Congenital Anomaly Register & Information Service

caris review

including 1998-2002 data

...visit our new website

...and inside

Welcome to the new slimline CARIS report.

CARIS is online - a new look website…

The improved CARIS website will be available from November 2003. It contains detailed information about congenital anomalies in Wales, based on data collected over the past 5 years. Access is available through the Internet and the Welsh Health Intranet* and the address is

www.caris.nhs.uk

What do you get on line?

Local information on specific anomalies and survival rates for individual conditions will all be included – details gleaned over the last five years. Our special reports will be there, including a review of cardiac anomalies, the picture of gastroschisis in Wales and an assessment of antenatal detection of anomalies. We will continue to add to these reports in the future. New for this year is a report on sex chromosome anomalies and an update on cleft lip and palate.

Use the website to pass on ideas to keep CARIS a useful resource for all those interested in the health of our babies and children in Wales.

…and a new look annual report

Our new look annual report is shorter than in previous years and gives a flavour of the information now available on the website. The report is now totally bilingual and is being made available to the public and many other agencies as well as NHS staff.

This report marks an important milestone for CARIS as it is based on our first 5 years of data collection and includes:

- **Congenital anomalies in Wales – an overall view**
- **Facial clefting – an update**
- **Sex chromosomal anomalies – a review with local data**

Thank you…

Reporting congenital anomalies to CARIS continues to be very important. The data is used to help plan and evaluate health services and to investigate possible causes of anomalies. Once again we would like to thank all the hard working professionals who have supported us.

* *also accessible through the HOWIS (NHS Wales) website at www.howis.wales.nhs.uk/caris*

What is CARIS?

CARIS is the Congenital Anomaly Register and Information Service for Wales. Based in Singleton Hospital, Swansea, it is funded by the Welsh Assembly Government as part of NHS Wales.

The fundamental aim of CARIS is to provide reliable data on congenital anomalies in Wales. With this valuable data, studies can be done on the profile of congenital anomalies in

- antenatal screening/interventions
- health service provision for affected babies and children
- possible clusters of birth defects and their causes

We collect data on any baby or fetus for whom pregnancy ended after 1st January 1998, where the mother was normally resident in Wales at the end of pregnancy.

CARIS uses a multiple source reporting system and at present over 100 individuals or agencies regularly send us information. Data from clinical and laboratory sources is reported via warning cards, reporting forms and data exchanges. CARIS co-ordinators in each Trust are responsible for much of the clinical reporting. In the CARIS office, data is collated, the information is coded and the data quality carefully checked. The data is then available for feedback to clinicians – paediatricians, ultrasonographers, midwives etc, as well as supplying information to the National Assembly of Wales, EUROCAT and the Office for National Statistics (for surveillance).

At the CARIS office we cannot underestimate the importance of the confidential nature of our data and we operate a strict security and confidentiality policy. Recently we have gained support under section 60 of the Health and Social Care Act 2001 meaning that the register can continue collecting and analysing this valuable information.

Over 35,000 recorded pregnancies occur in Wales each year. Of these, about three-quarters are registered as live or stillbirths, the rest ending in termination or spontaneous loss of the fetus before the 24th week of pregnancy.

About 3% of births take place at home. Wales has 16 consultant obstetric units and 10 midwifery/general practitioner units. The majority of births take place in these units. However, a significant number of births to Welsh mothers occur in hospitals across the English border. Good links with congenital anomaly registers that border Wales (Mersey, West Midlands and the South West of England) remain very important.

Clinical reporting is the most important source of information for CARIS especially for those babies who:

- die but do not have a post mortem
- survive and have anomalies not requiring immediate specialist help

Diagnostic services, particularly ultrasound scanning and pathology, can alert us to a case or give valuable further information.

Regional services including cytogenetics and specialist clinical services can help by providing more details of the anomalies involved.

Babies with congenital anomalies may be recorded on other databases such as Protos (Cardiff), the All Wales Perinatal Survey or the Standard Child Health Computer System.

The first five years of data ...a milestone!

