Difference of Sexual Development in neonates

Guideline Responsibilities and Authorisation

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Target Audience	Medical Officer, NNP or CNS working in NICU, registrar, SHO
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Guideline Review History

Version	Updated by	Date Updated	Description of Changes
2	David Bourchier	22/11/16	None
3	Natalie Ron	June 2022	Review of document

Difference of Sexual Development in neonates

1. Overview

1.1 Purpose

To provide guidance on initial assessment and management for babies referred to the Neonatal Intensive Care Unit and postnatal wards with Difference of Sexual Development (DSD).

1.2 Scope

Medical Officer, Neonatal Nurse Specialist, Clinical Nurse Specialist, Registrar, Senior House Officer.

1.3 Patient/client group

Neonates who present with Difference of Sexual Development.

1.4 Definitions and acronyms

Infants born with genitals that do not appear to be typically male or female, or that have an appearance discordant with the chromosomal sex

CAH	Congenital Adrenal Hyperplasia
DSD	Difference of Sexual Development
EMS	External Masculinisation
MDT	Multidisciplinary Team
NMS	Newborn Metabolic Screening
SPL	Stretched Penile Length

1.5 Classifications

Difference of Sexual Development are classified into three main groups based on the karyotype. Each main group encompasses several subgroups that indicate a specific diagnosis.

These groups are:

- Virilized XX
- Undervirilized XY
- Sex Chromosome DSD

See Appendix A for algorithm.

2 History Taking and Clinical Examination

2.1 History Taking

Terminology used is very important when communicating with families. Use gender neutral words (see table below).

Female	Gender Neutral	Male
She	Your baby/ Pēpe/They	He
Clitoris Labia	Folds	Penis Scrotum
Ovaries	Gonads	Testes
Vagina	Urethral opening	
	Sexual organs Genitalia	

Considerations during history taking

- Antenatal infections, drug exposure, teratogens during pregnancy, or maternal virilisation in pregnancy
  - Drug exposures include androgens (danazol, testosterone, synthetic progestins), or endocrine distributers (phenytoin, phenobarbital, finasteride)
  - Maternal virilisation in pregnancy (placental aromatase deficiency or maternal androgen-secreting tumour)
- Maternal family history of women unable to bear children +/- amenorrhoea
- History of consanguinity (increases risk of recessive disorders)
- Reduced male offspring in family on mothers side (suggesting X-linked inheritance)
- Previous siblings dying in neonatal period
- Previous siblings with early pubertal development

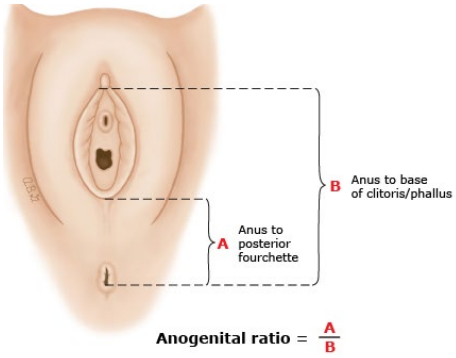
2.2 Examination

When examining neonates with DSD, consider setting of examination with additional privacy. Explain the basics of how the exam will proceed and ask parents' permission before examining. During examination, discuss findings and educate parents on anatomy.

- General full examination looking for dysmorphic features
- Blood pressure
- Evidence of dehydration or signs of hypoglycaemia
- Palpation of labioscrotal folds and inguinal regions for presence of gonads
- Number of urogenital openings
- Measurement of phallus/clitoris

- Stretch phallus to point of increased resistance, measure dorsal surface from pubic ramus to tip of phallus, stretch to point of resistance, helpful to use tongue depressor and measure

- Penile length should be >2.5cm and <4.5cm in full term infant, breadth usually ≥1cm
- Document pigmentation of genitalia
- Measurement of anogenital ratio
  - Distance between anus and posterior fourchette, divided by the distance between anus and the base of the clitoris/phallus
  - A ratio of >0.5 indicated posterior labial fusion due to androgen action
- Identify urethral opening with confirmation by observing urination



