Diagnosis and Management of DSD in the United Kingdom

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Conflict of interest disclosure

• Invited lectures
  – Merck
  – Sandoz
  – Diurnal

• International paediatric endocrine nurse advisory board
  – Merck
## Introduction

- Introduction to DSD
- Classification
- Embryology reminder
- Chromosomes reminder
- What is a DSD
- MDT approach in the UK
- Diagnostic process in the UK
- The CNS role in DSD
- UK statistics
- International differences
- Education and Support
What is a DSD?

• Congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical

• True genital ambiguity
  – 1 in 5000 / 1 in 4500 births

• Genital anomalies
  – 1 in 300 births
## Revised nomenclature: Chicago Consensus 2006

<table>
<thead>
<tr>
<th>Previous</th>
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<tbody>
<tr>
<td>Intersex</td>
<td>Disorders of sex development (DSDs)</td>
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<td>Male pseudohermaphrodite</td>
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<td>Undervirilization of an XY male</td>
<td>46,XY DSD</td>
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<td>XX male or XX sex reversal</td>
<td>46,XX testicular DSD</td>
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<td>XY sex reversal</td>
<td>46,XY complete gonadal dysgenesis</td>
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Classification of DSD

- **46,XY DSD (under virilised genetic male)**
  - Disorders of testicular development
    - Ovotesticular DSD
  - Disorders of androgen synthesis / action
    - Complete Androgen Insensitivity Syndrome
  - Others
    - Hypospadias

- **46,XX DSD (over virilised genetic female)**
  - Disorders of ovarian development
    - Ovotesticular DSD
  - Androgen excess
    - Congenital Adrenal Hyperplasia

- **Sex chromosome DSD (variable)**
  - Turner syndrome
  - Klinefelter syndrome
  - Mixed gonadal dysgenesis
Endocrinology in sex development
Formation of internal structures

- **Foetal ovaries**
  - Make small amounts of testosterone and AMH (anti Mullerian hormone)

- **Foetal testes**
  - Make lots of both hormones
  - The presence or absence of these hormones influences the development of the internal sex ducts:

- **Mullerian ducts**
  - Found in boy and girl foetuses, but disappear in boys when the testes make AMH (Mullerian Inhibiting Hormone)
  - Forerunners of the uterus, cervix, fallopian tubes and upper portion of the vagina

- **Wolffian ducts**
  - Found in all foetuses but disappear in girls as they have no testes to produce testosterone
  - Forerunners of vas deferens, epididymides, prostate gland and seminal vesicles
Genitalia development – 7-8 weeks

- **7-8 weeks**
  - Presence of XY chromosome
    - Triggers activation of SRY gene
    - Initiates development of a testis
    - Primary sex chords develop into Sertoli cells
      - AMH
      - Leads to regression of the Mullerian duct
  - Leydig cells produce testosterone
    - Stimulate Wolffian duct to form epididymis, vas deferens and seminal vesicles
External genitalia development

- A baby who doesn’t make a byproduct of testosterone called dihydrotestosterone (DHT) will grow a vulva

- If a baby does make DHT, they will grow a penis and scrotum

- DHT is made in our bodies when an enzyme called 5α reductase is available
  - This changes T to DHT
Different DSD

- 46 XY DSD
- 46 XX DSD
- Sex chromosome DSD
XX and XY chromosomes

- XX – genotypic female
- XY – genotypic male
- Half of sperm cells carry the X chromosome, and half carry the Y chromosome
- The SRY gene present on the Y chromosome will act as a signal for the pathway for maleness
  - Starts off virilisation
- Can also have a chromosomal arrangement that is contrary to phenotypic sex
  - XX males
  - XY females
  - Abnormal number of sex chromosomes may be present
    - DSD
Clinical Examination

• Thorough general physical examination
  – Any dysmorphic features
    • Syndromes associated with DSD
  – Signs of systemic illness
    • Metabolic problems

• Genital examination
  – Urethral opening position
  – Palpable gonads outside inguinal canal / Labio-scrotal folds
    • Usually be testes
  – Anogenital distance
  – Degree of rugosity
  – Pigmentation of labio / scrotal tissue
    • Virilisation
Clinical Rating Scales

- External Masculinisation Scale
  - Score of < 7 is considered ambiguous

- Virilisation of XX individuals (Prader)
Clinical Rating Scales

- Androgen Insensitivity (Quigley)

