor

Lower urinary tract
Urorectal septum divides cloaca into anorectal canal and urogenital sinus at 4 – 7 weeks
Ingrowth of Rathke folds divides cloacal membrane into urogenital membrane and anorectal membrane
Allantois vestigial tube formed by folding of fetus. Obliterated to form urachus (median umbilical ligament). Defective closure leads to either fistula, sinus or cyst,
Definitive urogenital sinus (at level of urogenital membrane) elongates to form penile urethra in male
Cranial ascent of ureters and growth of bladder (endoderm) lead to formation of trigone (mesoderm) and separation of mesonephric ducts from ureteric buds (see view from behind, below)

Mesonephric ducts become ejaculatory ducts in this area
Prostate develops at end of third month from prostate urethra buds penetrating into surrounding mesenchyme. Formation complete at 15th week

Genital system
Gonadal ridges form medial to mesonephros from week 3
Migration of primordial germ cells from yolk sac week 6 to form primitive sex cords in indifferent gonads: at same time paramesonephric duct develops adjacent to MD
Male genitalia
Presence of testis-determining gene (SRY) on Y-chromosome stimulates male differentiation at around week 7
Testis determining factor (product of SRY) causes:
- Medullary sex cord development into Sertoli cells*
- Regression of cortical cords
- Tunical albuginea development
* Sertoli cells produce Mullerian inhibitory substance (MIS), causing:
  (i) Regression of paramesonephric ducts (vestiges = appendix testis and prostatic utricle)
  (ii) Production of testosterone by Leydig cells (week 9). Leydig cells formed from mesenchyme of genital ridge
  (iii) First stage of testicular descent

Mesonephric (Wolffian) duct gives rise to: rete testis, ductuli efferentes, epididymis, appendix epididymis, ductus deferens (vas), seminal vesicle and ejaculatory ducts. Development of MD under T control.

Testis descent in 2 phases:
1. MIS stimulated along gubernaculum to inguinal ligament (wks 8-25)
2. T stimulated along gubernaculum to scrotum (wks 25-30)
Vaginal protrusion of peritoneum also follows gubernaculums, taking with it layers of abdominal wall to for inguinal ligament. Processus vaginalis obliterated at birth or shortly after (patent processus vaginalis lead to congenital hydrocoele – abnormal patency if still present at one year)
External genitalia
Under influence of dihydrotestosterone
Genital tubercle elongated to form phallus
Lateral growth and infolding forms penile urethra (endoderm)
Small ectodermal ingrowth from glans to form navicular fossa
Complete at 15 weeks

Testosterone
Half-life in serum 10-20 mins
Circulating testosterone in 3 forms:
2% free bioavailable
38% albumin-bound bioavailable
60% SHBG not bioavailable
Metabolised by glucuronidation by liver – excretion by kidney

Female genitalia
Default sex differentiation is female
In the absence of SRY gene indeterminate gonad develops into ovary: cortical cords develop, medullary cords degenerate and no tunica albuginea.
Primordial germ cells embark upon first meiotic division then arrest till puberty
Cranial genital ligament forms suspensory ligament of ovary. Caudal portion (rudimentary gubernaculum) forms ligament proper and round ligament (ending in labial fold)
Without SRY mullerian duct regresses (vestiges = epioophoron, paraoophoron +/- Gartner's cysts)

Descent of ovary and intracoelomic growth of genital ridges results in upper portion of paramesonephric deviating laterally, whilst lower portion fuses in the midline to form uterus and cervix and upper two-thirds of vagina. Fusion results in formation of broad ligament on each side. Sinovaginal bulb develops at urogenital sinus to form lower third vagina. Hymen separates vagina from urogenital sinus.

Abnormalities
Kleinfelter’s
47 XXY; phenotypically male
nondysjunction during spermatogenesis (40%) or oogenesis (60%); 1:500 males;
infertility, gynaecomastia, underandrogenisation

**Turner’s**
45 X; phenotypically female
streak ovaries, infertility, no puberty (no E)

**Pure gonadal dysgenesis**
46XX; phenotypically female. Failure of migration or development of germ cells.
Normal chromosome complement but absent ovary, pre-pubertal sex characteristics and infertile

**Testicular feminization**
aka androgen insensitivity syndrome
46 XY but phenotypically female
testis and MIS therefore no ovary/uterus and blind-ending vagina. UDT common

**Androgenital syndrome**
aka congenital adrenal hyperplasia
46 XX; phenotypically male
21-OH hydroxylase deficiency = androgens with virilisation of external genitalia (clitoral enlargement and partial fusion of labia)

**Rokitansky syndrome**
agenesis of upper two thirds of vagina – failure of fusion of paramesonephric ducts. Other fusion abnormalities include uterus didelphys (+/- double vagina), bicornate uterus etc.
Paediatric renal physiology
Fetal urine production commences at 10-12 weeks gestation.
Urine production reaches 30ml/hour at 32 weeks onwards
Nephron production ceases at 36 wks
Mean number of nephrons at term ~ 700,000 to 1 million
At birth:
All children void within 24 hours, irrespective of gestational age
Impaired concentrating ability
Impaired sodium handling
Impaired acid-base regulation (Mild mixed acidosis typical in neonates, due to impaired bicarbonate reabsorption)
Low renal blood flow
GFR 12ml/min/m² (doubles by 2 weeks; ‘normal’ by 2 yrs).
Improvement in GFR multifactorial:
- Diminished renal vascular resistance
- Increasing perfusion pressure
- Improved glomerular permeability
- Increased filtration surface
Elevated serum creatinine reflects maternal levels. Decrease by ~50% in first week of life.
Compensatory hypertrophy in unilateral renal agenesis occurs in utero

