Down's Syndrome 1995-1997

West Midlands Congenital Anomaly Register

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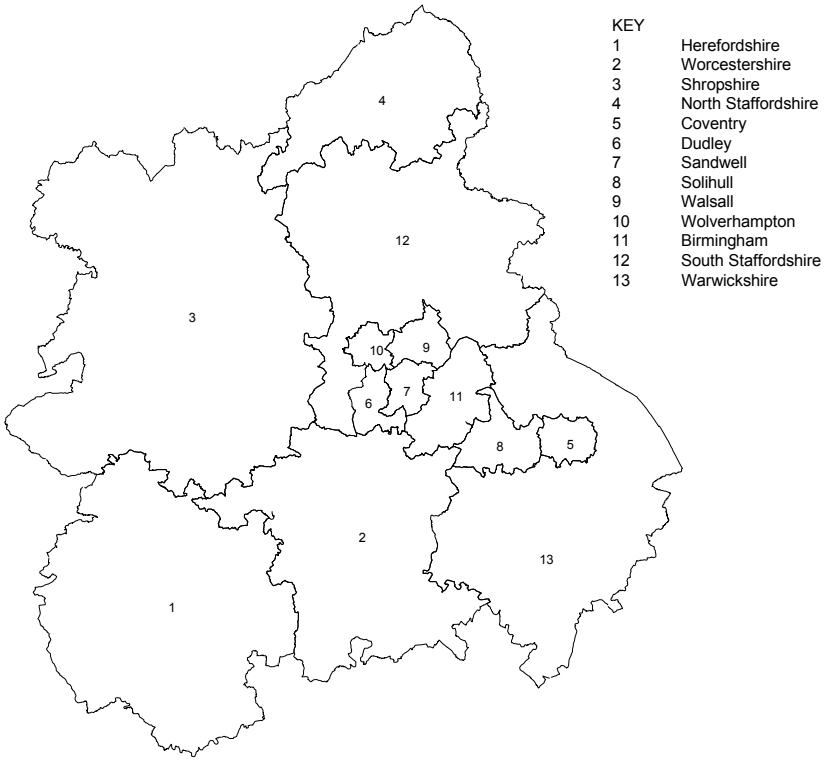

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The diagram of trisomy 21 non-disjunction is reproduced from "counseling aids for geneticists" produced by the Greenwood Genetic Center.

PREFACE

This report gives accurate and comprehensive information relating to all cases of Down's Syndrome resident in the West Midlands at birth over a 3-year period. It is vital that properly analysed and collated information escapes from the massive data collection exercise of the West Midlands Congenital Anomaly Register. We hope that the report is informative and is easy to understand and we recognise that specific additional questions may follow and will do our best to address any subsequent queries that arise from these data. We will no doubt revisit Down's Syndrome in the future, and it is hoped that this report will give a solid foundation of well validated data which can be used for comparative purposes in years to come. As the average age of women having children is increasing it seems likely that the issue of Down's Syndrome will attain greater prominence. The challenge for health care services is to ensure that the cutting edge of science is integrated rapidly into the delivery of optimal results. Developments are occurring frequently and it is only by the presentation of accurate information that standards can be agreed and targets set.

The standard of pregnancy and paediatric care is dependent upon medical technology and the collection of evidence, combined with the implementation of a health care strategy. This report is the latest in a series that aims to provide feedback on specific groups of congenital anomalies to the professionals providing pregnancy and infant care. Down's Syndrome is a relatively common congenital anomaly, and has a well-documented antenatal screening programme. Successful health care in this context is complex, and involves a large team of professionals from different backgrounds. Radiographers providing ultrasound are important in dating pregnancies and identifying structural anomalies, with the prospect of nuchal translucency becoming a primary screening procedure. Midwives underpin pregnancy care with an important role in counselling for screening tests, and providing expert support for the mother during pregnancy or in the emotionally difficult process of termination of pregnancy. Laboratory scientists undertake serum screening and karyotyping, with regular quality assurance and audit. Obstetricians undertake invasive procedures and manage pregnancy. Paediatricians and paediatric surgeons are involved in the medical care of children with the support of nursing and other allied professional staff.

The West Midlands Congenital Anomaly Register held an educational meeting on Down's Syndrome which covered a broad range of topics ranging from serum screening in pregnancy to educational outcomes of children. The meeting was well attended with representatives from all the maternity hospitals in the West Midlands. This gave a forum for personal contacts and discussion of the issues raised by speakers. The report has taken longer than we anticipated to produce, but we hope that it will stimulate further local consideration as well as being a source of continued education for professionals in the field. A glossary is provided for an explanation of the terms used.

Mike Wyldes
November 1999

TABLE OF CONTENTS

CLINICAL BACKGROUND OF DOWN'S SYNDROME

This syndrome was first described by John Langdon Down in 1866. Down's Syndrome is caused by an additional copy of chromosome 21 and is the most common condition associated with autosomal aneuploidy at birth. The majority of Down's Syndrome conceptions are lost through spontaneous miscarriage, mainly very early on, but with decreasing frequency throughout pregnancy. Without intervention, the incidence is about 1 in 700 live births in most populations. Down's Syndrome is an important cause of structural anomalies and it is the biggest single cause of learning difficulties.

GENETICS

Human cells contain 46 chromosomes which carry the estimated 70,000 genes needed for normal growth and development. There are 23 pairs: 22 pairs of autosomes, and two sex chromosomes, X and Y (XX in females, XY in males). Normal female and male karyotypes are abbreviated to 46XX and 46XY respectively. The correct number of chromosomes is called diploid. A gamete has one of each pair of chromosomes and is therefore haploid. The presence of an abnormal number of chromosomes is called aneuploidy. Down's Syndrome due to trisomy 21 is an example of this, with 47 chromosomes.

Normal cell division

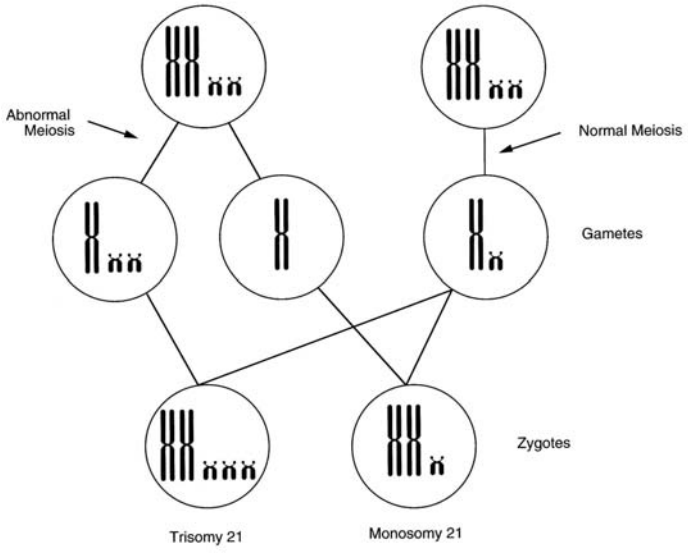
Cells divide as the body grows. In this process (mitosis) the chromosomes replicate into two identical copies and produce identical daughter cells. The other method of cell division is called meiosis and occurs in the formation of gametes in the ovaries and testes. Meiosis occurs in two stages during which there is an exchange of genetic material between pairs of chromosomes, and a reduction of the number of chromosomes in each cell to 23 (one of each pair). The diploid number is regained when the egg and sperm fuse at fertilisation.