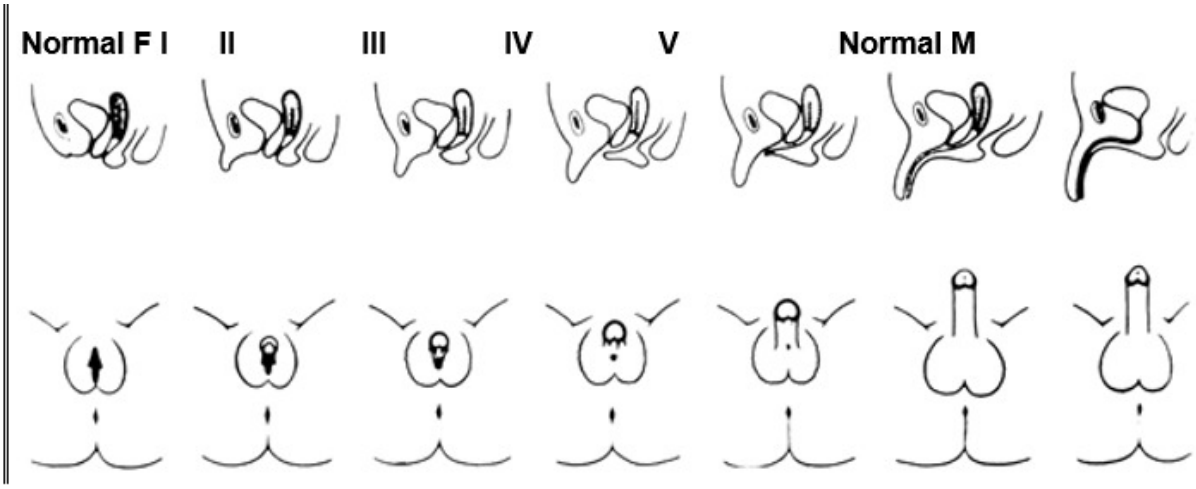


Figure 2.

Different degrees of virilization according to the scale developed by Prader

Stage I: clitoromegaly without labial fusion

Stage II: clitoromegaly and posterior labial fusion

Stage III: greater degree of clitoromegaly, single perineal urogenital orifice, and almost complete labial fusion

Stage IV: increasingly phallic clitoris, urethra-like urogenital sinus at base of clitoris, and complete labial fusion

Stage V: penile clitoris, urethral meatus at tip of phallus, and scrotum-like labia (appear like males without palpable gonads)

Prader, A. Helv Paediatr Acta, 1954. 9:230-248.

3 Management

- Initial stabilisation of newborn
- Gender neutral cot card and suggest to choose gender neutral name
- Address anxiety expressed by parents
- Delay in announcement of gender to family/friends/community
  - Can be weeks/months in some cases
- Participation from MDT
  - Endocrinologists
  - Geneticists
  - Surgeons
  - Psychologists
- Avoid assigning sex to child arbitrarily
- Use of gender-neutral language (see chart above)
- Avoid early sex-determining surgical procedure

4 Investigation

4.1 When to Investigate

- When genital appearance is disconcordant with sex chromosomes
- Combination of genital anomalies with an External Masculinasation Score (EMS) of less than 11 (See 4.1.1)
- Co-existence of systemic metabolic disorder, other malformations, or dysmorphic features
- Concerning family/whanau, maternal or antenatal history (see History taking)

In phenotypical males

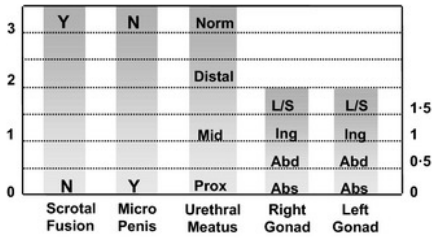
- Bilaterally nonpalpable gonads
- Severe hypospadias (perineal hypospadias)
- Familial hypospadias
- Any degree of hypospadias + uni/bilateral undescended testis +/- micropenis
- Isolated micropenis (SPL <2.5cm)

In phenotypical females

- Isolated clitoromegaly

- Posterior labial fusion
- Presence of urogenital sinus
- Gonads palpable in labioscrotal folds or inguinal regions

4.1.1 EMS Scoring



Calculating the external masculinization score (EMS) provides an objective aggregate score of the extent of masculinization of the external genitalia. Each individual feature of the genitalia (phallus size, labioscrotal fusion, site of the gonads and location of urethral meatus) can be individually scored to provide a score out of 12. Microphallus refers to a phallus below the male reference range. *L/S= labioscrotal; Ing= inguinal; Abs= abdominal or absent on examination.*

4.2 First Tier Investigations

Investigations should only be taken with informed consent by whanau/family.