Rates for Wales

Having collected data for 5 years, CARIS is now in the position to estimate congenital anomaly rates for Wales based on over 150,000 births.
But how do you work out a congenital anomaly rate? What are the best ones to use?

The answer is – it depends on what questions need to be asked.

Which rate?

Not all areas collect the same information. Some may just include liveborn babies; some may be collected in countries where termination of pregnancy is not allowed. So we need to develop a variety of rates using different combinations of outcome to make sensible comparisons with other areas.

How many cases can we possibly identify?
Every single case is needed to look for possible causes of anomalies. Here we use "gross rates" including miscarriages, terminations, live and stillbirths.

How many cases have led to livebirths, stillbirths or terminations of pregnancy?
We need this figure to look at the workload for antenatal services.

How many liveborn cases are there?
Carers for babies with anomalies after birth are interested in this.

What are the chances my baby will survive, born with a congenital problem?
Parents want up to date, reliable answers about the future.

Information from the CARIS website shows different rates in detail, but briefly:

- About 4% of established pregnancies are affected by congenital anomalies. Some of these end in spontaneous miscarriage or termination of the pregnancy following antenatal detection of anomalies.
- 3.8% of babies or fetuses having antenatal care will have some form of anomaly (although not all of these will be picked up before birth).
- 3.3% of liveborn babies in Wales have some form of congenital anomaly and may require additional help as they grow and develop.

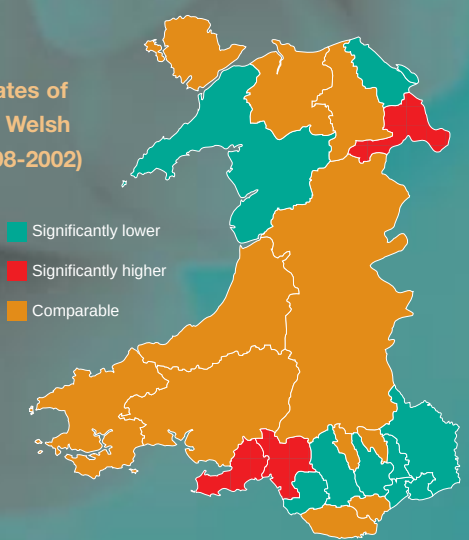
Just a reminder – as many as 30% of conceptions may be affected by a congenital anomaly but the vast majority miscarry in the very early weeks and never come to the attention of CARIS.

Congenital anomaly rates around Wales

Across Wales, there are differences between Unitary Authorities in reported rates of anomalies. Swansea and Neath Port Talbot have traditionally shown much higher rates than for the rest of Wales. CARIS is fortunate to have exceptionally good reporting arrangements for these two areas, which may well account for these differences. We keep the situation under close review.

Figure 1
Comparison of gross rates of congenital anomaly for Welsh Unitary Authorities (1998-2002)

Comparison with all Wales rate (as defined by 95% confidence limits)



The first five years of data

Are Welsh congenital anomaly rates too high?

Getting accurate reports of congenital anomalies is very challenging. We need links with many different sources to try and build up a detailed picture on each case. It's well known in other congenital anomaly registers around the world that finding information on every single case is really difficult.

We have been very fortunate in Wales that so many professionals have taken the time to send data to CARIS. As a result, the data tends to show higher rates for Wales than data from many other similar countries in the western world – such as EUROCAT data (combined from many different European registries). Because all congenital anomalies show high levels in Wales it is most likely that these higher rates are due to better reporting than in other areas. Welsh rates are not excessive when compared to the most comprehensive European Register in Mainz, Germany. However, the possibility remains that Welsh rates are truly higher than elsewhere – we are keeping the situation under review and looking for new ways to put Welsh data into perspective.

Meanwhile we still want to keep on improving reporting in Wales, at the moment concentrating on speeding up the time it takes to report a case and helping out with any local reporting difficulties when they occur.

What are the main types of congenital anomaly?

Depending on which body system is affected, CARIS classifies anomalies into broad groups. Cardiovascular anomalies are the largest group, followed by anomalies of the limbs and then the urinary system.