Down's Syndrome

The condition is caused by the presence of three copies of chromosome 21 in the cells. The presence of an additional set of genes from the extra copy leads to an imbalance in the function of the genes on chromosome 21 and disturbs normal development. Duplication of only part of chromosome 21, called the critical region, is necessary for the typical features to be present.

Non-disjunction

Non-disjunction is a failure of the normal separation of a pair of chromosomes during cell division, if it occurs during meiosis the resulting gamete will have 24 chromosomes and the complementary gamete with 22 chromosomes will be non-viable. If the sperm or, more commonly, the egg with the abnormal number of chromosomes combines with a normal gamete, the resulting zygote will be aneuploid.



The vast majority of cases of Down's Syndrome are due to non-disjunction. Trisomy 21, as well as other autosomal trisomies, is more common with increasing maternal age. This probably reflects the differences between male and female gametogenesis. In particular the primary oocyte ages while in "suspended animation" for up to 50 years within the ovary. Ninety-five percent of trisomy 21 cases are therefore maternal in origin. Trisomies of any chromosome can occur during gametogenesis, but the majority of resulting pregnancies are not viable and result in early miscarriage.

Translocation
Translocations involve the transfer of genetic material between chromosomes. They can be balanced, where there is no net loss or gain of genetic material and the individual is completely unaffected, or unbalanced, where there is duplication and/or loss of genetic material.

Translocations can be reciprocal or Robertsonian. The translocations causing a small percentage of Down's Syndrome are Robertsonian, i.e. involving the acrocentric chromosomes 13, 14, 15, 21, and 22. One copy of chromosome 21 is fused to another acrocentric chromosome, most commonly chromosome 14. In the unbalanced situation this leads to there being effectively three copies of chromosome 21, Down's Syndrome, which is indistinguishable clinically from trisomy 21. Translocation carriers have only 45 chromosomes, with one chromosome 21 being fused to one of the other acrocentrics i.e. no extra chromosome material is present.

Carriers of balanced translocations are at risk of having children with unbalanced chromosomes because some gametes will contain the chromosome with an extra copy of chromosome 21 fused to it, as well as the normal copy of chromosome 21. If this is fertilised the embryo will have Down's Syndrome. Some cases of translocation Down's Syndrome will occur de novo.

Mosaicism
In mosaicism, the individual has two or more cell lines with different karyotypes. In mosaic Down's Syndrome one of these cell lines will have a normal karyotype and the other trisomy 21. The mosaicism usually arises from non-disjunction in a cell division in the early embryo. Later in life it may only be detectable on fibroblast culture and not from lymphocytes. Gonadal mosaicism may be the explanation for some trisomy 21 recurrences.

Recurrence and frequency

Abnormality	Frequency	Recurrence risk in next pregnancy
Trisomy 21 non-disjunction	95%	1%
Translocation	3%	De novo 1% Male carrier, risk to offspring 1-3%. Female carrier, risk to offspring 10-15%
Mosaicism	2%	<1%
21q21q carrier	very rare	100%

PRENATAL DIAGNOSIS

Down's Syndrome has been studied extensively, because of the relatively large number of cases, and the implications for parents and family. There was early recognition that older women have an increased risk of their children being affected by trisomic conditions, the most common of which is Down's Syndrome. The identification of the chromosome anomaly underlying the condition offered an opportunity to make a prenatal diagnosis. In the early 1970's, technology was sufficiently well developed for the Department of Health to offer blind amniocentesis to women considered at high risk for Down's Syndrome because of their age. The intention was to culture amniocytes to establish the number of chromosomes present in the fetal cells. At the beginning of this programme, approximately 5% of mothers were 35 years or more, and this was initially chosen as a cut-off point at which to offer amniocentesis.

It was recognised that amniocentesis, undertaken as a blind puncture into the 16 to 18 week pregnancy, increased the risk of miscarriage. It held potential hazards for the fetus, and it was felt appropriate to offer the test to a selected group of women. Using this approach, approximately 30% of cases of trisomy 21 would be identified within the 5% of the population who were oldest.

The chromosome defects in Down's Syndrome is not amenable to treatment but pregnancy outcome can be altered by termination. Not all women choosing invasive prenatal testing will request termination of pregnancy if a trisomy is identified. However, if a woman decides that she would not terminate the pregnancy regardless of the karyotype then it is probably unwise to risk the potential hazards of invasive prenatal testing.

The style of the health care systems has changed considerably since the introduction of amniocentesis based on age. It is now customary to have a well-developed system of counselling, ensuring that women opting into a screening programme have been fully informed of the risks and benefits. This has led to most maternity units having several tiers of "screening".

Biochemical screening

Serum screening was developed during the 1980's. The principle of this method is to refine the risk for an individual by measuring pregnancy related hormones and proteins, which are present in different quantities in a population of trisomy 21 pregnancies, compared with unaffected ones.

Human chorionic gonadotrophin (HCG, either total or the beta sub unit alone), alphafetoprotein (AFP, a fetal blood protein), oestriol (e3, the major oestrogen of pregnancy) and some other placental products have been shown to have potential in screening for Down's Syndrome. Biochemical screening has traditionally been undertaken at 16 to 18 weeks of pregnancy. However HCG, particularly the free beta sub unit, and pregnancy associated protein A (PAP A) appear to be effective at 10 to 14 weeks gestation.

Maternal serum HCG, AFP, e3 and other proteins have been found to have a different distribution in Down's Syndrome pregnancies. The basis for these differences are not clearly understood, but they may relate to a relative lack of maturity in the Down's Syndrome pregnancies compared to those unaffected. Measuring the levels of serum hormones and comparing them to median values for the same gestation allows a multiple of the median (MoM) to be calculated. The risk can be further refined by standardising for maternal weight and ethnic group.

In biochemical screening an individual's risk of having an affected pregnancy, initially determined by the maternal age, is calculated by using the serum MoMs. Thus, older women are more likely to be high risk and younger women more likely to be low risk. The method of using these results varies in different laboratories, but most laboratories would expect to identify 60% of affected pregnancies by labelling 5% of their population as "high risk". The true picture is however more difficult to establish, because many older women will not wait for serum screening at 16 weeks. They will either elect to have early chorion villus sampling (CVS) at 10 to 12 weeks gestation, or will have an individual Down's Syndrome risk calculated by nuchal translucency measurement at 10 to 14 weeks. Thus, the population being screened at 16 weeks will be altered.

Ultrasound screening

Ultrasound is increasingly used to examine the fetus for structural anomalies. Ultrasound screening is often undertaken at 18 to 22 weeks gestation, with the express purpose of identifying structural congenital anomalies. Approximately 30% of Down's Syndrome pregnancies have structural anomalies that can be identified on ultrasound. Some specific diagnoses are commonly associated with trisomy 21; these include atrioventricular septal defects, Fallot's tetralogy, exomphalos, hydrocephalus, duodenal atresia and diaphragmatic hernia. These conditions, where there is a high chance of fetal trisomy, are known as "hard markers".

Soft markers

The other circumstance where ultrasound can raise suspicion of trisomy is when a number of sonographic "soft markers" are seen. These are not, in the real sense, congenital anomalies, and if they are not associated with trisomy, there is no known adverse outcome for the pregnancy. These include brachycephaly, nuchal pad, choroid plexus cysts, echogenic foci in the heart, echogenic bowel, mildly dilated renal pelvis, short femur, sandal gap, clinodactyly, and hypoplastic middle phalanx of little finger. Some of these findings may raise concerns other than trisomy, but a combination of these soft markers in a fetus is associated with an increasing risk of trisomy.

