Trisomy 21 (Down syndrome) is the commonest chromosomal disorder at birth, and has been considered in detail in previous annual reports\(^\text{23}\). Other relatively common trisomies include trisomy 13 (Patau syndrome) and trisomy 18 (Edward’s syndrome). Although not as common as Down syndrome, these two conditions still present significant challenges to both parents and health services.

**WHAT IS A TRISOMY?**

Human cells normally have 46 chromosomes that can be grouped into 22 pairs of autosomes (numbered 1 to 22, in order of their size) plus a pair of sex chromosomes (XX in females and XY in males). A normal human cell is said to be diploid as it contains 2 sets of each of the 23 chromosomes. Where this is not the case, and the cell contains an abnormal number of chromosomes it is described as aneuploid. Trisomy involves the presence of extra material from a specific chromosome in addition to that found in the normal pair. The total chromosomal complement is then 47 instead of 46. Thus, cases of Patau syndrome have an extra chromosome 13 (Figure 27) and cases of Edward’s syndrome have an extra chromosome 18 (Figure 28).

Additional chromosomal material may be present in the cell because of the presence of an entire extra chromosome (a true trisomy), or as a result of an additional part of a chromosome becoming attached to other chromosomes in the nucleus (a translocation). Mosaicism describes the situation where some cells have chromosomal defects while others are normal. In this situation, the degree of problems depends on the relative proportions of normal and abnormal cells, which may vary between organs within the same individual.

**Risk factors**

A number of risk factors have been identified that are common to many chromosomal disorders, including trisomies 18 and 13. These include:

- **Maternal age**
- **Environmental exposures** such as ionising radiation and some heavy metals. Recent studies have highlighted the possibility that living near landfill sites may also increase the risk of chromosomal disorders (among other congenital defects)\(^\text{24}\). Much more work is needed in this area before the risks become clearer.

Welsh data from the CARIS database illustrates how anomaly rates rise with maternal age for Patau and Edward’s syndromes. Rates for Down syndrome are also shown, for comparison (Figure 29).

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**Trisomies 13 and 18**

*(Patau and Edward’s syndrome)*

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\(^{23}\) CARIS Annual Reports 1998 and 1999

Figure 29: Rates of Trisomies 13, 18 and 21 by maternal age group: CARIS data 1998-2001

**PATAU SYNDROME – TRISOMY 13**

Patau syndrome (Figure 30) is reported to occur in 1:4000 to 1:10,000 live/stillbirths, although these figures are changing as the capacity for antenatal detection increases, giving parents the choice of termination of pregnancy. Affected infants tend to be small at birth with microcephaly, a sloping forehead, facial dysmorphism, eye defects and abnormal low set ears. Other features include loose skin at the back of the neck, haemangiomas, a single palmar crease, polydactyly, flexed fingers and a posterior prominence of the heel (rocker bottom feet).

A number of serious congenital anomalies occur in association with trisomy 13, including:
- Holoprosencephaly (failure of the forebrain to divide properly – 65% of cases)
- Myelomeningocele (50% of cases)
- Scoliosis
- Cleft lip and/or palate (almost all cases)
- Congenital heart defects (80% of cases) – especially VSD, ASD PDA or dextrocardia
- Exomphalos (10% of cases)
- Kidney defects
- Genitourinary defects

The outlook for babies with trisomy 13 is very poor. 45% of liveborn babies die in the neonatal period, and by the end of the first year of life, mortality is 75%. Those babies that survive have profound learning disability, deafness and visual disability. Apnoea, feeding difficulties, oesophageal reflux, and slow growth are very common in infants.

CARIS has received reports of 36 cases of trisomy 13 with pregnancy ending in 1998-2001, giving a gross rate of 2.8/10,000 live and stillbirths. Of these, 4 were spontaneous fetal losses. Of the remaining 32 cases, 24 (75%) resulted in termination of pregnancy and 8 were liveborn, of which only 1 survived to the end of the first year of life.