Figure 3
Main anomaly groups for all cases reported to CARIS, 1998-2002

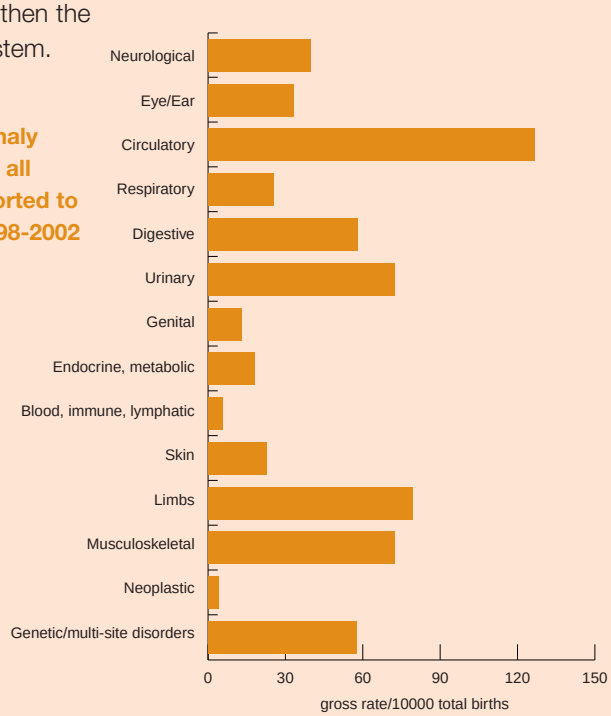
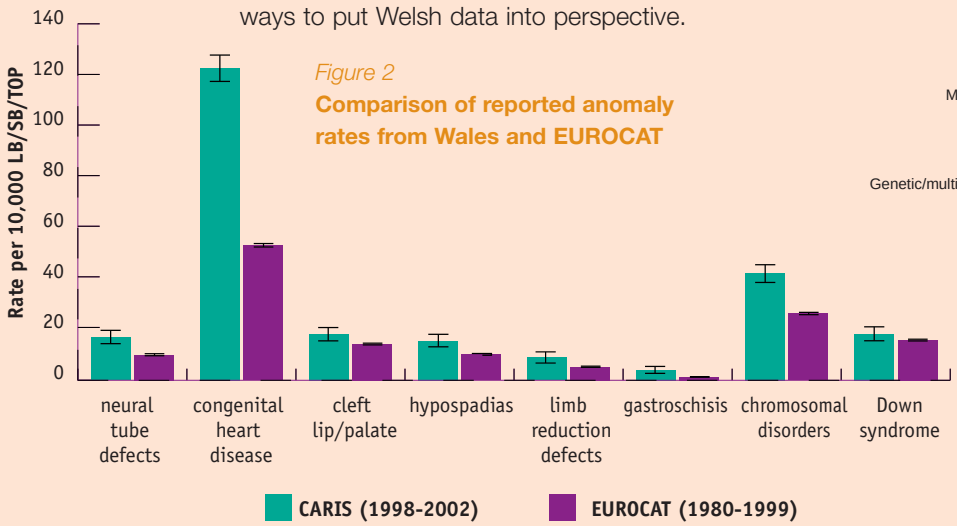


Figure 2
Comparison of reported anomaly rates from Wales and EUROCAT



The first five years of data

Cases and anomalies – what's the difference?

When looking at tables or lists of congenital anomalies it's important to remember the difference between a case and an anomaly.

A baby or case may have several anomalies. Some of these anomalies can indicate the presence of an underlying syndrome.

For example, a baby with Down syndrome may display some of the typical features. It may also have associated heart or gut anomalies. Alternatively, antenatal testing may confirm the presence of the Down syndrome during pregnancy, before any other features or anomalies are detected. Should the decision be made to terminate a pregnancy, the specific features and anomalies to be found in that particular case may never be known.

CARIS uses four broad patterns to describe the pattern of anomalies in cases.

