Prenatal diagnosis of rare diseases

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20% of the postnatal exomes in the DDD had an abnormal antenatal scan.
<table>
<thead>
<tr>
<th>Prenatal rare disease</th>
<th>Postnatal rare disease</th>
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<tbody>
<tr>
<td>Structural anomalies in 1-2% of fetuses – severe forms may die in utero or early neonatal deaths</td>
<td>Full phenotype usually ascertained May be structurally normal at birth</td>
</tr>
<tr>
<td>Family history of mutation or disease</td>
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<tr>
<td>May be genetic, chromosomal, sporadic, structural, deformation, vascular, infective, teratogenic</td>
<td>80% genomic component</td>
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<tr>
<td>Reproductive choice, birth planning, preparing, diagnostic uncertainty, termination of pregnancy</td>
<td>Diagnosis, support, therapies, research for patient benefit</td>
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Benefits of antenatal diagnosis

• Knowledge and counselling
• Reassurance
• Reproductive choice – to continue or TOP
• Preparation – family, siblings, professionals
• Planned delivery – place, time, team
• Support – teams, hospice/ palliative care, bereavement
• Recurrence risk
Challenges of prenatal diagnosis

- Limited by resolution of ultrasound/ prenatal genetic and biochemical tests
- Gestation/ size dependent
- See structure but not function
- Anomalies can be heterogenous
  - From normal outcome to severe disability/ lethal
- A false positive may lead to TOP of a normal baby
- A false negative may lead to a ‘wrongful birth’
Supporting the parents

• Fetal Medicine consultants and midwives
• Genetics and GCs
• Fetal cardiologists
• Neonatologists
• Paediatric specialties – neurosurgery, renal, surgeons
• Palliative care/ hospice and bereavement teams
• External bodies – ARC, support groups, CAFA
Making the diagnosis

• Only possible if fetus displays a phenotype OR a known risk is present
  – Eg family history
• A genetic abnormality needs to be both detectable AND highly likely to be causative
• Variation in penetrance, phenotype, expressivity is very challenging
• Parental counselling is key
FIRST TRIMESTER

- Often more severe
- May be lethal
- Increased NT is commonest referral
- Heterogenous anomaly with huge range in outcome
Combined screening

- Screens for T21 only
  - high hcg
  - low PAPP-A
- Cut off is 1 in 150
- Offered at 11+2 to 14+1 weeks (45 to 84mm)
- High risk -> CVS or amnio
Abdominal wall defects
SECOND TRIMESTER

• Majority of anomalies diagnosed at 18-22 weeks

• Risk of underlying rare condition depends on several factors
  – Nature of anomaly
  – Single v multiple
  – High risk group eg consanguinity, maternal age
### Screening standards

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% detection</th>
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<tr>
<td>Open spina bifida</td>
<td>90</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>75</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>60</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>98</td>
</tr>
<tr>
<td>Exomphalos</td>
<td>80</td>
</tr>
<tr>
<td>Serious cardiac abnormalities</td>
<td>50</td>
</tr>
<tr>
<td>Bilateral renal agenesis</td>
<td>84</td>
</tr>
<tr>
<td>Lethal skeletal dysplasia</td>
<td>60</td>
</tr>
<tr>
<td>Edwards’ syndrome</td>
<td>95</td>
</tr>
<tr>
<td>Patau’s syndrome</td>
<td>95</td>
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</table>
Thorax - CDH
Additional 2D findings – the genetic sonogram

- Subtle renal anomalies
  - Horseshoe kidneys

- Polyhydramnios
  - TOFs
  - Swallowing: think chin
  - Neuromuscular abnormality

- Macrosomia
  - Fetal overgrowth? Beckwith-Weideman
3D scanning in FM

- Dysmorphology
- Patient counselling
- Refining anomalies
- Planning surgery or place of birth
- Multidisciplinary benefits – visual
Micrognathia
Skeletal dysplasias
NTDs – surface skeleton
Genitalia
Corpus callosum 2D
FETAL MRI

• Routine practice for CNS anomalies
• Increased diagnostic accuracy and confidence
• Huge impact on outcome prediction
• Lung volumes, other anomalies still research areas
Invasive testing

- Offered when risk of underlying genomic disorder
- CVS 11-13 weeks +
- Amnio 15+
- Risk of miscarriage 0.8-1%
# Options for prenatal testing

<table>
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<tr>
<th>Method</th>
<th>Details</th>
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| Karyotype                   | 6 – 10Mb resolution  
Confirms trisomies, balanced rearrangements, mosaicism |
| Targeted DNA tests: FISH, QfPCR and mutation analysis | High resolution but need target                                         |
| Array CGH                   | High resolution, whole genome  
Concern about VOUS and IFs                                             |
| Exomes and genomes          | Increasingly available clinically  
Eg skeletal, cardiac panels                                              |
TOP and Fetocide

- Legal constraints with termination of pregnancy past 24 weeks – Clause E
- At 22+0 baby may be born alive

- Intracardiac injection of 3–10 mls of strong KCl
  - With pancuronium and morphine
  - Then induction of labour

Early diagnosis avoids fetocide.
Non-invasive prenatal testing

- 700 000 births
- 30 000 invasive tests
- Up to 460 miscarriages pa
Cell-free fetal DNA

- Cell free fetal DNA
- Rh disease
- Fetal sexing
- Single gene mutations
  - FGFR3
  - CF
- Aneuploidy screening
NIP...T or D?

• Non invasive testing is NOT non invasive diagnosis
• Advanced screening tests are NOT diagnostic for 13, 18 and 21.......yet
• Microdeletions and duplications are detectable
• Sex chromosomes are a problem
Principles of NIPT

Sequencing of two genomes, mother and fetus (96 chromosomes)

5% additional reads (97 chromosomes) in T21
NIPD for genetic disease

- Currently focus of massive research output
- Paternally-inherited mutations are currently available
- FGFR3 is accredited prenatally
- Recessive diseases with parental discordance eg CF
- Next-Generation sequencing will be the basis of all prenatal tests eventually
PAGE study

- NIHR UK prenatal study recruiting now
- Exome sequencing – all genes sequenced simultaneously with no introns
- Already reported on increased detection of point mutations in abnormal fetuses (10%)
- Potentially offers a ‘one-stop shop’ for genomic diagnosis – but at what cost?
Ethical concerns

- VOUS and IFs can be “toxic information”
- When does a fetal test become a family test?
- Will prenatal testing become too easy?
- NIPT is now a multi-million dollar business
Personalised prenatal diagnosis?

“A complete DNA read-out for every newborn will be technically feasible and affordable in less than five years, promising a revolution in healthcare….by 2019 it will have become routine to map infants’ genes when they are born”

Jay Leno, CEO Illumina, February 2009