The use of soft markers for Down's Syndrome screening is fraught with difficulties. The pregnant woman will already have considered the issues of Down's Syndrome screening and will have made a decision regarding her preferences. If she has undergone nuchal translucency measurement or serum screening she will either have been considered low risk or made a decision regarding karyotyping. To introduce another series of findings at this late stage in pregnancy is extremely difficult and has relatively little scientific foundation.

Nuchal translucency

Screening for trisomy 21 using nuchal translucency measurements by ultrasound is a relatively recent development. The principle is the same as for serum screening but is undertaken at 10 to 14 weeks. A measurement is taken of the sonolucent layer within the skin at the back of the fetal neck and compared with a median value for that gestation. The age-related risk is then adjusted up or down to give an individual risk for that pregnancy.

Theoretically, this method can be used in conjunction with any other information that might become available, for example serum screening. However, when the results are available at different times the counselling of the patient is complex and may need to be deferred until all information is available. Although nuchal translucency is currently in use in some centres, there is no NHS supported program operating within the West Midlands. The widespread introduction of this method throughout is unlikely before the publication of the large multi-centre study (SURUSS) which has been designed to evaluate this area.

PAEDIATRIC MANAGEMENT

In the newborn period, Down's Syndrome babies are usually hypotonic and sleepy. Characteristic facial features are epicanthic folds, up-slanting eyes, brachycephaly, small ears, and a protruding tongue. The hands are characterised by single palmar (Simian) creases, short in-curving fifth fingers, and the feet by a sandal gap. None of these features is unique to Down's Syndrome and can occur in unaffected individuals as minor variants. Not every person with Down's Syndrome will have every feature but it is the clustering of features that makes the phenotype so easily recognisable.

A main concern for parents is the fact that people with Down's Syndrome have moderate to severe learning difficulties. Other congenital malformations are common in babies with Down's Syndrome, particularly congenital heart disease (including atrioventricular septal defect, common atrioventricular canal and patent ductus arteriosus), but also duodenal atresia. Other common findings include short stature and squint.

Survival in Down's Syndrome has improved considerably over the years, particularly with improvements in the correction of congenital heart defects. Overall, 85% of infants now survive to one year, compared with 70% of those with congenital heart disease. More than 50% now live beyond 50 years. Other deaths are mainly due to other congenital malformations and respiratory infections.

METHODS

West Midlands Congenital Anomaly Register

The West Midlands Congenital Anomaly Register (CAR) was set up in June 1994 and is administered by the West Midlands Perinatal Institute. The register aims to collect information on suspected and confirmed congenital anomalies, detected before and after birth from conception to outcome, up to the first two years of life. A number of minor anomalies are excluded from the register.

Notification system

Notifications are received by two methods. The first method is a notification card (Appendix A), which is used to notify the register of suspected anomalies. The card includes details of the type of anomaly and the estimated date of delivery. It is most often completed by ultrasound departments. The second method is through a notification form (Appendix B), which contains much of the data set used for the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) but has additional details relating to the date that the anomaly is first suspected and the final postnatal diagnosis. The notification forms are usually completed by midwifes, obstetricians and paediatricians.

The Congenital Anomaly Register is maintained on the same database as the register of CESDI notifications. In this way, the number of infants with lethal fetal anomalies can be validated. All anomalies are coded using the International Classification of Disease version 10 (ICD 10).

Additional information is also received from cytogenetics laboratories and public health departments. Inpatient episode data of infants with anomalies are also received from hospital information departments. These extra data are matched to the existing notifications to give an estimated level of ascertainment, and additional clinical information is added in some cases.

Table 1 - Source of notification to CAR, Down's Syndrome cases, West Midlands residents 1995-97

Notification source	no. of notifications
Geneticist	470
Midwife	173
Paediatrician	77
Ultrasound Department	69
Postmortem	63
CESDI Co-ordinator	59
Information Department	59
Obstetrician	24
Department of Public Health	17
Total	**1,011**

Table 2 - Number of notifications per Down's Syndrome case, West Midlands residents 1995-97

no. of notifications	no. of cases
1	92
2	107
3	109
4	54
5	17
6	9
7	1
8	2
Total	**391**

Table 1 and Table 2 show that the majority of Down's Syndrome cases have multiple notifications to the Congenital Anomaly Register. Data received annually from the Regional Cytogenetics Service allows validation of diagnoses reported.

Criteria for inclusion

All cases of Down's Syndrome with a cytogenetic diagnosis are included in this report. In addition a small number of cases are included in which a perinatal pathologist considered the underlying diagnosis to be Down's Syndrome when karyotyping had failed.

Two cases notified to us by the National Down's Syndrome Cytogenetics Register (NDSCR) were excluded from this report. The first was diagnosed at one year of age at a West Midlands hospital and the second had prenatal cytogenetic testing in London. Neither was confirmed to be resident in the West Midlands at birth.

Denominators

The numerator comprises reported cases of Down's Syndrome. The denominator includes the numerator, plus all babies who had any possibility of being affected. As the number of cases of Down's Syndrome is small, the use of denominators in calculating incidence rates provides us with inter-district comparisons. Comprehensive clinical information is available for cases of fetal anomaly, however similar denominator data on all births are relatively difficult to obtain.

The appropriate denominator for calculating incidence rates is the total number of deliveries regardless of gestation, but this information is unavailable. This report uses instead the sum of the number of births (live and stillborn), the number of terminations of pregnancy for fetal anomaly (less than 24 weeks) and any late fetal losses notified to the West Midlands Perinatal Institute. The denominator should also include all fetal losses less than 24 weeks, however this information is not available. The numerator for incidence rates also includes cases of fetal loss due to Down's Syndrome.

Outcomes

This report divides outcomes of pregnancy into the following groups:

Late fetal loss less than 24 weeks (LFL),
Stillbirth 24 weeks or more (SB), } spontaneous or following termination of pregnancy
Neonatal death under 28 days (NND),
Postneonatal death 28 days up to one year of age (PNND),
Alive.

Termination of pregnancy (TOP) is defined as a therapeutic termination undertaken under the 1967 Abortion Act, and excludes inductions following spontaneous fetal death in utero. Some terminations of pregnancy may result in a registerable stillbirth, or indeed a live birth regardless of gestation.

Data sources

Numerator data West Midlands Congenital Anomaly Register
Denominator data Office for National Statistics - registerable births
West Midlands Perinatal Institute - fetal losses and terminations of pregnancy

INCIDENCE RATES

There were 391 cases of Down's Syndrome born to West Midlands residents between 1995 and 1997. Of these, there were 380 singleton pregnancies and 11 twin pregnancies. In all the twin pregnancies, there was only one affected twin. Of the 380 singleton pregnancies, six affected siblings were born to three mothers during this time.

Table 3 - Down's Syndrome cases ascertainment, 1995-97

Register	1995	1996	1997	Total
West Midlands CAR				
DS cases	128	124	139	391
DS rate per 10,000 births	18.8	18.1	20.6	19.2
Births	68,004	68,413	67,426	203,843
England & Wales NDSCR				
DS cases	1,264	1,380	1,460	4,104
DS rate per 10,000 births	19.4	21.1	22.6	21.0
Births	651,315	653,028	645,532	1,949,875

Table 3 shows that the 3-year incidence rate for all Down's Syndrome cases in the West Midlands was 19.2 per 10,000 births (1 in 521 births). This is comparable with the rate for England and Wales (1 in 475 births) reported by the National Down's Syndrome Cytogenetics Register (NDSCR). The data from the NDSCR are a more accurate estimate of the national rate than reported by the Office for National Statistics (ONS).