- single anomaly e.g. a single heart defect like a VSD
- multiple anomalies but only affecting one body system e.g. multiple heart anomalies
- multiple anomalies affecting more than one body system e.g. a baby with both heart and limb defects
- syndrome - in which an underlying recognisable syndrome has been identified, regardless of the number of anomalies reported. Syndromes may relate to
  - chromosomal disorders
  - non chromosomal syndromes

About half of cases reported to CARIS have a single anomaly.

Over a third have anomalies affecting more than one body system or an underlying syndrome.

Demographic features

Gestational age

As we would expect, there are two peaks in gestational age at end of pregnancy for babies with congenital anomaly.

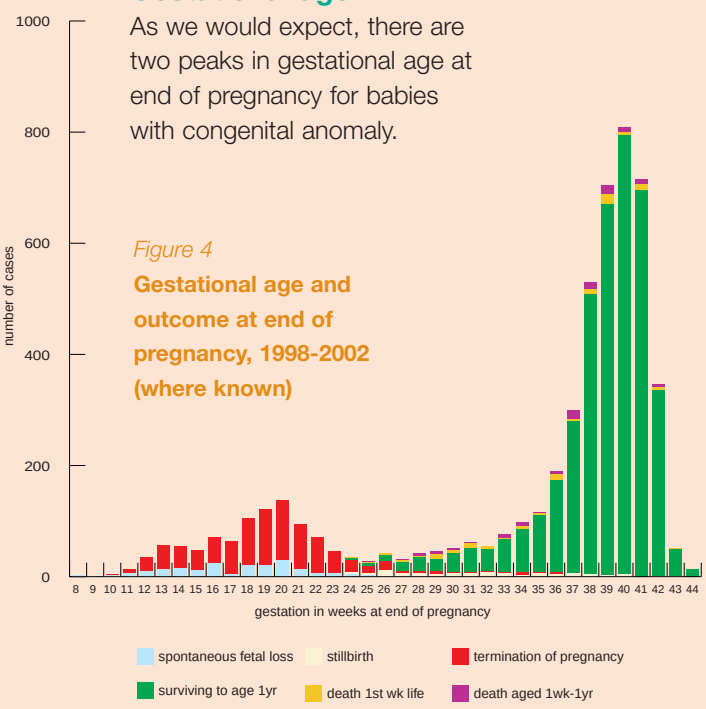


Figure 4
Gestational age and outcome at end of pregnancy, 1998-2002 (where known)

The first occurs between 16 - 22 weeks of pregnancy and is largely accounted for by terminations of pregnancy following antenatal detection of anomalies. The second and much larger peak occurs around term. As with the majority of births, most term babies with congenital anomalies are liveborn.

Multiple pregnancies

In the 5 years of data available, 263 cases (4.2%) were part of a multiple pregnancy.

Using ONS data for the same years, the percentages of pregnancies in which at least one fetus was affected by a congenital anomaly were:

4.0% of all pregnancies (n = 6238/156121)

3.9% of singleton (single fetus) pregnancies (n = 4067/153862)

9.7% of multiple (twins, triplets) pregnancies (n = 218/2259)

The relative risk of having a fetus affected by a congenital anomaly in a multiple pregnancy is 2.5 times that in a singleton pregnancy.

The 218 pregnancies affected included 2 quadruplet, 17 triplet and 199 twin pregnancies. In 39/218 pregnancies (17.9%), all the fetuses were known to be affected. Twin studies can give us unique insights into the causes of congenital anomalies, and, as the CARIS database grows, we may be able to help with further information.