- Hypospadias classification
• Absence of secondary sexual characteristics in an adolescent boy
• Hypospadias
• Ambiguous genitalia at birth
• Primary amenorrhea in an adolescent child with a complete female phenotype
• Variation depends on 2 factors:
  – Degree in disturbance of androgen production or action
  – Point at which this disturbance occurs during sex development
• Anatomic presentation can be classified by using clinical rating scales
46XY- Androgen Insensitivity Syndrome

- **Complete** absence of androgen action from the time of early foetal development results in a child with a typical female external phenotype (CAIS)
- **Partial** action of androgens during foetal development causes hypospadias (PAIS)
  - Micropenis can occur
  - Cryptorchidism
- Mullerian structures may be present or absent
  - If AMH not released, then internal structures may remain as female
  - Must determine if present as will have a bearing on fertility if raised female
- Gonadal germ cell cancer risk
  - Increased in testes with impaired development and presence of Y chromosome material
    - PAIS and raised as male – strict cancer surveillance
    - CAIS and raised as female – prophylactic gonadectomy - ? Childhood / Puberty
Model Hanne Gaby Odiele reveals she is intersex to 'break taboo'

24 January 2017 | Europe

Hanne Gaby Odiele had two major operations, as a child and a teenager.

A top fashion model has revealed that she is intersex, saying that she speaking out will help break a taboo.

Hanne Gaby Odiele, 29, was born with undescended testicles, which were removed when she was 10 after doctors warned that they could cause cancer.

Intersex people are born with a mixture of male and female sex characteristics.

According to the United Nations, the condition affects up to 1.7% of the world's population.

Ms Odiele, originally from Belgium, was born with androgen insensitivity syndrome (AIS).
• **PAIS**
  - Showing minimal virilisation of phallus and genital folds
  - More virilised, where the genitalia show unfused labio-scrotal folds, but pigmentation and wrinkling more noticeable, with a larger phallus

• **CAIS**
  - Showing normal female external genitalia, but visible gonads in the groin
46XY - Persistent Mullerian Duct Syndrome

- Mutations in the gene encoding AMH
  - Lead to persistence of Mullerian duct organs in a 46XY individual
- Usually present
  - Cryptorchidism
  - Uterine remnants only apparent on examination, or later inguinal herniation
46XY Gonadal Dysgenesis

• This occurs when there is disruption in the testicular developmental pathway toward mature Sertoli and Leydig cells

• Usually leads to:
  – Small testes with poor androgen-production capacity
  – Presence of mullerian structures
  – Elevated gonadotrophins from puberty
    • Primary gonadal failure
  – Inadequate early androgen production leading to bifid scrotum and severe chordee of phallus
46XX Presentation

• Ambiguous genitalia
  – More than half of all infants born with AG are 46XX
    • Due to in utero exposure of androgens
    • Source may be adrenal (CAH) or testicular

• Complex congenital malformations
  – Cloacal extrophy, or bladder extrophy

• Gradual clitoris enlargements during childhood
  – Non classical CAH

• Abnormal developments at puberty
  – Primary amenorrhoea
    • No breast or pubic hair development (46XX gonadal dysgenesis or steroid biosynthetic defects) OR
    • Normal breast and pubic hair development (Mullerian duct agenesis)
    • Normal breast development but little or no pubic hair (CAIS)
46XX CAH

- Baby will have been exposed to excess male hormone in-utero
- The genitalia will look like a boy’s:
  - Labia will fuse to look like a scrotum
  - Clitoris enlarges and looks like a penis
- Can sometimes be so severe, sex assignment is difficult
  - Need karyotype
  - Will still have normal internal structures
  - Surgery may be needed to correct outer appearance
    • CONTROVERSIAL

- Exposure to prenatal androgens and Prader 3 virilisation at birth
- Same baby at age 8 weeks at the time of genital reconstruction, showing some regression of virilisation after starting steroid treatment
- Another baby girl with a more severe form of 21OHD, leading to more severe virilisation (Prader IV)
46XX Gonadal Dysgenesis

- Mutations in FSH receptor gene has been identified
- ‘Pure’ without features of TS
- Streak gonads are present due to germ cells not forming properly
  - Mostly composed of fibrous tissue
- Characterised by primary amenorrhoea with or without secondary sexual characteristics
46XX Mullerian Duct Agenesis

- Vaginal agenesis usually associated with an absent uterus and fallopian tubes but with normal ovarian development
  - Mayer–Rokitansky–Küster–Hauser syndrome
1 in every 20,000 males with testes has a 46XX karyotype
Translocation of SRY to the tip of one of the X chromosomes has occurred
Phenotypical similarities between 46XX men and those with Klinefelter Syndrome
- 46XX men shorter
Sex Chromosome DSD