Table 4 - Down's Syndrome live and stillbirths only, 1995-97

Register	1995	1996	1997	Total
West Midlands CAR				
DS cases	71	59	76	206
DS rate per 10,000 registerable births	10.5	8.7	11.4	10.2
Registerable births	67,500	67,920	66,888	202,308
West Midlands ONS				
DS cases	30	33	18	81
DS rate per 10,000 registerable births	4.4	4.9	2.7	4.0
Registerable births	67,500	67,920	66,888	202,308
England & Wales ONS				
DS cases	598	622	598	1,818
DS rate per 10,000 registerable births	9.2	9.5	9.3	9.3
Registerable births	651,315	653,028	645,532	1,949,875

Table 4 shows the rates reported by the West Midlands CAR and ONS for registerable births only (i.e. live and stillbirths). The 3-year incidence rate for live and stillborn Down's Syndrome cases in the West Midlands was 10.2 per 10,000 registerable births (1 in 982 births). This rate is lower than that for all cases as it excludes terminations of pregnancy and fetal loss. The West Midlands CAR rate is higher than that reported for the same cohort by ONS, illustrating the deficiencies in the national system locally.

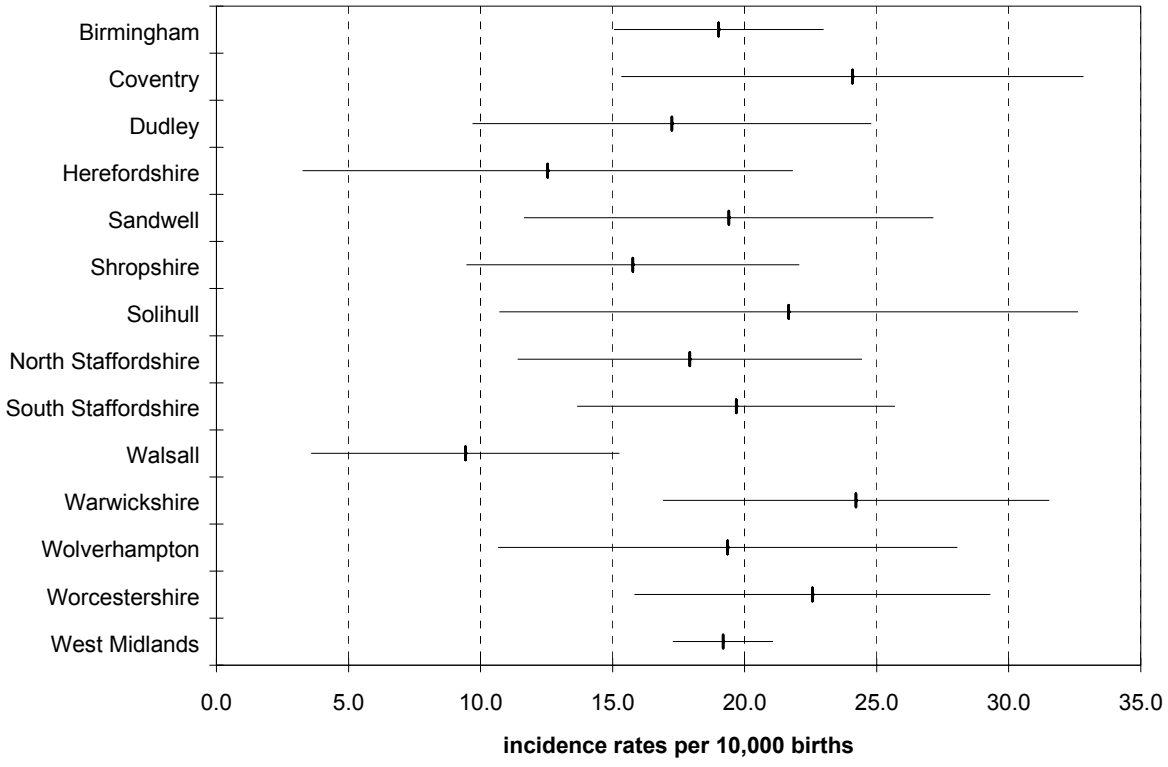
Table 5 - Down's Syndrome cases by district of residence, West Midlands 1995-97

				Total				
District	**1995**	**1996**	**1997**	**n**	**rate**	**LCI**	**UCI**	**Births**
Birmingham	24	31	33	88	19.0	15.0	23.0	46,269
Coventry	11	10	8	29	24.1	15.3	32.8	12,043
Dudley	6	4	10	20	17.2	9.7	24.8	11,597
Herefordshire	2	1	4	7	12.5	3.3	21.8	5,583
Sandwell	4	11	9	24	19.4	11.6	27.1	12,373
Shropshire	9	7	8	24	15.8	9.5	22.1	15,224
Solihull	8	0	7	15	21.7	10.7	32.6	6,923
North Staffordshire	10	13	6	29	17.9	11.4	24.4	16,178
South Staffordshire	18	11	12	41	19.7	13.7	25.7	20,833
Walsall	5	2	3	10	9.4	3.6	15.3	10,612
Warwickshire	12	13	17	42	24.2	16.9	31.5	17,342
Wolverhampton	9	7	3	19	19.4	10.7	28.1	9,815
Worcestershire	10	14	19	43	22.6	15.8	29.3	19,051
West Midlands	**128**	**124**	**139**	**391**	**19.2**	**17.3**	**21.1**	**203,843**

Rate: rate per 10,000 births
LCI: lower 95% confidence interval
UCI: upper 95% confidence interval

Table 5 and Figure 1 show considerable variation in district incidence rates, from 9.4 to 24.2 per 10,000 births. It is unlikely that failure of ascertainment explains the significantly low rates reported from Walsall residents, as validation from laboratory results has been possible for these cases. The maternal age of residents is a possible confounding variable and may explain some of the variation seen. The confidence intervals are wide and further years will be required before true comparisons can emerge.

Figure 1 - Down's Syndrome incidence rates by district of residence, West Midlands 1995-97



95% confidence intervals shown

Maternal age

Table 6 - Down's Syndrome cases by maternal age at birth, West Midlands residents 1995-97

Age (yrs)	n	Births	rate	RR	1 in
<20	10	16,066	6.2	0.3	1,607
20-24	38	44,368	8.6	0.4	1,168
25-29	68	67,840	10.0	0.5	998
30-34	88	52,988	16.6	0.9	602
35-39	117	19,150	61.1	3.2	164
40-44	65	3,264	199.1	10.4	50
45+	5	167	299.4	15.6	33
Total	**391**	**203,843**	**19.2**	**1.0**	**521**

The incidence of Down's Syndrome is known to be affected by maternal age, with an increasing risk of an affected pregnancy with the increasing age of the mother. There is currently a general trend for women to have babies at an older age. This has implications for both the incidence of Down's Syndrome, and for the prenatal screening programmes which need continued audit and alteration if screen positive rates are to remain constant over time.

