MCN for Neonatology
West of Scotland
Neonatal Guideline

Disorders of Sex Development (DSD):

Management of Atypical Genitalia & Suspected DSD in the Neonate

This document is applicable to all medical, nursing and midwifery staff caring for the newborn in hospital or the community. The main focus of this document is on the management of the child with suspected disorder of sex development (DSD).

Contents

A. Introduction

Disorders of sex development (DSD) are relatively rare conditions with diverse pathophysiology. These conditions are very heterogeneous and can present in a variety of different ways, most commonly with atypical genitalia in the newborn period or as a disorder of puberty in adolescence (Appendix 1). These clinical situations can often be difficult to manage, particularly when sex assignment is difficult. The needs of each individual patient must be fully considered, along with the needs of their families and cultural practices. The multidisciplinary team should be involved from an early stage. Families should be provided with as much information as possible (Appendix 3).

B. Incompletely descended testes or unilateral undescended testes

If a patient presents only with palpable but incompletely descended testes or with an isolated unilateral undescended testis, send a letter to the GP and ask them to re-check them at the 6 week check and refer to Paediatric Surgery or Urology if warranted.

C. Mild hypospadias

If a patient has hypospadias that is **not** penoscrotal or perineal 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 Urology Team at RHC. A good urinary stream should be observed prior to discharge.

D. Suspected disorder of sex development

A child with a suspected DSD may present with one or more of these features:

- severe hypospadias
- a bifid scrotum
- bilateral impalpable testes
- clitoromegaly, or
- micropenis

E. Communicating with parents when sex assignment is uncertain

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. The baby should be referred to as 'your baby' or 'the baby' but not 'it', 'he' or 'she' and a 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. Please contact the Clinical Psychology Service at RHC, Glasgow on 0141 451 6574 (Tue, Wed, Fri am) or 0141 232 4333 (Mon, Thu, Fri pm).

F. Encountering a neonate with suspected DSD on a postnatal check

In the event that the above features are picked up late, i.e at neonatal discharge check when sex may have already been assigned, the neonatal consultant on-call should be informed on the day so that the concerns regarding the baby can be conveyed to parents. 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.

G. Initial Investigations in a case of suspected DSD

- The neonatal consultant on call should be informed about the baby.
- History and examination should be carried out by an experienced clinician (Appendix 2).
- The patient should be discussed during working hours with the Endocrine Registrar at the Royal Hospital for Children (RHC), Glasgow, who can be contacted on bleep number 18301, and who will liaise with the Endocrinology Consultant on-call.

First Line Tests

Sample	Test	Why do you do it?	How do you do it?	Where does it go?
Blood	QF-PCR	This test will identify the presence or absence of the Y chromosome which will help with sex assignment	Send EDTA sample. Contact the Duty Geneticist, Molecular Genetics lab (59310) to say the request is urgent. Although the lab has a 3 day turnaround time for this test, a QF-PCR will usually be available within 24 hours, if received before 3pm. **Important:** 1. Tick 'Unknown' box for sex 2. In Clinical Details box, state '?DSD, for urgent sex determination	Queen Elizabeth University Hospital Genetics laboratories
Blood	Karyotype / microarray	This test will confirm the presence or absence of the Y chromosome identified by QF-PCR and provide further information on chromosomal rearrangements	Send Lith Hep and EDTA samples as soon as possible. Contact the Duty Geneticist, Cytogenetics lab (59323) to say the result is urgent. Detailed processing usually takes at least 3-5 days. **Important:** 1. Tick 'Unknown' box for sex 2. In Clinical Details box, indicate '?DSD, for urgent genetic sex determination	Queen Elizabeth University Hospital Genetics laboratories
Imaging	USS Pelvis	This test can identify the presence or absence of Mullerian structures and help with sex assignment	Discuss with the duty radiologist at local hospital for an urgent scan	If a transfer is planned to RHC then liaise with Endocrine Team

Second Line Tests - These tests should be performed after discussion with RHC Endocrine Team and will depend on the clinical presentation

Specimen	Investigations	How do you do it?	Where does it go?
Blood	UE, cortisol	Lithium heparin sample after day 3.	Local laboratory
Blood	Glucose	Fluoride oxalate	Local laboratory
Blood	Androgen profile (which includes 17-OH progesterone, testosterone, androstenedione)	Lithium heparin sample (2ml). Ideally take >36 hours after birth to allow the postnatal surge to subside. Contact Duty Biochemist (89060) to inform of sample sent	Local Lab who will send to GRI Biochemistry labs
Blood	AMH, FSH, LH	Lithium heparin samples (2ml)	Queen Elizabeth University Hospital Biochemistry labs
Blood	Store sample for ACTH, DHAS	EDTA (minimum 2ml)	Queen Elizabeth University Hospital Biochemistry labs
Urine	Steroid profile	15-20ml non-sterile collection in universal container, ideally with collection starting on/after day 3 Give as much clinical details as possible to aid interpretation of results	Local Lab who will send to GRI Biochemistry labs

Further investigations to identify the cause of DSD (Appendix 3) :-
- hCG stimulation test, this will normally be carried out at RHC
- DNA analysis
- Imaging by Laparoscopy/Genitogram/Genitoscopy

H. Time frame for results

The process of bringing together some of the initial information usually takes about 5 working days. If the karyotype is complicated, laparoscopy may be required, and the process may take longer and often up to 2 weeks. It is important to try to avoid burdening the parents with too much information during the process, as this may give conflicting messages about the sex before the full conclusions are reached. This is especially true where some investigations such as ultrasound maybe difficult to interpret in a newborn. Although it is important to explain why tests are being done, it is probably best to try and bring things together for the parents once all the information is available. To this end it is helpful to have a surgical opinion early, as this gives a view of the long-term anatomical possibilities. Results will be explained to the family by a consultant member of the DSD team. Different parents will have different information needs and therefore all information given should be individualised.

