Disorders / Differences of Sexual Development in the Neonatal Period

Introduction

- Any suspected diagnosis of Disorder/Difference of Sexual Differentiation (DSD) should be considered a psycho-social and potential medical emergency. DSDs should be identified and diagnosed early in the neonatal period in order to:
  - Diagnose congenital adrenal hypoplasia before the occurrence of adrenal crisis;
  - allow parents to make informed decisions about assigned gender and potential treatment/management options;
  - enable the child to go through infancy and childhood with a positive body image and gender identity;
  - provide genetic counselling;
  - identify those at increased risk of developing a gonadal tumour.
- Prevalence of atypical genitalia as high as 1:300 but prevalence of those requiring specialist input in neonatal period is 1:3000. Prevalence of those in whom sex assignment is delayed is as low as 1:11,000.

Which newborns should be investigated?

- Sex assignment not possible at birth due to appearance of genitalia
- Phenotypically male infant ≥28/40 or ≥1500g with an EMS (External Masculinization Score) <11/12 or EGS (External Genitalia Score) <10.5; including:
  - Isolated perineal hypospadias (any gestation/weight)
  - Isolated bilateral undescended testes
  - Isolated micropenis (stretched penile length <22.5mm)
- Cliteromegaly (>8mm) in a phenotypically female infant, at any gestation/weight
- Genitalia appearance at birth inconsistent with prenatal genetic test to determine sex
- Radiological findings (which could be incidental) that suggest incomplete or abnormal development of the reproductive organs (eg: absent uterus in a female infant)
- Family history of DSD in specific instances (genetically inherited conditions)
- Hypospadias in the presence of significant family history of hypospadias

Male infants with isolated glandular or mid-shaft hypospadias and/or with isolated unilateral inguinal/undescended testes do not require investigations for DSD.

History, examination and first actions in suspected DSD

- The midwife or SHO or ANNP who identifies possible DSD should contact the Registrar and Consultant as soon as possible
- Parents should be counselled by a consultant; both parents should be present if possible, and as part of the discussion the infant's genitalia should be examined with the parents

- The regional DSD service should be involved early; the role of the neonatologist is to provide an initial explanation to parents, to initiate first line investigations and to deliver medical management of the unwell infant
- Initial discussions can be with paediatric endocrine team at RACH Dr Kanukamala/Dr Ismail however there is no out of hours cover so if unable to contact go directly to GOSH

History:

- Pregnancy history:
  - Antenatal scan results
  - Drug history (particularly androgens, teratogens)
  - Result of any genetic investigations undertaken in pregnancy (including genetic determination of sex)
- Family history: the presence of any of these family history markers should lower the threshold for investigation
  - Consanguinity
  - Stillbirth, multiple miscarriage, fertility problems
  - Genital abnormalities, hernias, delayed puberty, genital surgery
  - Unexplained deaths
  - Steroid replacement

Examination (document the following:

- Fusion of labioscrotal folds
- Size of phallus
- Site of the urinary meatus on the phallus or in relation to the phallus (true site of the urinary meatus may not be identifiable on clinical examination)
- Presence and location of testes on palpation
- Presence of hyperpigmentation
- Full systems examination & review for possible dysmorphism (25% of cases of XY DSD are part of a complex multisystem condition
- Birth weight – DSD is associated with low birth weight and IUGR

Clinical examination findings can be used to generate an External Masculinization Score (EMS) or External Genitalia Score (EGS) (see Appendices)

Normal external genital examination findings in the newborn:

Female

- Vaginal opening fully visible (3 to 4 mm slit or still at orifice with heaped up mucosa, i.e. no posterior labial fusion); posterior pole polyp is normal.
- Clitoris width 2 to 6 mm
- Absence of palpable gonads in the labia majora or in the inguinal region.

Male

- Fully fused scrotum
- Penis of normal stretched length (2.5 to 5 cms) and diameter (0.9 to 1.3 cms)

- Urethral meatus located at tip of glands (which may be inferred by a fully developed foreskin) with no additional urethral openings
- Fully developed foreskin (encloses the glans penis, ie no “hooded” or partially open appearance)
- Bilateral testes of normal size (8 to 14 mms) located within the scrotum on palpation

Examination tips for measuring the genital tubercle:

- To measure penile length, depress any suprapubic fat and make a measurement of the stretched penis from its base to the tip of the glans on the back of the penis. Do not include excess foreskin. Width of the stretched penis is measured at the midshaft.
- The shaft of the clitoris can be gently compressed between the thumb and forefinger to exclude excess skin from the measurement.

First-line Investigations:

Check bottles for investigation on Brighton and Sussex Pathology Website or phone the biochemistry lab if necessary to look up processes (e.g. bottles to use, timing, where to send, how to label)

- **Urine collection:**
  - Request “urine steroid profile”
    - Must be in a plain (white lidded, no additives) bottle or container
    - **Obtain before commencing any steroid therapy (very important)**
    - At least one spot urine sample (minimum 5ml, preferably >10ml) or ideally 24h collection (accounts for fluctuations in metabolites during the day)
    - Send to the biochemistry lab on a yellow form marked as urgent
    - Samples are sent away to the referral lab at Frimley Park Hospital, where the expected turnaround is 7 days
    - Be aware that urine samples can be frozen and additional investigations ordered later – consider doing this before beginning any steroid replacement, if possible
- **Serum biochemistry:**
  - **17 hydroxyprogesterone** (17OHP)
    - should be sent in a 1ml red top bottle (without gel)
    - ideally after 36 hours of life, as before this time it is unreliable and may be falsely elevated in prematurity or conditions of stress
    - rare forms of CAH may also present with depressed 17OHP levels
    - Samples are sent to Frimley Park Hospital expected turnaround is 10 days
  - **Plasma glucose and U&E – monitor daily until at least day 5**
    - Send glucose in a grey top (fluoride oxalate) bottle
  - **Cortisol and Short-synacthen**