- 46XX Ovo-testicular DSD
- Klinefelter Syndrome
- Turner Syndrome
- 45X / 46XY
46XX Ovo-Testicular DSD

- Specific type of gonadal dysgenesis
  - Presence of ovarian follicles and seminiferous tubules in the gonads
- Distribution in the gonads vary
  - 89% of ovotestes, ovarian and testicular elements are evenly distributed
- Testicular tissue undergoes atresia at a faster rate than ovarian tissue
- Phenotype varies
  - Often testis on right and ovary on left
- Small number of women can become mothers
- Paternity never reported
  - Gonad most likely to function will be the ovary
  - Gonadal cancer risk in 46XX ovo-testicular DSD is low risk
    - May be fertile oocytes
    - Spermatogenesis absent
Klinefelter syndrome 47XXY

- Affects sexual development
  - Testes don’t fully develop
    - Oligospermic
  - Lower levels of testosterone
- Taller than average
- Many men only discover this when they seek help for infertility
Turner syndrome

- Only affects girls
- Affects growth and sexual development
  - Ovaries aren’t developed properly
- In TS the second sex chromosome is either:
  - Completely absent (45,X) (Monosomy X)
  - Partially absent
  - Forms an isochromosome (isoXq), possessing a long arm duplication (q) and being devoid of a short arm (p)
  - In a ring formation (rX)
  - Is devoid of the homeobox gene, SHOX (short stature homeobox)
- Any of these variations of the second sex chromosome may occur with or without cell line mosaicism
  - Missing the X in only some of the cells
  - May have fewer symptoms
45X/46XY DSD

- Right gonad has a reasonable testis which has descended into a hemi-scrotum
- Left side gonad was intra-abdominal streak gonad
- Vaginal cavity present
- Raised a boy, gonads left insitu
- Re-presented in adolescence with a tumour arising from the streak gonad

- Wide range of phenotypes
  - 95% - normal male
    - SS and dysgenetic testes
  - Female phenotype
    - Features of TS (where karyotype has Y chromosome)
- Mixed gonadal dysgenesis
  - Asymmetrical appearance
- 75% have a uterus
- SS in 84%
  - GH therapy
- Abnormalities of urinary tract and CVS may be present
  - Similar to those of TS
Receiving a referral

• On call registrar receives a telephone call from referring Doctor from another hospital
• Alerts main DSD team
• Plan admission
  – Within 5 days if newborn
• Asks referring Dr to undertake specific investigations
• Plans investigations
  – Pelvic ultrasound, medical photography
• Clinical Nurse Specialist..
**NEW DSD REFERRAL CHECKLIST**

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<th>Date:</th>
<th>Receiving Dr.</th>
<th>Consultant on call</th>
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<tbody>
<tr>
<td>Referring Hospital:</td>
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<tr>
<td>Patient Name:</td>
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<td>Gestational Age:</td>
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<td>Patient history:</td>
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<td>Family history:</td>
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<tr>
<td>Clinical status:</td>
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<td>Investigation done:</td>
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<td>Team to liaison with:</td>
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<td>☐ Endocrine Consultant on call</td>
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<td>☐ Kingfisher admissions and Sister Carly Hadfield</td>
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<td>☐ Professor John Asherwood</td>
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<td>☐ Urology Consultant, Mr Imran Mutchton or Miss Neima Smalldon</td>
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<td>☐ DSD Clinical Nurse Specialist Kate Devlin</td>
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<td>☐ Dr Polly Corbett, Consultant Psychologist</td>
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<td>☐ Endocrine Registrar</td>
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<td>Consult:</td>
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<td>☐ Transport for baby / nurse escort</td>
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<td>☐ Stock of medication (LBHNI / TVG / Synacthen) on ward</td>
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<td>☐ Interpreter</td>
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<td>☐ Breast pump / bottles / milk on ward</td>
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<td>Plan:</td>
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- Emailed to lead consultant
- Filed in patient notes
- Filed in DSD file
Making the diagnosis
To ARRANGE:
- Pelvic and abdominal (renal) USS
- Clinical photography (if parents consent)
- General Bloods: U&E, Cortisol, ACTH, testosterone, inhibin B and AMH, FSH and LH
- USP (if not done or as back up sample); urinalysis for proteinuria (if not done)
- Bloods for DNA storage (if parents consent)
- Consider other investigations as required (e.g. synacthen test, LHRH test, PRA, aldosterone, prolactin/TFTs/IGF1)
- Cancel tests if samples not necessary (e.g. AMH in CAH) or duplicated (e.g. USP being done)

ON ADMISSION “MEET AND GREET” THE PARENTS, EXPLAIN WHAT WILL HAPPEN AND WHO THEY WILL SEE, AND FOCUS ON SUPPORT AS WELL AS THE PLANNED “TESTS” – appreciate how tired and stressed they are, and maintain their privacy; let them have time together to talk and reflect.