Table 6 shows that 81% all of babies are born to women aged between 20 and 34. In the West Midlands 11% of babies were born to women aged 35 or more, whereas 48% of Down's Syndrome pregnancies occurred in women in this age group. The over 40 year old population comprises less than 2% of the maternal population, within which 18% of the Down's Syndrome cases occurred.

Figure 2 - Down's Syndrome cases by maternal age, West Midlands residents 1995-97

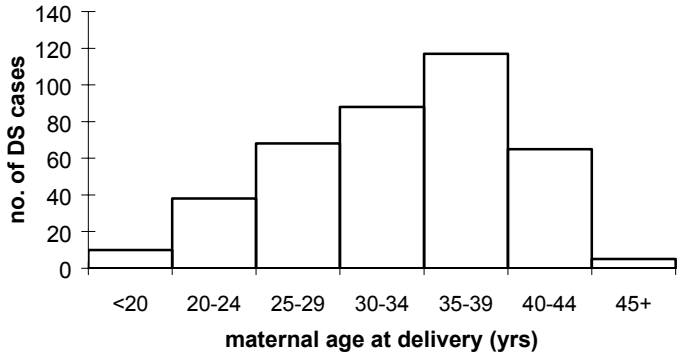


Figure 3 - Down's Syndrome incidence rates by maternal age, West Midlands residents 1995-97

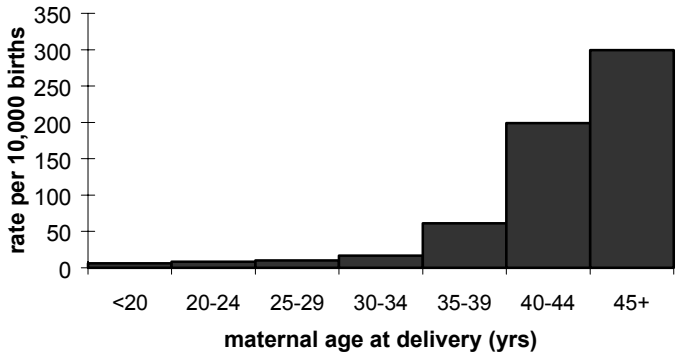


Figure 2 shows the actual number of Down's Syndrome cases in each maternal age group with the majority of cases born to women in their thirties, in contrast Figure 3 shows the increasing incidence in older mothers. This risk is less than 1 in 900 for women aged less than 35 and increases steeply after the age of 35.

OUTCOMES

Forty five percent (176 of 391) of Down's Syndrome cases were terminated. Of those pregnancies with no intervention, 86% of babies survived until 28 days (184 of 215). The stillbirth and neonatal mortality rate for Down's Syndrome cases (excluding terminations of pregnancy) was 44 per 1,000 births (9 of 206). The outcome of affected pregnancies is dependant on both prenatal diagnosis and the presence of additional major structural anomalies.

Table 7 - Down's Syndrome outcomes by district of residence, West Midlands 1995-97

	Late fetal loss		Stillbirth		Neonatal death		PNND	Alive	Total
District	**spont**	**TOP**	**spont**	**TOP**	**spont**	**TOP**			
Birmingham	7	29	2	2	1	3		44	**88**
Coventry	2	10	1			2	1	13	**29**
Dudley	1	4					1	14	**20**
Herefordshire	1	3						3	**7**
Sandwell	3	8	1	1		1		10	**24**
Shropshire	1	11					1	11	**24**
Solihull	1	7					1	6	**15**
North Staffordshire	2	12						15	**29**
South Staffordshire	1	24				1	1	14	**41**
Walsall		6			1			3	**10**
Warwickshire	2	19		2	1			18	**42**
Wolverhampton		8	1	1		1	2	6	**19**
Worcestershire	4	19			1	2		17	**43**
West Midlands	**25**	**160**	**5**	**6**	**4**	**10**	**7**	**174**	**391**

spont: spontaneous loss
TOP: termination of pregnancy

Figure 4 - Down's Syndrome outcomes by district of residence, West Midlands 1995-97

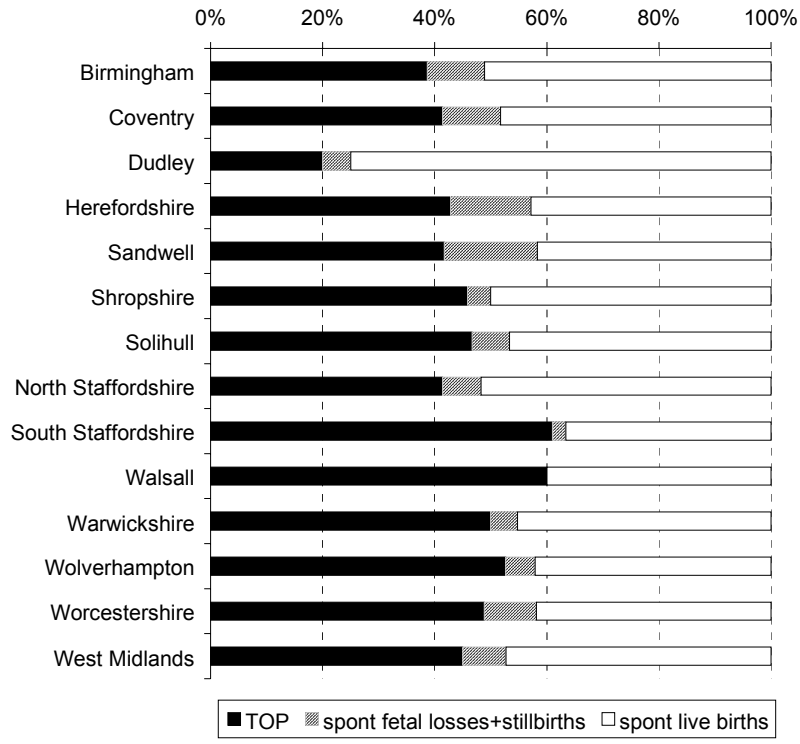


Figure 4 illustrates the variation in the outcomes of Down's Syndrome pregnancies between districts. Dudley residents appear to have a low proportion of cases in which the pregnancy was terminated (20%), compared to other districts where 40 and 61% of outcomes were terminations of pregnancy.

PRENATAL DIAGNOSIS

Table 8 - Down's Syndrome outcomes by prenatal diagnosis and maternal age, West Midlands residents 1995-97

	under 35 yrs		35 yrs and over		All ages		
Outcome	**Prenatal diagnosis**	**No prenatal diagnosis**	**Prenatal diagnosis**	**No prenatal diagnosis**	**Prenatal diagnosis**	**No prenatal diagnosis**	**Total**
Late fetal loss	4	4	2	15	6	19	25
Late fetal loss - TOP	65	0	95	0	160	0	160
Stillbirth	2	0	1	2	3	2	5
Stillbirth - TOP	3	0	3	0	6	0	6
Neonatal death	1	1	0	2	1	3	4
Neonatal death - TOP	5	0	5	0	10	0	10
Post neonatal death	1	5	0	1	1	6	7
Alive	7	106	6	55	13	161	174
Total	**88**	**116**	**112**	**75**	**200**	**191**	**391**

Table 8 shows how the proportion of cases diagnosed prenatally is increased in older women, this reflects the fact that these women will be given higher risk estimates and are therefore much more likely to undergo karyotyping than younger women.