Initial investigations should be undertaken to define sex chromosomes and delineate by pelvic ultrasound, the internal genitalia and exclude life threatening Congenital Adrenal Hyperplasia (CAH)

Investigation	Date	Result
Pelvic Ultrasound		
FISH analysis for karyotype • 1-2ml micro-heparin tube • "Rapid FISH for karyotype" on form		
Karyotype • 0.5ml Micro-EDTA		
Daily Glucose		
Serum 17-OH-Progresterone (17OHP)* • After 36 hours of age (Guthrie)		
Daily serum electrolytes		

*Note: Serum 17-OH-Progesterone 17OHP

- Ideally after 36 hours of age (Newborn metabolic screening - NMS)
- Can be sent early & can be analysed early -
  - call National Testing Centre to discuss on 021 745 847 (office hours)
  - email nmsp@adhb.govt.nz with NHI as reference
- Note: preterm babies have higher levels making interpretation more difficult – please include gestational age on Newborn Metabolic Screening Cards

If CAH likelihood is high, and infant needs immediate steroid replacement therapy

- Additional samples collected before starting steroids
- Sufficient volume to analyse 17OHP (*0.5ml Paediatric Micro-EDTA)*, testosterone (*0.5ml Paediatric Micro-PST)*, Androstenedione (*0.5ml Paediatric Micro-EDTA)*, Renin (*1ml Paediatric Micro-EDTA)*,
  - In that order of priority
- At least one random or 24h urine sample (>5ml) for a urine steroid profile

A virilised infant with impalpable gonads, karyotype of 46 XX, significantly elevated serum 17OHP, and presence of uterus makes diagnosis of congenital Adrenal Hyperplasia (CAH) very likely. A urine steroid profile can confirm this diagnosis.

4.3 Second Tier Investigations

To be completed only in consultation with regional paediatric endocrinologist

For infants with sex chromosomes other than 46, XX. A second tier of investigations is required to determine presence of testes and adequacy of androgen production and action. These tests are non-urgent, and should be done following discussion with appropriate teams.

May include:

- Serum Anti-Mullerian hormone (AMH)
- hCG stimulation test
- Urinalysis for proteinuria
- Further detailed imaging eg Genitogram
    - Genitogram – placement of a small catheter in the urogenital opening and injection of contrast to delineate urogenital anatomy
- Laparoscopy

5 Counselling

Parents should be appropriately counselled throughout the investigation process. Involvement of a multidisciplinary team involving endocrinologists, social workers, surgeons, geneticists and psychologists is essential. The period of time before a specific diagnosis is established can be an especially challenging time for parents. Families may experience significant stress and difficulty adjusting to the diagnosis.

Use of gender neutral language by medical and nursing teams is extremely important.

Families should be encouraged to consider postponing birth announcements describing the sex of the infant until more information is known. Birth certificates only need to be filled out by 6 weeks of age.

If the diagnosis remains unclear and will likely not occur for months, family should be offered counselling and support to postpone the birth announcement about baby's sex. Suggest family choose a gender-neutral name

Remember, and remind the family that gender and sex of rearing are not the same. Gender identity develops with age and that the child's adult gender identity is not known at birth.

Surgical management is not a key focus in the early management of DSD. Surgery should be reserved for instances of life/organ preserving procedures, to achieve continence, to manage infection or risk of infection, and reduce risk of malignancy. If the surgery can be delayed with the same outcome achieved, then it should wait until the child is old enough to be included in the decision-making process.