46,XX
If CAH suspected (common):
PRIOR TO TREATMENT: Cortisol, PRA, Aldosterone, 17-OHP, A4, DHEAS, 11-deoxycortisol, USP
Short synacthen test only after day 3

Ovotesticular DSD (rare):
AMH, inhibin B, testosterone, consider early EUA and laparoscopy

Aromatase deficiency (v rare); also clitoromegaly of prematurity and structural variants

46,XY
Ensure adrenal function adequate (rare):
ACTH, cortisol, synacthen
Is it dysgenesis, steroidogenic defect or androgen resistance?
AMH, inhibin B, testosterone, LH/FSH, USP;
Consider 3 day/3 week hCG stimulation test

45,X/46,XY
AMH, inhibin B, testosterone, LH/FSH;
Consider 3 day/3 week hCG stimulation test or early EAU/laparoscopy;
ECHO, TFTs, renal USS, Turner screening, audiology etc
Diagnostic pathway

**IDENTIFICATION**
- Receiving centre contacted by referring team

**INFORMATION NEEDED:**
- Clinical status
- Clinical history
- Family history
- Investigations done
- Family knowledge

**REFERRAL**

**INFORMATION TO GIVE:**
- Bloods to perform
- Monitoring
- Family knowledge

**ASSESSMENT**

**INFANT REFERRED:**
- Arrange day admission
- MDT
- Imaging
- Endocrine investigations
- Family knowledge and support

**DIAGNOSIS**
- 46, XX
- 46, XY
- MSC
- Further investigations

**MANAGEMENT**
- SOR
- Discharge home / hospital
- Further OPD management
- Family knowledge and support
Monthly MDT meeting

• Every 2\textsuperscript{nd} Monday of the month
• All meet
  – Lead Consultant Endocrinologist with DSD interest chairs the meeting
  – Registrars (Residents) present new cases
    • Discuss previous cases
      – Attended outpatients clinic
      – Attended the endocrine day case unit (Kingfisher)
      – Had EUA (Woodpecker)
      – Had surgery (Squirrel)
  – CNS
    • Makes notes on planned outcomes and proposed interventions.
      – CNS team ipad
      – Emailed to relevant people with tasks to be done
### DSD MONDAY MDT ACTION PLAN

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<th>Diagnosis</th>
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Clinical Nurse Specialist roles

- Consultant
- Liaison
- Educator
- Research
- Collaborator
- Leader
- Change Agent
- Patient advocate
CNS advocate role – at diagnosis

- Ensure referring team has parents admission leaflet
- Liaising with the MDT
  - From the referring team and also the team being referred to
  - Is the baby well / hospitalised
  - Are they requiring transport / nurse escort / will that nurse stay with patient
  - Liaising with the various members of MDT to arrange ward visit
  - Liaising with Biochemistry / Ultrasound / Photography
- Liaising with the ward
  - Ensure GnRH, Synacthen and HCG in stock on ward if need be
- Liaising with the parents!
- Prepare information packs for parents
  - DSD families leaflet
  - Cortisol deficiency booklets
  - CAH information
  - CNS contact details

- How is the baby feeding
  - Breast pump, bottles, quiet area available
  - Bottle feeding – enough milk
- Ensure parents bring
  - Phone chargers, nappies, wipes, books etc, lists of questions
  - Maternity notes, child health care notes, referral letters
  - Money for parking
- Can they speak English
  - Arrange interpreter, prepare translated information
Specifics..

- Making notes in MDT meeting
  - Ensuring full follow up
- Maintaining DSD database
- Consent forms for research
- Maintaining referrals folder and spreadsheets
- Arranging admissions
- Creating pathways, protocols and information sheets
- Teaching
- Presenting / lecturing
- There for the family on the day
- Support when discharged
- Liaison with Psychology – support group days
CNS advocate role - ongoing

• Key liaison and support for family

• Involvement in support groups / support group days

• Be knowledgeable in specific condition and long term implications
  – Prepared for discussions on puberty and adolescence and beyond

