Disorder of Sex Development (DSD) Assessment of a neonate.

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1.0 Purpose

To guide initial investigation and management of a newborn baby with a suspected disorder of sex differentiation (DSD)

For initial investigations out with the newborn period please refer to the guideline covering initial investigations of DSD presenting after the newborn period.

2.0 Scope

For use by paediatricians and health care professionals involved in the care of newborn babies at SCRH, RHCYP and St John's Hospital.

3.0 Definitions

Disorder or difference of Sex Differentiation DSD / Ambiguous genitalia

4.0 Roles and responsibilities

Insert text here

5.0 Main content

Introduction:

Sensitive communication is paramount- please ensure that you have read the information about speaking with parents on the SDSD website before meeting with the family

https://www.nn.nhs.scot/sdsd//wp-content/uploads/sites/27/2021/04/SDSD-Neonatal-Pathway-V3-March-2021.pdf

Investigations and management should be consultant led.

Background:

Disorders or differences of Sex Development (DSD) are a heterogenous group of rare conditions which occur at an approximate rate of 2-3 per 1000 births. DSD can present in a variety of ways one of the most common presentations is that of atypical genitalia in the newborn period.

There are three broad groups: sex chromosome DSD, 46,XY DSD and 46,XX DSD.

Sex chromosome DSD

Sex chromosome DSD includes conditions such as 47,XXY (Klinefelter syndrome and variants), 45,X (Turner syndrome and variants), 45,X/46,XY (mixed gonadal dysgenesis) and 46,XX/46,XY (chimerism). These are sometimes diagnosed antenatally with confirmation of the diagnosis after birth. Antenatal diagnosis allows for focussed evaluation of the other complications associated with these disorders, for example, cardiac anomalies in Turner syndrome. It also provides the opportunity to offer counselling to families prior to the birth.

46,XY DSD

46,XY DSD has three broad categories:

- disorders of gonadal (testicular) development
- disorders in androgen synthesis or action
- other causes, including hypogonadotropic hypogonadism, cryptorchidism and isolated hypospadias. They are a heterogeneous group of disorders, where the phenotype is consistent with reduced male sex hormone action.

46, XX DSD

46, XX DSD encompasses disorders of gonadal (ovarian) development, such as gonadal dysgenesis and disorders secondary to androgen excess.
Most commonly, the high levels of androgens responsible for virilisation in 46,XX DSD patients are secondary to production by the foetal adrenal glands. Congenital adrenal hyperplasia (CAH) caused by deficiency of 21 hydroxylase enzyme is the most common disorder seen.

When a baby is born with a DSD it is important to diagnose treatable life-threatening conditions such as CAH and establish a diagnosis to allow sex assignment in a timely manner.

Initial

The multidisciplinary team should be involved early to support the family and staff and provide clear information.

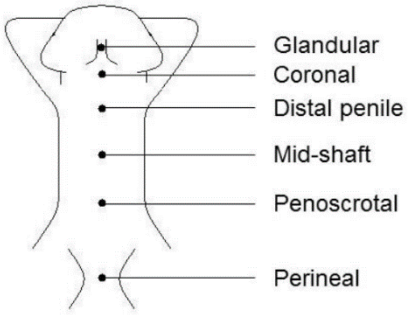
More specific guidance in supporting parents and families can be found in the SDSD Neonatal Guideline available via the SDSD website

sdsd.scot.nhs.uk/health-care-professionals/sdsd-professional-resources/

Presentation:

A child with a suspected DSD may present with one or more of these features, it is impossible to tell by looking at a baby whether they are a virilized female or under virilized male. The consultant on call should be informed about the baby if any of the following are noted:

- severe hypospadias[#]: penoscrotal (urethral opening located where the shaft meets the scrotum) or perineal hypospadias (scrotum is abnormally divided and the urethral opening is located along the centre of the divided sac)
- a bifid scrotum
- bilateral impalpable testes*
- clitoromegaly (clitoral length >0.8 cm in a term baby) or
- micropenis (penile length < 2 cm in a term baby) *See below for measurement technique and length according to gestational age.*



History and examination should be carried out by an experienced clinician.