Table 9 - Down's Syndrome serum screening uptake, West Midlands maternity units 1995-97

District	Maternity unit	Uptake
Birmingham	Birmingham Women's	61%
	City	55%
	Good Hope	68%
	Heartlands	64%
Coventry	Walsgrave	80%
Dudley	Wordsley	27%
Herefordshire	Hereford County	N/A
Sandwell	Sandwell	72%
Shropshire	Royal Shrewsbury	81%
Solihull	Solihull	74%
North Staffordshire	North Staffs Maternity	74%
South Staffordshire	Queen's	76%
	Stafford	63%
Walsall	Walsall Manor	70%
Warwickshire	George Eliot	77%
	St Cross	
	Warwick	77%
Wolverhampton	New Cross	50%
Worcestershire	Alexandra	71%
	Ronkswood	54%

During the period 1995 to 1997 the majority of pregnant women were offered maternal serum screening for Down's Syndrome using AFP/HCG, the uptake is presented in Table 9. The highest uptake was 81%, in women attending the Royal Shrewsbury Hospital and the lowest was 27% for women attending Wordsley. The only unit not offering serum screening was Hereford County Hospital, the data from St Cross Hospital are not available.

These data may contain inaccuracies as in some cases information was extracted from audit reports for different time periods and for many hospitals the screening population differs from that delivering at the unit. There is no gold standard for serum screening uptake as informed maternal choice will lead to women declining screening. Screening is not possible in women who book late in pregnancy or with multiple pregnancies.

Table 10 - Down's Syndrome cases diagnosis by district of residence, West Midlands 1995-97

	Prenatal diagnosis				
District	**< 16 wks**	**16-23 wks**	**>= 24 wks**	**none**	**Total**
Birmingham	11	26	4	47	**88**
Coventry	4	9		16	**29**
Dudley	2	3		15	**20**
Herefordshire	2	1		4	**7**
Sandwell	1	10	1	12	**24**
Shropshire	3	9		12	**24**
Solihull	1	7		7	**15**
North Staffordshire	2	12	1	14	**29**
South Staffordshire	2	23		16	**41**
Walsall	1	5		4	**10**
Warwickshire	7	16	2	17	**42**
Wolverhampton	3	8	1	7	**19**
Worcestershire	10	12	1	20	**43**
West Midlands	**49**	**141**	**10**	**191**	**391**

Figure 5 illustrates the proportion of cases identified prenatally as shaded areas, and the timing of prenatal diagnosis. This reflects the style of screening available to women in different districts. North and South Staffordshire residents have the smallest proportion of cases diagnosed prenatally prior to 16 weeks and a relatively higher proportion of diagnoses made between 16 and 24 weeks. Presumably, this is due to the use of serum screening at 16 to 20 weeks. Overall, 13% of cases are diagnosed prior to 16 weeks, which constitutes 25% of prenatal diagnoses being made before the usual time of serum screening. Ten cases were prenatally diagnosed after 24 weeks gestation by ultrasound.

Figure 5 - Down's Syndrome cases diagnosis by district of residence, West Midlands 1995-97

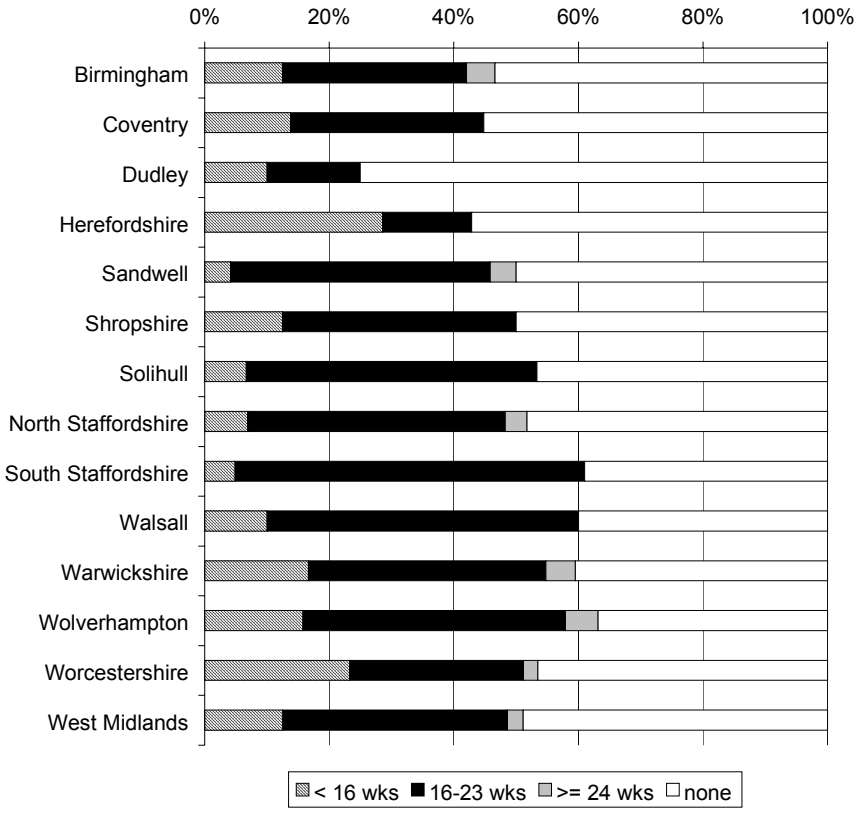
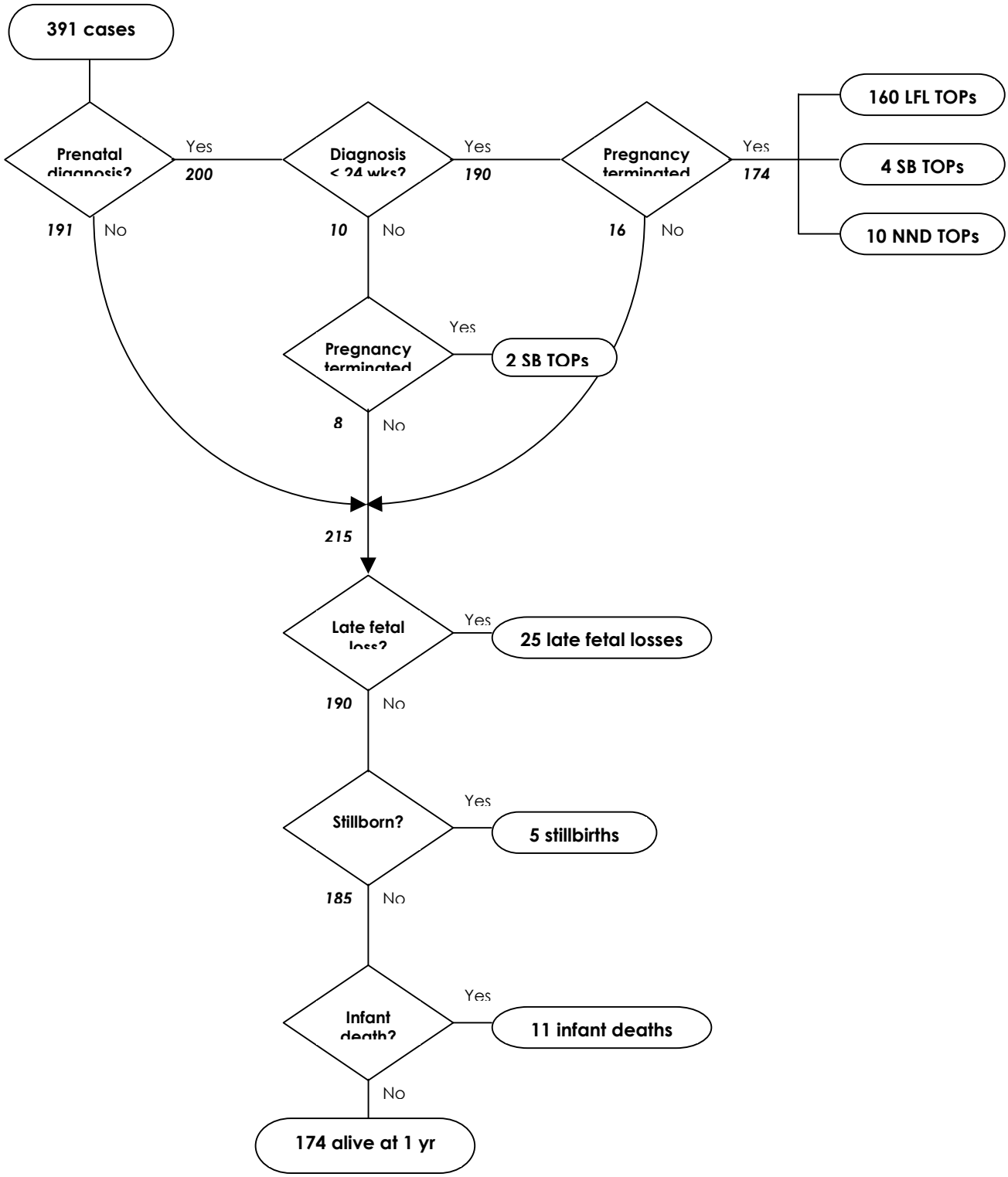