Maternal age

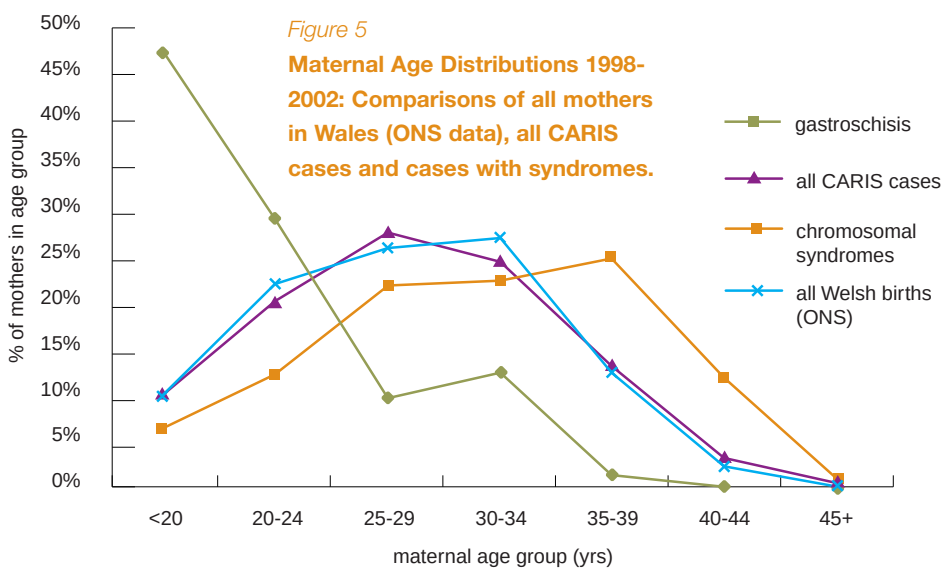
It's well known that maternal age can influence the numbers and types of congenital anomaly that occur. Our data shows how the age patterns of mothers of babies with some congenital anomalies are different to the pattern of mothers in Wales as a whole.

Most dramatically, over three quarters of mothers of babies with gastroschisis (a defect in the wall of the abdomen) are under the age of 25, although for the mothers of babies without this condition, less than a quarter are under 25. The reasons for this difference are not completely clear and research continues around the world into this condition.

Greater proportions of mothers of babies with chromosomal syndromes are in the 35 year + age group compared with the general population of expectant mothers. This is due to the increasing incidence of chromosomal anomalies with advancing maternal age.

Figure 5

Maternal Age Distributions 1998-2002: Comparisons of all mothers in Wales (ONS data), all CARIS cases and cases with syndromes.



Sex of fetus

More male babies are born each year than females (ONS birth data).

In Wales, for the years 1998 – 2002) the ratio of males to females among live and stillbirths was 1.1 to 1.

The trend is even greater for congenital anomaly cases, with a gross male: female case ratio for the same years of 1.2 to 1.

The gross rate* of congenital anomalies for male fetuses reported to CARIS was 419/10,000 total births (95% CIs 406 to 433).

For females the corresponding rate was significantly lower at 357/10,000 total births (95% CIs 344 to 370).

Looking at the data, the excess of male cases is associated mainly with anomalies of the urinary and genital systems. There are also more male cases of anomalies of the digestive and musculoskeletal systems. The website includes tables of the male to female proportions for many groups of anomalies.

Significantly more boys than girls are born with congenital anomalies

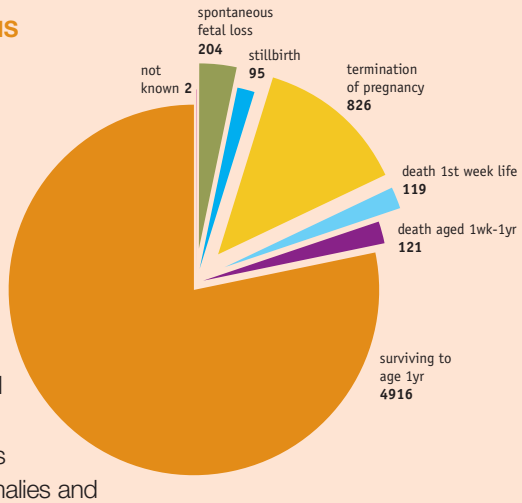
Survival of CARIS cases

Well over three quarters of babies with congenital anomalies survive to the end of the first year of life.

CARIS keeps a record of how each pregnancy ends and, if the baby is liveborn, whether he/she survives to the end of their first year of life. This shows that well over 75% of all cases survive to this point. Over half of the remainder result in termination of the pregnancy with the rest due to natural losses or postnatal deaths.