[#]*If a patient has hypospadias that is **not** penoscrotal or perineal (termed 'mild hypospadias') and no other features of concern are present, no immediate action is required. Advise the parents against circumcision until after surgical review and refer to the Paediatric Surgery/Urology at RHCYP. A good urinary stream should be observed prior to discharge.*

**Incompletely descended (but still palpable) testis or unilateral undescended testis:*

- Term babies refer to Paediatric Surgery/Urology RHCYP for follow up.
- Preterm babies if no descent by 40 weeks (corrected gestational age) for referral to Paediatric Surgery/Urology RHCYP for follow up.

Clinical history:

- Parental consanguinity, history of salt-losing, unexplained infant deaths or DSD in relatives. These elements may indicate autosomal recessive genetic disorders associated with disturbed steroidogenesis.
- Maternal ingestion of drugs or exposure to specific environmental factors capable of inhibiting virilisation of the foetus during the pregnancy. Danazol, progestins or potassium sparing diuretics. Exogenous androgen exposure during pregnancy can also cause posterior fusion of the labia, clitoral enlargement and increased degrees of androgenisation.
- Whether the pregnancy was planned - some of the progestogen-containing drugs used for assisted-conception techniques are associated with a higher likelihood of male offspring with genital anomalies.
- In cases where parents have had some prenatal advice and discussion, it is useful to have access to these previous discussions and to seek parents' recollection of these discussions.
- Results of prenatal tests- amniocentesis /chorionic villous sampling if available.
- Social history with an enquiry about the family's social network.

Examination:

- Any dysmorphic features, in particular midline defects (suggesting abnormalities of the hypothalamic-pituitary axis), GH and LH/FSH deficiency/hypogonadotropic hypogonadism can be associated with micropenis.
- The state of hydration and blood pressure (daily measurement until formal diagnosis)
- Jaundice (conjugated hyperbilirubinaemia is associated with hypopituitarism)
- Examination of the external genitalia

1. Phallus:

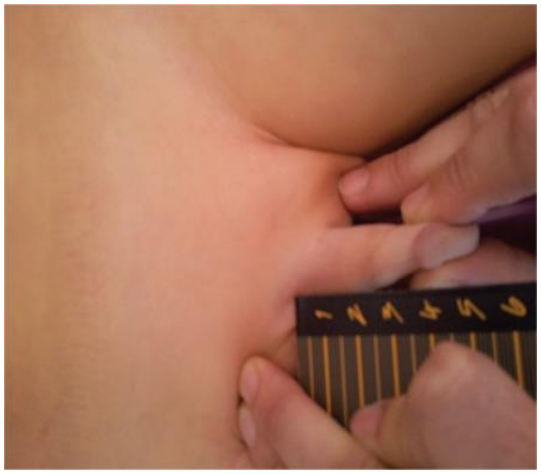
clitoromegaly (> 0.8 cm in a baby presumed female irrespective of gestation), or

micropenis (penile length < 2 cm in a term baby presumed male)

- *Endocrinology, Custer, J and Rau, R The Harriet Lane Handbook 18th edition 269-300*

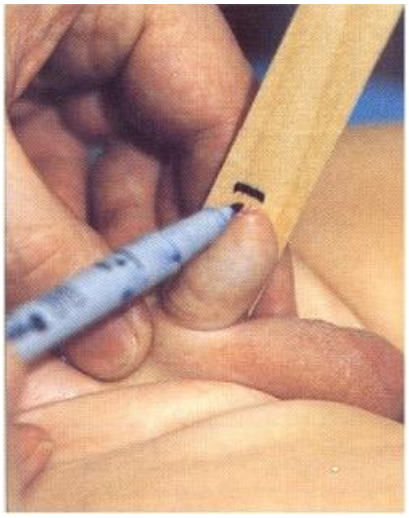
Gestation	Average length (cm) +/- 2 SDS	Mean -2.5 SD (cm)
Newborn 30 wk	2.5 +/- 0.4	1.5
Newborn 34 wk	3.0 +/- 0.4	2.0
Term	3.2 +/- 0.4	2.5-2.4
0-5 months	3.9 +/-0.4	1.9

Penile length should be measured when the penis is fully stretched, the glans penis should be held with the thumb and forefinger, and the measurement should be taken from the pubic ramus to the distal tip of the glans penis over the dorsal side. The suprapubic fat pad should be pressed inwards as much as possible.