Figure 6 - Flow diagram of prenatal diagnosis and outcomes, West Midlands residents 1995-97



Two hundred of 391 (51%) Down's Syndrome cases were diagnosed prenatally. Prenatal diagnosis after 24 weeks gestation was rare (5% of prenatal diagnosis) and led to termination of pregnancy in 2 cases (20%) compared with 174 terminations (92%) following diagnosis before 24 weeks.

When a prenatal diagnosis was not made or women choose to continue the pregnancy following a prenatal diagnosis, 215 cases in total, the outcomes were 25 late fetal losses (12%), 5 stillbirths (2%), 11 infant deaths (5%) and 174 infants surviving to 1 year of age.

CYTOGENETICS

Table 11 - Down's Syndrome cases prenatal cytogenetics, West Midlands residents 1995-97

Prenatal cytogenetics	under 35 yrs	35 yrs and over	All ages
None	116	75	191
CVS +/- amnio	10	24	34
Amnio	72	78	150
FBS +/- amnio	5	6	11
Unspecified	1	4	5
Total	**204**	**187**	**391**

Figure 7 - Down's Syndrome cases prenatal cytogenetics by maternal age, West Midlands residents 1995-97

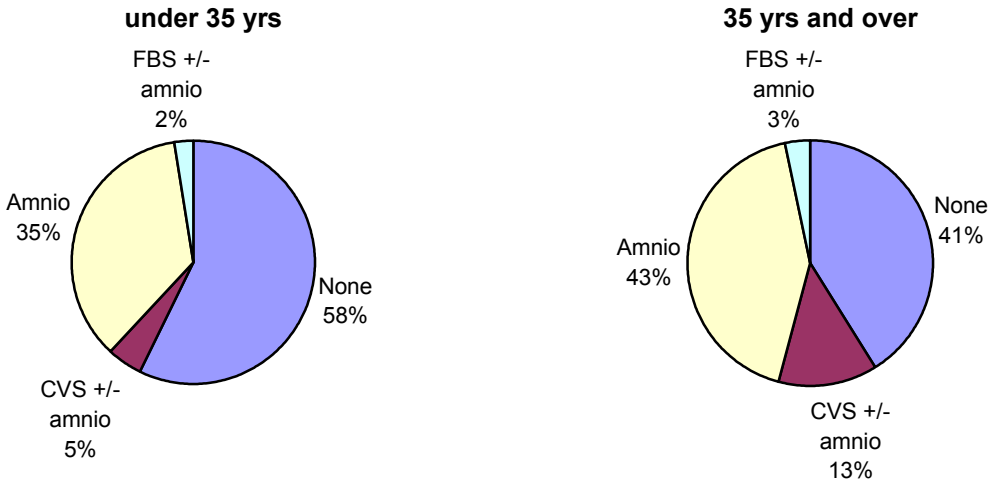


Figure 7 illustrates the methods of prenatal karyotyping. A regional CVS service ran during this time, aimed at providing a karyotype diagnosis by 13 weeks gestation for high-risk women, usually based on their age. The charts illustrate that CVS was used to make the diagnosis in 13% of cases in the older mothers, compared to 5% in those under 35 years of age. Fetal blood sampling is usually reserved for a small number of cases in which a rapid karyotyping procedure is required at 18 or more weeks gestation. This usually follows the finding of a structural anomaly on ultrasound, and is a small but consistent proportion of cases in the two age groups. Amniocentesis is the most common method of prenatal diagnosis with early amniocentesis before 14 weeks gestation accounting for a small number of cases. The majority of amniocenteses are undertaken at the traditional time of 16 to 18 weeks following serum screening. The favoured method of obtaining a fetal karyotype is debated. The risks and benefits of the various methods used in the West Midlands are a legitimate subject for review, but this information was felt to be beyond the scope of this report.

Table 12 - Down's Syndrome cases karyotypes, West Midlands residents 1995-97

Karyotype	n
47XY+21 or 47XX+21	370
Robertsonian Translocation	17
Mosaic Trisomy 21	2
Other complex mosaic	1
Karyotype failed to grow	1
Total	**391**

The Down's Syndrome cases caused by Robertsonian translocations involved chromosome 14 in nine cases, chromosome 15 in one case, and chromosome 21 in seven cases. Three cases occurred to mothers carrying a balanced translocation.

ADDITIONAL STRUCTURAL ANOMALIES

Additional structural anomalies were reported in 112 (29%) of Down's Syndrome cases. The following table lists the additional anomalies. Cases with multiple additional anomalies may be counted in more than one group.

Table 13 - Down's Syndrome cases with associated anomalies, West Midlands residents 1995-97

Associated anomaly	n
Cardiac/cardiovascular	88
Digestive/abdominal wall	14
Central nervous system	7
Renal	5
Eye	4
Limb/skeletal	2
Respiratory	1
Liver	1
Other	2

Table 13 shows that 88 cases had major cardiac anomalies, with significant numbers of digestive tract and central nervous system defects.

Cardiac anomalies

Table 14 - Down's Syndrome outcomes with/without cardiac anomalies, West Midlands residents 1995-97

Outcome	cardiac	no cardiac	no investigation	Total
Late fetal loss	1	5	19	**25**
Late fetal loss - TOP	13	63	84	**160**
Stillbirth	2	1	2	**5**
Stillbirth - TOP	1	4	1	**6**
Neonatal death	2	2		**4**
Neonatal death - TOP	3	7		**10**
Post neonatal death	6	1		**7**
Alive	60	114		**174**
Total	**88**	**197**	**106**	**391**

Table 14 displays the outcomes for those cases identified as having cardiac anomalies. The outcome in each case of Down's Syndrome is partly dependant upon a prenatal diagnosis. It is possible that cases with a prenatal diagnosis will undergo termination of pregnancy and therefore reduce the chances of any cardiac anomaly present being identified, but it is also possible for the cardiac anomaly to act as the initial trigger for consideration of karyotyping, independent to other risk factors. The number of cases identified as having cardiac anomalies in those cases terminated will therefore be a balance between these competing influences.