IF COMMENCING STEROIDS IN SUSPECTED CAH

Please test for 17OHP (even if <36h of age), testosterone, androstenedione, renin activity and aldosterone in that order of priority BEFORE commencing steroids

(Request is sent on a yellow form to biochemistry)

- 17OHP, testosterone and androstenedione: 2.5-5ml required; can be sent together in one adult gold top (clotted) bottle. Testosterone is processed RSCH with a same day turnaround. Androstenedione is sent to the referral lab at Frimley Park Hospital, where the expected turnaround is 12 days

- Renin, aldosterone: 2.5ml required; can be sent together in one adult or 2 paediatric purple top (EDTA) bottles. These are sent to the referral lab at Frimley Park Hospital, where the expected turnaround is 10 days

- **Serum genetics:**
  - Rapid FISH for X and Y chromosomes
  - Karotype
    - Send minimum 2ml in a lithium heparin bottle, samples cannot be frozen & need to reach the genetics lab preferably within 24h of sampling
    - Turnaround time for Rapid FISH X/Y chromosomes is usually 2 days
    - Turnaround time for Karyotype is 4-7 days
  - DNA storage and genomic testing
    - 2-3ml in an EDTA bottle
    - Obtain consent & send a sample without requesting a specific investigation at this stage, unless instructed by the regional DSD service

Samples should be sent to our pathology department. They are couriered to the genetics reference laboratory at Guy's Hospital, London. Take samples in the morning Monday-Thursday and speak with the send-away team. The genetics service has a website with links to forms and samples.

- **Imaging:**
  - **Ultrasound**
    - USS should include the adrenals, kidneys, pelvis, inguinal regions +/- labioscrotal folds.
    - The uterus, ovaries, and adrenals are usually identifiable on USS. Intrabdominal testes and streak gonads can be difficult to identify on USS

Further investigations should be taken under guidance from the regional DSD service*.*

Communication tips:

- Use language carefully:
  - Parents' recollections of initial conversations with professionals may have long lasting effects upon them.
  - Use language that reflects "diversity", "variation", "difference" etc
  - Beware the term "ambiguous genitalia" – the term "atypical genitalia" is recommended instead
- Consider the appropriate environment & person to speak with parents:
  - Use a quiet and peaceful setting for discussions, and avoid interruption
  - Access translation services if needed
  - Be very careful of confidentiality; eg: a family translator is not appropriate
  - Parents should be counselled by a consultant, who should be the one to explain the next steps in investigations and management
  - For consistency, it is better for parents to hear investigation results from one (or as few as possible) individual(s), ideally a consultant
- What to avoid:
  - Do not guess the sex of the baby. Bonding to the infant by parents may be seriously impaired if the professionals change their mind about the sex
  - Please avoid off-handedly sharing important investigation results with parents
  - Do not breach confidentiality
- Written communication:
  - Provide written information to parents
  - Document a summary of the discussions with parents, and give a copy to parents and copy into the Badger discharge letter – this record is invaluable to the DSD tertiary service
- Practical advice for families:
  - Parents have 6 weeks to register the birth of their baby (which includes sex, name) and need not rush to name their baby.
  - Parents should be advised not to attempt to register the baby's birth before the sex has been determined
- Resources for families:
  - dsdfamilies.org
  - livingwithcah.com
- Referral for counselling and support to social worker or counsellor may be helpful

APPENDIX 1

External Masculinisation Score (EMS)

Scrotal Fusion	Scrotum fused = 3 Scrotum unfused = 0		
Micropenis	Normal penis = 3 Micropenis = 0 (defined as <25mm rounded to the nearest 5mm)		
Urethral Meatus	Normal = 3 Glandular = 2 Penile = 1 Perineal = 0		
Left gonad	Scrotal = 1.5 Inguinal = 1 Abdominal = 0.5 Absent = 0	*Right gonad*	Scrotal = 1.5 Inguinal = 1 Abdominal = 0.5 Absent = 0

98% of newborn boys will have an EMS of 12/12;
EMS < 11/12 in a term, phenotypically male infant warrants investigation for DSD

APPENDIX 2

External Genitalia Score (EGS)

Labioscrotal Fusion	Fused = 3 Posterior fusion = 1.5 Unfused = 0
Genital tubercle length	>31mm = 3 26-30mm = 2.5 21-15mm = 1.5 10-20mm = 1 <10mm = 0
Urethral Meatus	Top of the genital tubercle = 3 Coronal glandular = 2.5 Along the genital tubercle = 2 At the base of the genital tubercle = 1.5 Labioscrotal = 1 Perineal = 0

Left gonad	Labioscrotal = 1.5 Inguino-labioscrotal = 1 Inguinal = 0.5 Impalpable = 0	*Right gonad*	Labioscrotal = 1.5 Inguino-labioscrotal = 1 Inguinal = 0.5 Impalpable = 0

Normal EGS for a female infant is 0/12; this is not dependant on birthweight or gestation, or age from 0-24 months

Normal EGS varies in male infants dependant on gestation and birthweight (see table below):

Gestational age (weeks)	Median	P10	P90
<28	10	8.6	11.5
28-32,9	11.5	9.2	12
33-36,9	11.5	10.5	12
>37	12	10.5	12
Birth weight (g)	Median	P10	P90
<1000	10	8.7	11.9
1000–1499	11.5	8.4	11.5
1500–2499	11.5	10.5	12
2500–4000	12	10.5	12
>4000	12	10.8	12
Age (months)	Median	P10	P90
0–1	12	10.5	12
1–6	12	11.5	12
6–12	12	11	12
12–24	12	11.9	12