Figure 6

Outcome for CARIS cases to end of first year of life, 1998-2002



As you would expect, there is a difference in outcome between the patterns of anomalies. Survival is higher among babies recorded as having single anomalies and poorest for those recorded as having chromosomal syndromes. Non chromosomal syndromes appear to have better outcomes than cases of multiple anomalies affecting more than one body system. In general, poorer rates of survival can be accounted for by higher rates of termination of pregnancy. The poorer rates may also be related to post-mortems in the babies who have died, revealing additional anomalies not apparent in survivors.

Survival is best in babies with single anomalies and poorest in babies with chromosomal syndromes

* *including miscarriages, terminations, live and stillbirths*

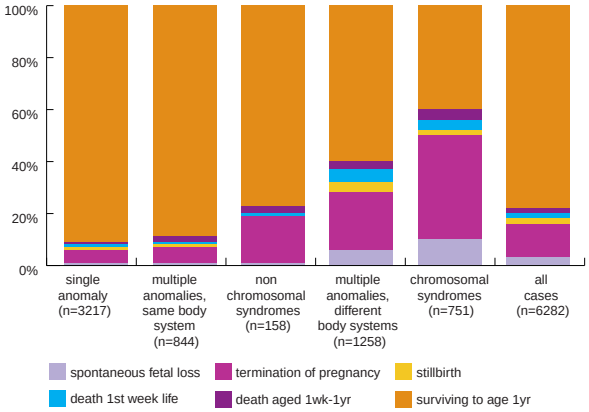


Figure 7

Outcome of pregnancy by pattern of anomalies: Confirmed CARIS cases 1998-2002

The CARIS website has further details of outcomes for cases with specific conditions. This shows, for example:

- no babies with anencephaly survived more than a few days (a form of neural tube defect causing severe malformations of the head and brain).
- Over 90% of liveborn babies with heart defects were still alive at 1 year.
- With improved treatment, over a quarter of liveborn babies in Wales with hypoplastic leaft heart syndrome condition are recorded as surviving to the end of their first year. (Until recently, this condition was inevitably fatal within a few weeks or months of birth)

Despite using 5 years worth of data, the numbers of cases involved are still relatively small and figures should be interpreted with care. The figures are recorded retrospectively and should not be taken as a predictor of outcome.

Survival is obviously only one outcome for babies with congenital anomalies. CARIS does not collect data on other factors such as levels of disability, quality of life or the need for further medical treatment.

Variations in survival across Wales

Survival rates for CARIS cases appear to vary across Wales. The website gives greater detail for all the Welsh Unitary Authorities.

Overall, survival rates appear to be:

- Significantly better in Swansea, Neath Port Talbot and Merthyr.
- Significantly poorer in Conwy, Monmouthshire, Newport and Torfaen.

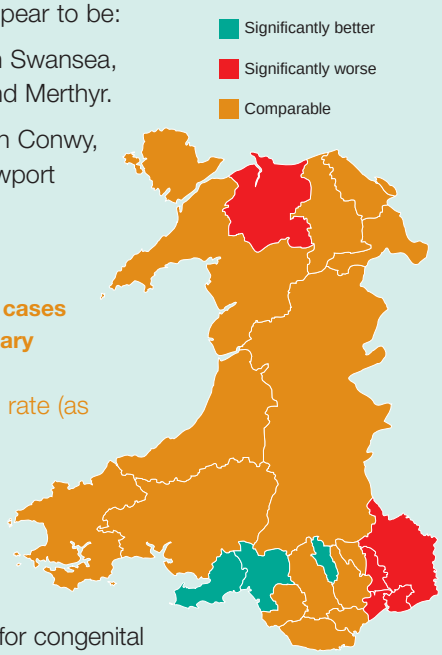


Figure 8

Survival rates for CARIS cases 1998-2002 by Welsh Unitary Authorities

Comparison to all Wales rate (as defined by 95% confidence limits)

Swansea and Neath Port Talbot are the Unitary Authorities with the highest overall rates for congenital anomalies and the highest survival rates. It is likely that good reporting in these areas has resulted in better reporting of cases with less severe anomalies. It is not yet clear how much of the variation in survival rates is due to differences in clinical reporting of survivors rather than true differences in outcomes.