For 5 CARIS cases, details of additional anomalies are not known. The remaining 31 cases included:
- 17 cases (55%) with heart defects – including 12 VSDs (39%), 2 ASDs and 1 PDA
- 6 cases (19%) of holoprosencephaly
- 17 cases (55%) of cleft lip and/or palate
- 2 cases (7%) of neural tube defect
- 12 cases (39%) with renal or urinary system anomalies
- 20 cases (65%) with limb deformities, mainly polydactyly
- 4 cases of tracheo-oesophageal atresia/fistula and 4 cases of congenital diaphragmatic hernia

The percentage of additional anomalies in CARIS cases are generally lower than might be expected. This may be due to data quality, with fewer associated anomalies reported in cases that have not died and undergone post mortem.
EDWARD’S SYNDROME – TRISOMY 18

Edward’s syndrome (Figure 31) occurs in about 2/1000 livebirths or stillbirths. As for trisomy 13, this frequency is falling as antenatal detection improves.

Fetuses typically tend to be small for gestational age with poor movements. Polyhydramnios, a small placenta and single umbilical artery are common features in the pregnancy. After birth, infants tend to be small and frail with a feeble cry. They have feeding difficulties and failure to thrive is common.

Affected infants typically have microcephaly, a small mouth and jaw, facial dysmorphism, eye defects and abnormal low set ears. Redundant skin at the back of the neck, joint contractures and numerous abnormalities of fingers and toes are present. Clenched fists with the index fingers overlapping the 3rd and 4th fingers are almost distinctive of this condition (Figure 32). Children have significant learning difficulties and developmental delay.

Major associated anomalies are not as common as for trisomy 13, but include:
- Congenital heart defects (90% of cases), especially VSD, ASD and PDA.
- Cleft lip and/or palate
- Myelomeningocele (6% of cases)
- Radial aplasia (5-10% of cases)
- Kidney defects and associated hypertension
- Scoliosis

20-30% of cases die within a month of birth, with only 10% of liveborn babies surviving to 1 year of age. Despite this, a few children have been reported to reach their second decade. CARIS is aware of 56 cases of trisomy 18 with pregnancy ending in 1998 - 2001, giving a gross rate of 4.4/10,000 live and stillbirths. Of these, 5 were spontaneous fetal losses. Of the remaining 51 cases, 31 (61%) resulted in termination of pregnancy, 2 were stillborn and 18 were liveborn, of which 6 (33% of liveborn cases) survived to the end of the first year of life.

For 5 CARIS cases, details of additional anomalies are not known. The remaining 51 cases included:
- 33 cases (65%) with heart defects
  - including 18 VSDs (35%), 5 ASDs and 3 PDA
- 6 cases (12%) of cleft lip and/or palate
- 2 cases (4%) of neural tube defect
- 17 cases (33%) with renal or urinary system anomalies
- 33 cases (65%) with limb deformities, including
  - 5 cases of absent thumb and 2 cases of radial aplasia
- 4 cases of tracheo-oesophageal atresia/fistula and 4 cases of congenital diaphragmatic hernia
POTENTIAL FOR ANTENATAL DETECTION

Although there is increasing potential to include other chromosomal abnormalities in screening programmes, it is not current UK policy to undertake antenatal screening for any chromosomal disorder other than Down syndrome.

Antenatal ultrasound

A number of antenatal ultrasound findings have associations with various chromosomal anomalies. A recent review of these findings by Nicolaides et al.\(^{25}\) illustrates how, although many ultrasound findings are associated with chromosomal anomalies other than Down syndrome, they lack the sensitivity and specificity to be used as stand alone screening tests.

A recent review by Wald et al. of published studies looked at markers for trisomies 13 and 18.\(^{26}\) The review recommended that amniocentesis should be undertaken to exclude these 2 trisomies if any of the following were identified on antenatal ultrasound scanning:

- agenesis of corpus callosum
- diaphragmatic hernia
- cleft lip / palate
- exomphalos
- obstructive uropathy
- double outlet right ventricle
- limb reduction defects (trisomy 18 only)

Analysis of CARIS data shows that

- 26/36 cases of Patau syndrome had reports of antenatal scans. Of these, 11 (42%) had evidence of ultrasound soft markers and 21 (81%) had evidence of structural defects.
- 41/56 cases of Edward’s syndrome had antenatal scan findings reported to CARIS. Of these, 32 (74%) had scan evidence of soft markers. 32 (74%) had evidence of structural abnormalities. (Figure 33).