Only 10% of terminations of pregnancy were identified as having a cardiac anomaly, compared to 33% of those cases not terminated. The outcomes for infants with cardiac anomalies are generally good, with 60 of the 174 survivors having a cardiac anomaly diagnosis. Eleven infant deaths occurred (excluding terminations of pregnancy) of which eight had a cardiac diagnosis, demonstrating that cardiac defects are the significant cause of infant mortality in Down's Syndrome cases.

Table 15 - Down's Syndrome cases with cardiac anomalies, West Midlands residents 1995-97

Cardiac anomaly	n
Atrioventricular septal defect (AVSD)	24
AVSD + other malformation of valves	3
Atrial septal defect (ASD)	19
ASD + coarctation of aorta + peripheral arteriovenous malformation	1
Ventricular septal defect (VSD)	17
VSD + pulmonary atresia	1
VSD + other malformation of valves	1
VSD + ASD	8
VSD + ASD + other malformation of valves	1
Tetralogy of Fallot	7
Total anomalous pulmonary venous drainage	1
Other malformation of valves	1
Unspecified cardiac defect	4
Total	**88**

Table 15 lists the cardiac diagnoses, the majority are within the groups that are well recognised as being associated with Down's Syndrome, almost all having some form of septal defect with associated complications.

RECOMMENDATIONS

1. DOWN'S SYNDROME SCREENING

1.1 Each maternity unit should have:

- a clinical lead for Down's Syndrome screening.
- a named person who is responsible for liaison between community and hospital services.
- a written policy for the provision of Down's Syndrome screening services, a copy of which should be sent to the Regional Genetics Service. Suggested details of policy areas to be covered are included overleaf.

1.2 Information relating to Down's Syndrome should be made widely available to women.

1.3 Laboratories should audit the screening programme at least every 2 years and communicate to midwives and obstetricians.

1.4 The hospital services should work in partnership with their purchasers to provide information about the services offered to patients.

2. HIGH RISK CASES

2.1 In the event of a screen positive result expert counselling should be offered within three working days.

2.2 All women with a previously affected pregnancy should be offered karyotyping regardless of their age.

2.3 Karyotyping should be undertaken by an experienced individual who performs at least 30 (RCOG recommendation) and ideally 100 procedures annually.

2.4 Prenatal karyotyping should be considered before termination of pregnancy for structural abnormalities.

3. CONFIRMED CASES

3.1 Facilities should exist for a rapid second opinion.

3.2 Rapid access to a tertiary referral centre should be considered in cases where an abnormal karyotype is suspected or confirmed in the third trimester.

4. PAEDIATRIC CARE

4.1 Every child suspected to have Down's Syndrome should be karyotyped.

4.2 Parental karyotyping should be undertaken in all cases of translocation trisomy but there is no need to karyotype parents in cases of straightforward trisomy 21.

4.3 Expert paediatric assessment should be available for all children suspected of having Down's Syndrome. Facilities should be available to undertake cardiac assessment, and to treat affected cases appropriately. The finding of Down's Syndrome should not affect the clinical decisions regarding paediatric assessment or treatment.

DOWN'S SYNDROME POLICY FOR MATERNITY UNITS

Written policy should include details of:

Screening policy, including:

- Gestation of screening (including method of gestation age assessment).
- Communication of high risk screening results to patients.
- Communication of low risk screening results to patients.
- Facilities for post test counselling.
- Trust policy of management of cases identified as high risk by screening programmes from other trusts.

Maternal age limit for karyotyping.

Agreed standard for waiting time for a karyotype procedure to be undertaken.

Names of clinicians who will undertake karyotyping.

Communication of karyotyping results to parents.

Disclosure of fetal sex following karyotyping.

Management of abnormal karyotype results.

Policy for referral to genetic counselling services.

Post termination counselling facilities.

DEFINITIONS & GLOSSARY

Acrocentric
A chromosome in which the centromere (point where the different parts of the chromosome are joined) is near one end.

Amniocytes
The fetal cells floating in the amniotic fluid, mostly skin cells.

Analytes
The chemical substance in a biochemical sample which is analysed.

Aneuploid
A chromosome number that is not an exact multiple of the haploid number (i.e. not 23, 46, or 69).

Autosome
Any chromosome which is not a sex chromosomes (X or Y).

Brachycephaly
Head shape which is flattened at the back.

Chromosome
Thread-like, darkly staining bodies within the nucleus, made up of chromatin and DNA, which carry the genetic information.

Clinodactyly
Small inward curving little finger.

De novo
Occurring for the first time, rather than inherited.

Denominators
The population at risk in the calculation of rate or ratio.

Early neonatal death
Death during the first week of life, 0-7 completed days (on or before the 7th day of life, 0-6 days 23 hours 59 minutes).

Epicanthic fold
Fold of skin at the inner canthus of the eye. Particularly common in Down's Syndrome but can be seen as a normal variant in some unaffected children.

Fibroblast
The precursor cells which are found in connective tissue.

Gamete
Eggs and sperm.

Gametogenesis
The process of creating gametes.

Gonadal
Referring to the gonads. Ovaries and testes.

Late fetal losses
For CESDI a late fetal loss is defined as a spontaneous abortion (miscarriage) occurring from 20 weeks 0 days (140 days) up to the end of 23 weeks 6 days (167 days). If gestation is unknown or uncertain, birthweights of 300 grams or above are reported.

Lymphocytes
A sub-group of white blood cells.

Meiosis (meiotic)
The type of cell division which occurs in gamete formation, with halving of the somatic number of chromosomes so that each gamete is haploid.

Mitotic
The type of cell division which occurs in replication of somatic cells.

Neonatal death
Death during the first 28 days of life, 0-28 completed days (on or before the 28th day of life, 0-27 days 23 hours 59 minutes).

Oocyte
Haploid female gamete.

Perinatal mortality rate
The number of stillbirths and early neonatal deaths (i.e. those occurring in the first week) during a stated year per 1,000 live and stillbirths occurring in the same year.

Phalanx/phalanges
The bones in the fingers and toes.

Post neonatal death
Death between one month and one year of age (28 days and over, up to just before 1st birthday).

Registerable births/deaths
Births or deaths that must be legally notified to the Registrar for Birth and Deaths include all those delivered after 24 completed weeks of pregnancy, and all live births.

Robertsonian translocation
A translocation between two acrocentric chromosomes, involving fusion at the centromeres.

Sandal gap
The gap between the big toe and the other four toes.

Sonolucent
Allowing ultrasound to pass through without reflection. Giving a dense black appearance on an ultrasound scan, implying fluid filled.

Stillbirth
Legal definition England & Wales.
"A child which has issued forth from its mother after the 24th week of pregnancy and which did not at any time after being completely expelled from its mother breathe or show any other signs of life".

Translocation
Transfer of chromosome material from one chromosome to another. If there is exchange of genetic material from one chromosome to another this is called a reciprocal translocation.

Trisomy
Three, rather than the usual two, copies of a chromosome.

Appendix A - Congenital Anomaly Register Notification Card

Appendix B - Congenital Anomaly Register Notification Form

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