The bottom line for Wales is to collect the best possible congenital anomaly data from every possible source – CARIS then has the best chance to build up an accurate picture of survival of babies with congenital anomalies in Wales.

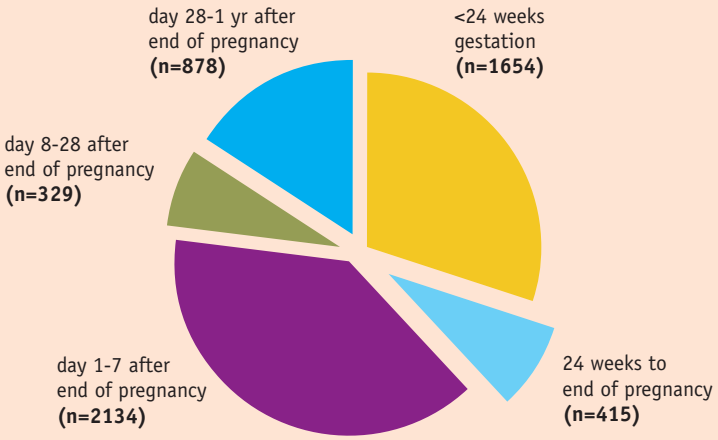
The first five years of data

When are anomalies first suspected?

CARIS collects data on when cases are first suspected to have some form of congenital anomaly. This information is available for 5410/6283 cases reported from 1998 to 2002 (86%). Overall, 38% of cases were first suspected to have some form of congenital anomaly antenatally (30% by the 24th week of pregnancy). 39% were first detected in the week after pregnancy ended. This included detection following fetal loss or termination of pregnancy as well as livebirths. Antenatal detection varies between anomalies and further details for individual birth defects can be found on the website.

Figure 14

Reported stage of pregnancy/infancy at which case first suspected to have an anomaly. (5410 cases for which information available, 1998 – 2002)



Surveillance of congenital anomalies

The Office for National Statistics (ONS) operates a surveillance system to detect potential rises in the number of babies born with congenital anomalies. In this, the number of anomalies reported for a particular geographical area and time period are compared with the expected number, based on the previous year of reporting. If the number of actual anomalies exceeds the number expected, a warning is sounded to alert to a potential problem. Analyses are based on numbers of births and do not include termination data.

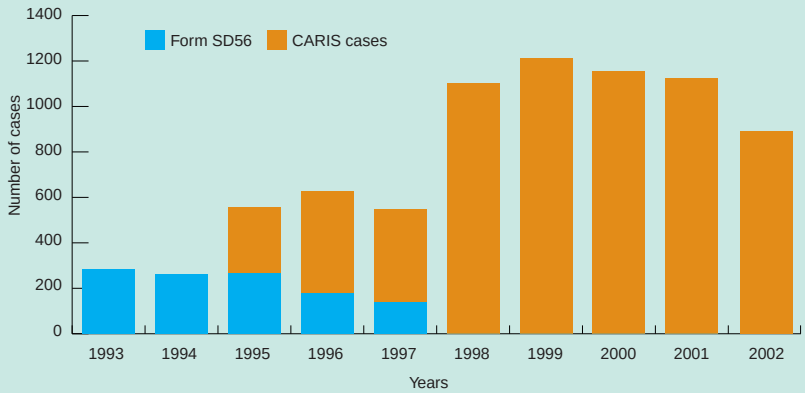
Warnings may be triggered by a true rise in rates of a particular congenital anomaly. However other factors may also be involved, including:

- Improved reporting leading to increased numbers of cases being identified
- Variations in rates of termination of pregnancy
- Changes due to small numbers.

Since starting data collection, CARIS has replaced the old paper based system of reporting (on form SD56) by a modern electronic system. This has led to a dramatic rise in cases from Wales and numerous surveillance warnings. Over the next year, CARIS intends funding a project to look at ways to improve surveillance of congenital anomalies in Wales. This will aim to make better use of the available data, ensure that warnings are issued more appropriately and to develop protocols setting out how warnings should be investigated and managed.