I. Follow-up arrangements

Depending on the case, ongoing management may require the help of several members of the DSD MDT. The extent and frequency of this will be decided by the DSD team prior to discharge in the more complex cases. As a default, all cases of suspected DSD should be reviewed at the second Monday of the month clinic held by Prof Ahmed at RHC which is also attended by Dr Ruth Hind from Clinical Psychology and Dr Ruth McGowan from Clinical Genetics.

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Document Title

WoS_DSD_Neonates

Implementation / Review Dates

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Appendix 1

Biology of DSD

Primordial germ cells migrate to the genital ridge from the yolk sac at approximately 6 weeks of gestation in the human embryo. Wilms Tumour 1 (WT1) and Steroidogenic Factor 1 (SF1) genes result in the development of bipotential gonads from these cells.

Usually, if a Y chromosome is present, the development of Mullerian structures is inhibited by the production of a glycoprotein called Anti-Mullerian Hormone (AMH). With the production of testosterone by the Leydig cells, the mesonephric (Wolffian) duct increases in size and differentiates into the epididymis, vas deferens and prostate. 5-dihydrotestosterone (DHT) is produced by the conversion of testosterone by the enzyme 5α-reductase, resulting in the development of male external genitalia and testicular descent. If there is no Y chromosome present, the Mullerian structures usually develop into female internal genitalia and ovaries develop. The absence of DHT also results in the development of female external genitalia. There are many factors involved in the differentiation of the sex organs into male or female and there is potential for a disruption of this process at multiple different stages. The clinical phenotype will therefore depend on the nature of disruption.

Classification of DSD

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 often 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 and other causes, including hypogonadotrophic 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 and amongst them 21 hydroxylase deficiency CAH is the most common disorder. Androgen excess during pregnancy may be endogenous (secondary to an adrenal adenoma, dermoid cyst, Sertoli-Leydig tumour, sex cord stromal tumour or metastatic carcinoma) or exogenous (secondary to danazol, progestins or potassium sparing diuretics). Exogenous steroids taken during pregnancy can also cause posterior fusion of the labia, clitoral enlargement and increased degrees of androgenisation. Where clinically possible, mothers should be advised of the potential risks associated with taking medications which increase androgen production during pregnancy and an alternative sought.

Appendix 2 – History & Examination In Infant With Suspected DSD

A focussed clinical history should be taken from the parents, addressing the following issues:

- 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.
- 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 if available.
- Social history with an enquiry about the family's social network.

In particular the clinician should look out for:

- Any dysmorphic features, in particular midline defects (suggesting abnormalities of the hypothalamic-pituitary axis). Hypopituitarism should be considered if there is a history of hypoglycaemia/conjugated hyperbilirubinaemia.
- The state of hydration and blood pressure (daily measurement until formal diagnosis)
- Jaundice (associated with hypopituitarism)
- Urine dip for protein (associated with renal anomalies)
- Pre feed blood glucose – commence hypoglycaemia screening protocol (see neonatal guidelines)
- Examination of the external genitalia
    - Inspection - Is there more than expected pigmentation of the genitalia with a genital anomaly? If so the baby may have congenital adrenal hyperplasia (CAH)
    - Palpation for gonads or swellings in labioscrotal fold or inguinal region. If there are palpable gonads, the baby is probably a male (but don't share this opinion with parents)
    - 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.

3points	Yes	No	Normal			
2 points			Distal			
				Labioscrotal	Labioscrotal	1.5
1 points			Mid	Inguinal	Inguinal	1
0 points	No	Yes	Proximal	Impalpable	Impalpable	0
	Scrotal fusion	Micropenis	Urethral meatus	Right gonad	Left gonad	

Appendix 3 –References

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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 time line for the medical care of DSD children and young adults
Who's who in the medical team
Sex assignment

Appendix 4

SAAG was launched in June 2013 to survey the early care of newborns with suspected DSD who require specialist input from surgery or endocrinology in Scotland and relies on the generous cooperation of members of SPEG and SDSD Managed Clinical Networks. The monthly notifications are also verified with the help of the cytogenetic labs and questionnaires are also sent to parents after discharge of the notified infant from the maternity hospital. The audit has been approved as a health service evaluation by the R&D Ethics Officer of the R&D department of Greater Glasgow and Clyde and also has Caldicott approval. Regular feedback of SAAG is provided at the annual SPEG and SDSD meetings.

If you are a clinician involved in the care of newborns with atypical genitalia and would like to receive our monthly email for this audit, or you would like more information please do not hesitate to contact Dr Martina Rodie (martina.rodie@glasgow.ac.uk).