Hatipoglu and Kurtoglu J Clin Res Pediatr Endocinol Dec 5(4): 217-223

- It may be helpful to use a tongue depressor, mark the stretched penile length and then measure in cm.



A dorsal length measurement of the phallus. Reproduced from Arch. Dis. Child. 2006;91;554-563 and J. Pediatr. 2007; 83(5):441-6

2. Palpation for gonads or swellings in labioscrotal fold or inguinal region.

- There are various scoring systems available to assess the external genitalia. We recommend the use of the External Masculinising Score initially, shown below. This is useful to tell the Endocrine team when referring the patient. A normally masculinised male score is 12.
-

Score	Scrotal fusion	Micropenis	Urethral meatus
3	Yes	No	Normal
2	-	-	Distal
1	-	-	Mid
0	No	Yes	Proximal

Score	Right testis	Left Testis
1.5	labioscrotal	labioscrotal
1	inguinal	inguinal
0	impalpable	impalpable

Referral Process:

Same day referral to the Endocrinology Team at RHCYP who will access DSD MDT.

- Within working hours: bleep Endocrine Registrar on 9187
- Out of hours contact Endocrine Consultant via switchboard.

Communicating with parents when sex is uncertain (see also the SDSD website for guidance).

If there is uncertainty about the sex of the baby, explain to the parents that it is not possible to tell whether their infant is a girl or a boy. Do not guess the sex, or even voice your suspicions as this can be unhelpful to the parents. It is extremely difficult to 'change' the sex of a baby in the light of results if the parents have started to adjust to the baby being a particular sex. It may be helpful to have a discussion with the child's parents about whether they want to name their baby or not at this stage; some parents will have a preference about how their baby is referred to. It is helpful to discuss with parents who they want to tell of their child's birth to optimise parental support and coping. A single room would allow more frequent private discussions, however, there are counselling rooms that can be used for private discussions away from the Ward or Neonatal Unit. Registration of the birth must be delayed until the sex has been assigned, registrations up to 30 days are routine and an extension can be requested if needed.

The baby should be referred to as 'your baby' or 'the baby' or 'they' but not 'it', 'he' or 'she' and a white generic cot card (not blue or pink) can be used.

Clinical psychology support should be offered to the parents of every newborn where sex assignment is delayed.

The Neonatal Family Wellbeing Team have enhanced psychological practitioners who can provide psychological support for babies in the NNU and for up to a year after discharge. Babies can be referred by sending a referral form to mnpi.mail@nhslothian.scot.nhs.uk

Formal referral for psychological support can also be made via PPALS.

Initial

Encountering a neonate with ambiguous or different genitalia when sex has already been assigned.

In the event that the above features are picked up late, i.e at neonatal discharge check when sex may have already been assigned, there should be involvement of the senior clinician caring for the baby and urgent discussion with the endocrine team. Advise the parents that the sex of the baby is uncertain, and further assessment will need to be carried out over the next few days.

INVESTIGATION

First line Investigations

Day 1		Sample	Details	Results
Blood	Urgent QFPCR	1 ml EDTA	Send to clinical genetics Call to inform lab that sample is for urgent sex determination	Within 24 hours Monday to Friday
Blood	Karyotype/microarray	1 ml Lithium heparin		Within 3-5 normal working days
Blood	ACTH	1 ml EDTA to lab immediately	Inform lab	If high suggestive of problem with steroidogenesis
BG	Pre feed BG			If low may indicate hypoadrenalism/ GH deficiency
Urine dipstick	Protein			May indicate DSD associated with renal anomalies (e.g. WT1 mutation)
Imaging	USS pelvis		To assess position of gonads / presence of internal Mullerian structures	Please note that uterus is small and often difficult to see on USS if it is not seen this does not mean that it is absent

Second line investigations- please discuss with RHCYP Endocrine Team as will depend upon clinical presentation