See "Resources" below for suggested reading for families

6 Resources

- https://dsdfamilies.org/application/files/1615/4236/8548/firstdays-dsdfamilies.pdf
- https://pie.med.utoronto.ca/htbw/module.html?module=sex-development
- https://dsdfamilies.org/application/files/4115/3780/1476/Top_Tips_for_Talking.pdf
- http://www.ianz.org.nz/
- http://www.intersexyouthaotearoa.com/

7 References

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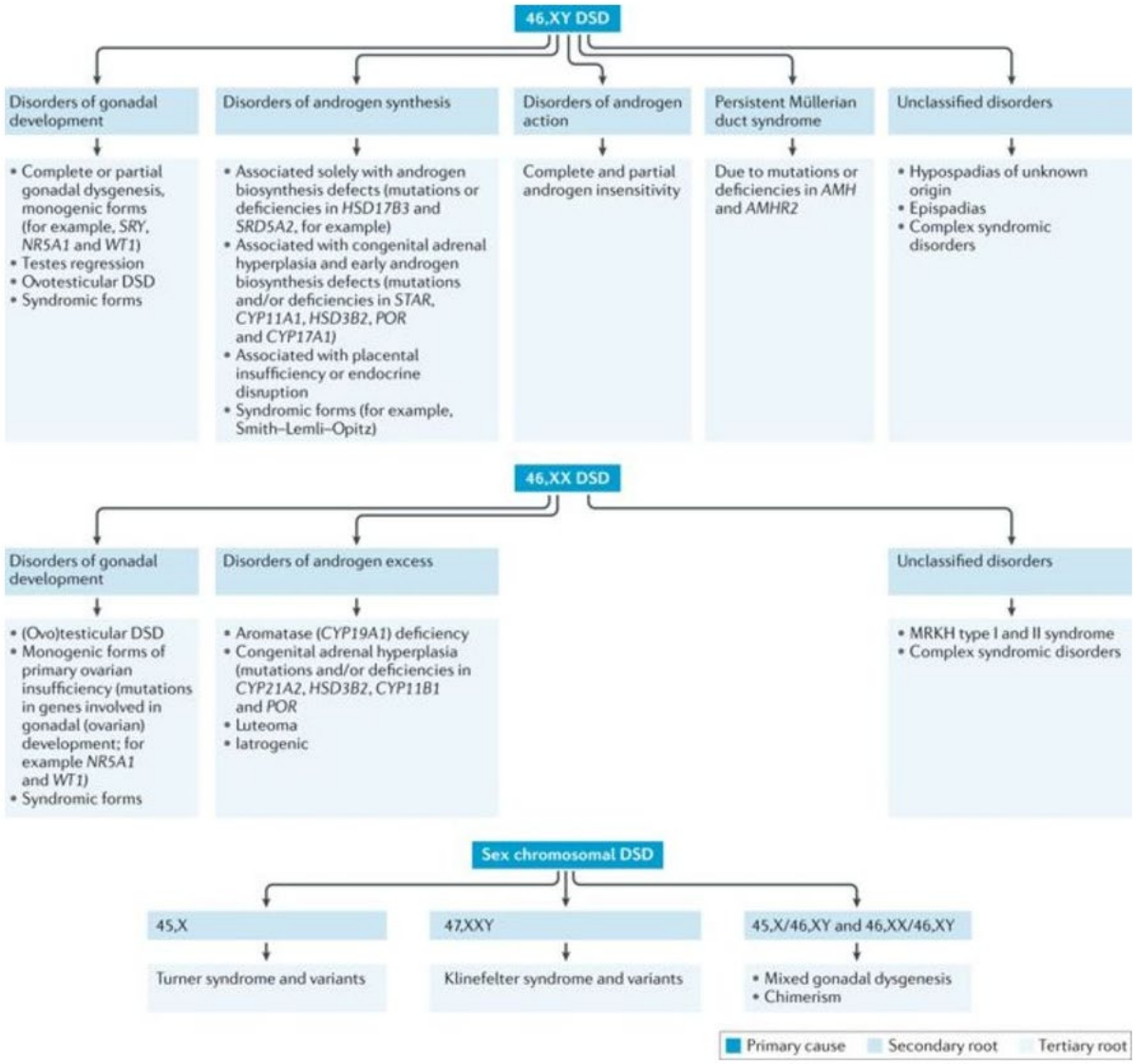
Appendix A – Difference of Sexual Development Classification



MRKH, Mayer-Rokitansky-Küster-Hauser syndrome

From: Caring for individuals with a difference of sex development (DSD): a Consensus Statement. Cools et al. Nature Reviews Endocrinology **volume 15**, pages 415-429 (2018).