• Liaise with adult DSD / gynaecology teams

• Patient and family empowerment
UK Statistics
Relative sizes and population

- USA population: 318.9 million
- UK population: 64.1 million
- South Africa Population: 57.72 million
  - Capetown: 433,688
  - London: 8.6 million
  - Los Angeles: 10 million
GOSH DSD diagnosis statistics - 2015

- 53 new referrals over one year
- Averaging 6 a month
DSD referral areas

Location:
- London
- Norfolk
- Bedford
- Brighton
- Stevenage
- Watford
- Reading
- Worthing
- Ashford
- Southend
- Leicester
- Luton
- Peterborough
- Dublin
- Kuwait
- Malta
- Qatar
DSD ages of referral at GOSH

- Infants
  - Usually present with atypical genitalia

- Adolescents
  - Atypical sexual development
    - Micropenis
    - Cryptorchidism
    - Referrals from other centres
      - Previous hypospadias surgeries
      - Familial atypical genitalia
      - CAIS
GOSH DSD data over 21 years N= 657
International Statistics
South Africa (Ganie et al, 2016)

- 416 children
  - 46 XY - 57.5%
    - Androgen synthesis action
    - Ovotesticular DSD
    - Single most common diagnosis amongst black African patients with ambiguous genitalia
  - 46 XX - 33%
    - CAH
  - MSC - 9.5%
    - TS – 2/3
      - Late presentation

- Lack of biochemistry tests
- Lack of advanced molecular techniques (WES)
  - Likely to alter classification of their cohort
  - WES
    - Can detect mutations in known DSD genes
South Africa

- Ethnicity
  - 86% African
  - 9% Indian
  - 3% White
  - 2% Mixed ancestry

- Statistically significant relationship
  - Different population groups
  - Diagnosis

- High prevalence of ovotesticular DSD in the African population
  - Further analysis necessary

Figure 3: Race by aetiological classification (n=346).
Sudan (Abdullah et al., 2012)

- 5 year retrospective study of PE clinic
- 156 DSD patients
  - 46 XX - 44%
    - CAH
  - 46 XY – 29%
    - AIS

- 60% referred to specialized clinics
  - Some families refuse
    - Finance
    - Stigma
  - Some left without action
    - Aetiology spiritual
      - Not treated by Western medicine

- 70% deliveries at home
  - Midwives and young Drs not trained

- Sex assignment
  - Guesswork
    - Has to be done before naming ceremony
      - No later than 2 weeks

- SSIS
  - Sudan Scientific Intersex Society
    - MDT only in Khartoum

- Investigations
  - Costly ($300 per patient)
  - Unavailable

- Early surgery opted for
  - Culture
  - Religious directives

Disorders of sex development among Sudanese children: 5-year experience of a pediatric endocrinology clinic

Mohamed Ahmed Abdullah*, Umsalama Saeed, Asjad Abass, Karib Lubna, Arabi Weam, Abdelbassit S. Ali and Imad F. Elmwa
• 208 patients 2000 – 2005
  – 46 XY – 66%
  – 46 XX
    • 75% CAH
  – High rate of consanguinity – 61%
  – Preference of male sex of rearing
    • Regardless of karyotype
    • Despite severe genital ambiguity
      – Female infertility
        » Precludes marriage
        » Employment prospects
Finland (Kohva et al, 2018)

- 550 patients 2004 – 2014
  - 46 XY – 54%
  - MSC – 37%
  - 46 XX – 9%

- Most common
  - Bilateral cryptorchidism
  - Klinefelter
  - TS (child health care clinic)
    - Mean age of diagnosis 4 years
    - Decceleration of growth
      - Finnish growth data?
      - National child measurement programme UK – Reception / Year 6
      - Finland – 20 height measurements from post birth – 12 years
Family Support - dsdfamilies

- dsdfamilies.org
- UK based support group
  - Information and support resource for families with children, teens and young adults with a DSD
  - Links to other support groups throughout the UK
    - CAH, TS, Hypospadias, Klinefelter, AIS
  - Links to international DSD support groups
dsdfamilies.org

- Advice
  - How to talk to others
  - How to talk with teenagers
  - Dilatation

Top Tips for Talking about differences of sex development
Conclusion..

- Brief overview of DSD service in the UK
  - Many more complex variants
  - Diagnosis
  - Management
  - Treatment
- International practice review
  - Cultural aspects important to consider
  - Practical elements – growth data
  - Access to molecular analysis and biochemical testing
    - Variance in diagnosis
    - Variance in classification
- Clinical Nurse Specialist role
  - Liaison
  - Organisation
    - Specifics of the role
- Future for more advanced nursing roles?
  - Midwives / Community Doctors
  - Further training