	Test	Sample	Comments
Blood	U+Es Cortisol	Lithium heparin sample 0.6 ml	Continue to check daily U+Es for neonate with suspected congenital adrenal hyperplasia – rising potassium and low sodium suggestive of salt loss.
Blood	Glucose	Fluoride oxalate 0.2 ml	Low BG may indicate adrenal problem / GH deficiency
Blood	Androgen profile: 17 OHP Testosterone Androstendione DHAS	Lithium heparin sample Minimum volume 2 ml	>36 hours after birth to allow the postnatal surge in androgens to subside. Please contact biochemistry to let them know that 17 OHP is urgent
Blood	Renin Aldosterone	EDTA 2 ml	Perform if potassium rises and sodium drops to under 130 nmol/l or after confirmation of CAH
Blood	LH/FSH	Lithium heparin 0.2 ml	Day 5-7 if low needs repeat after a further 7-14 days
Blood	Anti Mullerian hormone AMH	Lithium heparin 0.5 mls	Produced by Sertoli cells - indicates testicular tissue present
Blood	TFTs GH PRL	Lithium heparin	Complete other pituitary function tests if indicated Random GH within 6 weeks of birth expected to be >10 micrograms/dL
Urine	Urine Steroid Profile	15-20ml non-sterile collection in universal container, ideally with collection starting on/after day 3 (72 hours)	Give as much clinical detail as possible to aid interpretation of results

Further investigations to identify the cause of DSD:

- hCG stimulation test,

In the normal male child HCG increases testicular secretion of testosterone. This test examines the capacity of the Leydig cells to respond to HCG and secrete testosterone. It is used to detect functioning testicular tissue in some cases of undescended testes. It can also be useful in the differential diagnosis of male hypogonadism, androgen insensitivity and inborn errors of androgen synthesis.

HCG cross reacts with LH in most assays and so if samples for LH are to be taken this should be done before the HCG is administered.

Three doses of IM HCG 1500 IU are given on three consecutive days.

	10 am	Blood
Day 1	IM HCG 1500 IU	Pre-test sample LiHep 3.0 ml Testosterone DHT Androstendione
Day 2	IM HCG 1500 IU	
Day 3	IM HCG 1500 IU	
Day 4		10 am post-test sample LiHep 3.0 ml Testosterone DHT Androstendione
Day 5		10 am post-test sample LiHep 3.0 ml Testosterone DHT Androstendione

- DNA analysis, DSD panel provided by genetics laboratory in Glasgow using electronic referral form available on endocrine shared drive.

- Imaging by Laparoscopy/Genitogram/Genitoscopy if required following assessment by the surgical team.

Initial

Websites

Scottish DSD network

DSD Families - An information and support resource for families with children, teens and young adults who have a DSD

Information Leaflets

The following information leaflets are available on the Scottish DSD network website:-

SDSD Network Information Leaflet on Hypospadias
SDSD Network Information Leaflet on Congenital Adrenal Hyperplasia (CAH)
SDSD Network Information Leaflet on Undescended Testes
SDSD Glossary of Terms

The following information leaflets are available on the DSD Families website:-

When your baby is born with genitals that look different… The first days

Anticipatory timeline for the medical care of DSD children and young adults

Who's who in the medical team
Sex assignment

6.0 Associated materials

Please list here

7.0 Evidence base

Ahmed, S.F., Achermann, J.C., Wiebke, A., Balen, A.H., Conway, G., Edwards, Z.L., Elford, S., Hughes, I.A., Izatt, L., Krone, N., Miles H.L., O'Toole, S., Perry, L., Sanders, C., Simmonds, M., Watt, A. and Willis, D. (2016). Society for Endocrinology UK guidance on the initial evaluation of an infant or adolescent with a suspected disorder of sex development (Revised 2015). *Clinical Endocrinology*, **84**, 771-88.

Ahmed, SF and Rodie M. (2010). Investigation and initial management of ambiguous genitalia. *Best Practice and Research in Clinical Endocrinology and Metabolism*, **24**, 197-218.

Hatilpoglu, N and Kurtoglu, S (2013) Micropenis: Etiology, Diagnosis and Treatment Approaches. *J Clin Res Pediatr Endocinol* Dec 5(4): 217-223.

8.0 Stakeholder consultation

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9.0 Monitoring and review

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