Renal impairment in children
CRF in children leads to growth retardation, sexual immaturity and psychomotor or intellectual retardation
CRF defined as GFR 25-30% normal
Main causes in children
- Glomerulonephritis (focal segmental glomerulosclerosis)*
- Congenital (hypoplastic/dysplastic/reflux)
- Collagen vascular disease
- Obstructive nephropathy

* diseases a/w immune complex deposition (SLE, post-infectious membranoproliferative, not IgA nephropathy) result in low circulating complement levels

Serum creatinine at 6 months reliable indicator of outcome

<table>
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<tr>
<th>Serum creatinine, µmol/l at 6 months of age</th>
<th>Prognosis (predicted age of onset of end-stage renal disease)</th>
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<tbody>
<tr>
<td>&lt;150</td>
<td>Good</td>
</tr>
<tr>
<td>150–300</td>
<td>ESRD 10+ years</td>
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<tr>
<td>200–350</td>
<td>ESRD 5–10 years</td>
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<tr>
<td>350–600</td>
<td>ESRD &lt;5 years</td>
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<tr>
<td>&gt;600</td>
<td>Uncertain outcome</td>
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</tbody>
</table>
Visible haematuria and respiratory tract infections
After URTI Post-infectious (streptococcus etc.)
Concomitant IgA nephropathy
Alport’s hereditary nephritis

Consequences of renal failure in kids
Malnutrition anorexia, N+V
Renal osteodystrophy rickets* in young
Slipped epiphysis, long bone
abnormalities in older kids**
Anaemia impaired epo production

* rickets = rachitic rosary (prominent costochondral joints), metaphysical widening, frontal bossing, craniotabes (abnormal softening of skull bones)
** often varus/valgus deformities. X-ray features = subperiosteal resorption, ground-glass mottling, focal lucency or sclerosis. Also heterotopic calcification

Resuscitation in children
20ml/kg fluid bolus
4ml/kg/hr maintenance infusion

Antibiotic treatment in kids
4ml/kg gentamicin IV
4mg/kg timethoprim PO
2mg/kg trimethoprim PO prophylaxis

Bladder compliance
3 components:
(i) Bladder unfolding
(ii) Elasticity
(iii) Viscoelasticity

Elasticity Property of a body or substance that enables it to resume its original shape after a distorting force is removed
Viscosity Resistance of a subject to flow – related to the concept of shearing force. Usually different layers of a fluid exerting a shearing force on each other
Paediatric radiology

USS  Expected bladder capacity
    < 1 year   Weight in kg x10
    Alternatively Holmdahl formula (ml)
                38 + (age in mo. x 2.5)
    > 1 year   Koff formula (ml)
                (age+2) x 30
Significant residual volume if >10% expected capacity
Bladder wall thickening highly suggestive of BOO
AP diameter > 10mm suspicious for PUJO or reflux
Liver usually brighter than kidney, except in first 3 months, with
infection or end-stage kidney

MCUG  Requires catheterization for filling, followed by removal and voiding
NICE recommends 3 days oral antibiotic cover for MCUG
Gold-standard for reflux; only way of imaging urethra, but high
radiation, distressing and UTI
Steep oblique/lateral views to exclude valves in boys
Entire penile urethra needed to exclude anterior lesions (rare)
May be substituted for indirect MAG-3 cystography, which a/w low
radiation and not as distressing, but low sensitivity for lower grades of
reflux and requires co-operative kids. Best reserved for follow-up

DMSA  99-tecnetium labeled dimercaptosuccinic acid
Scintigraphy or renography
Gold-standard for scarring – typically polar areas of decreased
uptake; also good for ectopic kidneys
Initial injection followed by scan at 3-4 hours
Relative uptake should be equal within 10% tolerance
False positives in acute infection – transient ‘nephronia’: allow 8
weeks after infection for DMSA to be accurate

MAG-3  99 metastable technetium labeled dimercaptoacetyltriglycine
99-tecnetium manufactured in a cyclotron
90% MAG-3 filtered, 10% secreted cf. filtration only with DTPA
(diethylenetriaminepentaacetic acid) - therefore good signal to
background ration and easy to interpret curves.
Better for patients with renal impairment but still unreliable if GFR <
15ml/min
Dynamic renography
0-10 secs Vascular phase
10secs – 5mins Uptake phase
    (used to calculate split function)
5 mins onwards Excretory phase
Diuretic administration
Maximum effect of frusemide after 18 mins
Therefore maximum effect at 38 mins on standard F+20
Equivocal rate of 15% for F+20; most accurate F-15 (reduces
equivocal rate to ~7%) but difficult to perform
Interpretation

I  Normal
II  Obstructed
IIIa Hypotonic (Baggy)
IIIb Equivocal
IV  Delayed decompensation (Homsey’s curve) – obstruction with increased urinary flow

NB.  F-15 renogram recommended for Type IIIb and IV curves

CT  Excellent for renal lesions (trauma and tumour). Better for pulmonary mets than MRI

MRI  Better for pelvic tumours, bony metastases and intraspinal extension
      Gadolinium for vascular tumours

*99-Technetium extracted from molybdenum 99 generator; half-life 6 hours