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Figure 33: Antenatal scan findings reported to CARIS 1998-2001 for Trisomy 13 and Trisomy 18

<table>
<thead>
<tr>
<th>Trisomy 13 / Patau (n=26)</th>
<th>Trisomy 18 / Edward’s (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soft markers</strong></td>
<td><strong>Soft markers</strong></td>
</tr>
<tr>
<td>11 any soft marker</td>
<td>21 any structural defect</td>
</tr>
<tr>
<td>5 increased nuchal translucency</td>
<td>8 with no 4 chamber view or other cardiac anomalies</td>
</tr>
<tr>
<td>2 strawberry skull</td>
<td>7 echogenic gut</td>
</tr>
<tr>
<td>1 echogenic bowel</td>
<td>7 with orofacial clefting</td>
</tr>
<tr>
<td>1 echogenic kidney</td>
<td>6 holoprosencephaly</td>
</tr>
<tr>
<td>1 dilated renal pelvis</td>
<td>6 ventriculomegaly</td>
</tr>
<tr>
<td>1 lemon head</td>
<td>4 cystic hygroma</td>
</tr>
<tr>
<td>1 banana cerebellum</td>
<td>4 polydactyly</td>
</tr>
<tr>
<td>1 rockerbottom feet</td>
<td>1 exomphalos</td>
</tr>
<tr>
<td>1 double stomach bubble</td>
<td>1 neural tube defect</td>
</tr>
<tr>
<td>1 no stomach bubble</td>
<td>1 oesophageal atresia</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

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ANNUAL REPORT 35
Maternal serum markers

A 2nd trimester maternal serum screening test for Trisomy 18 was first proposed in the early 1990s, following the observation that serum levels of a number of markers used to detect Down syndrome were also low in cases of fetal Edward syndrome. An early screening test was proposed involving maternal age, maternal serum alpha-fetoprotein and free beta human chorionic gonadotrophin. With a published detection rate of 50% for a false positive rate of 1%, this was suggested as being comparable to serum screening for Down syndrome. However, Edward’s syndrome is much less common than Downs, so that many more amniocenteses would have to be performed per case detected than was the case for Down syndrome. It was suggested that a screening programme for a condition which was likely to prove fatal in pregnancy or infancy would cause considerable anxiety for parents and the abortion of at least as many normal fetuses as it would detect cases of trisomy 18. Ultrasound scanning was already thought to offer a better chance of detecting trisomy 18 and serum screening has only developed subsequently in isolated programmes.

Enhanced 2nd trimester serum screening involving maternal age related risk, alpha-fetoprotein, unconjugated estriol and human chorionic gonadotrophin has recently been shown to be able to detect a number of chromosomal abnormalities, including trisomy 18.

No antenatal serum screening programme exists for trisomy 13 or 18. It is however interesting to note that CARIS has reports on 12 mothers of babies with Edward’s syndrome who opted for serum screening. Of these, 2 were reported as high risk for Down syndrome. Similarly, 1/5 mothers of babies with Patau syndrome who opted for serum screening were reported as high risk for Downs.

Amniocentesis

Obtaining a sample of fetal cells for chromosome analysis is indicated if serum screening or antenatal ultrasound suggest the possibility of a fetal chromosomal anomaly. Alternatively this may be chosen as the first line of investigation for older mothers or those perceived at increased risk of carrying a fetus with a chromosomal disorder. Samples are usually obtained by amniocentesis or chorion villus sampling.

Chromosome analysis may be undertaken by karyotyping, through polymerase chain reaction (PCR) or fluorescence in situ hybridisation (FISH) techniques. These latter two procedures have the advantage of being much faster to perform than conventional karyotyping, but can only be used to detect pre-specified chromosomal disorders. They are not routinely available to the NHS at present. CARIS data includes karyotype results on 34/36 cases of Patau syndrome and 55/56 cases of Edward’s syndrome. The method (and therefore the stage of pregnancy /infancy) by which these samples were obtained is illustrated in Figure 34. This suggests that about 64% of cases of Patau syndrome and 55% of cases of Edward’s syndrome were detected antenatally.

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27 Mallard SK, Coombes EJ, Maeri JN. Prenatal screening for trisomy 18 with free beta human chorionic gonadotrophin as a marker BMJ 1993; 307:1455-8 (4 December)