Figure 15

Cases of congenital anomaly reported to the Office for National Statistics, 1993-2002. Comparison of numbers reported by Health Authorities and CARIS



Cleft lip and palate...an update

What is cleft lip and palate?

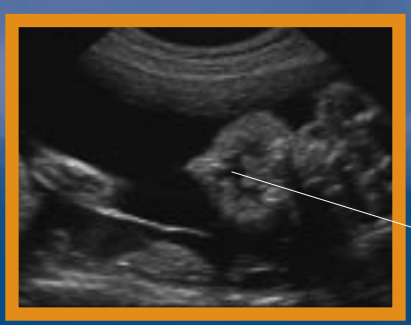
"Cleft" means a split or separation. The face develops from several different areas that then fuse together. This occurs by about 5 weeks after conception for the lips and by about 9 weeks for the palate (the roof of the mouth). Clefts may develop if this process doesn't work properly. Clefts of the upper lip and the palate are the commonest of these anomalies and are diagnosed in about 1 in 700 births.

Clefts of the lip may vary from a notch in the coloured part of the lip (the vermilion) to a complete split reaching up into the nose. They can occur on one side (a unilateral cleft) or both sides (bilateral clefts).

The palate is made up of two parts – the hard (bony) palate at the front and the soft (muscular) palate at the back, ending with the uvula. Cleft palate can occur alone or in combination with cleft lip. It may involve one side of the mouth or (more rarely) the midline when it is associated with higher rates of other birth defects. Small clefts affecting only the soft palate at the back are often not diagnosed at birth, especially if the overlying membranes remain intact (sub mucous clefts). These milder defects often present in the first years of life when associated speech problems become more apparent.

Babies with clefts may have a variety of difficulties with feeding, speech development, hearing problems and dental conditions. Sometimes, affected babies also have a small jaw (Pierre Robin Syndrome), leading to severe swallowing difficulties.

The birth of a baby with a cleft lip can cause a mix of emotions for parents who need information and support. On the clinical side, successful treatment involves a multidisciplinary approach, including nursing, speech therapy, paediatrics, and plastic surgery.



cleft lip seen on antenatal ultrasound

Causes of orofacial clefts include both environmental and genetic factors, although these are not well understood. Factors include:

- A family history of facial clefts.
- Maternal use of medicines, alcohol and tobacco.
- Deficiency of folic acid before and during early pregnancy.
- Congenital constriction bands.

Cleft lip and/or cleft palate have been associated with over 400 different syndromes and affected children are at increased risk of having additional congenital anomalies.

Reported detection rates by antenatal ultrasound range from 25% to 43% Detection is more common for defects involving a cleft lip than isolated cleft palate. Polyhydramnios or difficulty visualising the fetal stomach may be suggestive of a facial cleft. This is probably due to leakage of amniotic fluid through the cleft and back into the amniotic cavity without being swallowed. Following the diagnosis of a cleft, the ultrasonographer will review the fetus in detail for additional anomalies. Chromosome analysis may also be recommended.

Clefting involving the palate alone appears to be a related but different condition to clefting involving the lip (or lip and palate) and there is evidence of interesting differences between them.

unilateral cleft lip

bilateral cleft lip

Cleft lip and palate

For the 5 years 1998-2002, a total of 318 cases of cleft lip and/or palate have been reported to CARIS, giving a gross rate of about 20 per 10,000 births. Among these cases, 164 (52%) had a cleft lip (plus or minus cleft palate) and 154 (48%) had cleft palate alone.

Cleft lip (with or without cleft palate)

What do we know from the literature?

- About 70% of cases of cleft lip occur together with cleft palate.
- Cleft lip occurs unilaterally and on the left in 80% of cases.
- The condition is found in about 1 per 1000 live births, although this figure may be changing as increasing numbers are identified antenatally.
- Boys are affected more commonly than girls.
- Additional birth defects are found in 13% of cases.
- There is an association with maternal use of antiepileptic drugs.

The picture in Wales

Rates of cleft lip (with or without cleft palate) in Wales are slightly higher than the most recent rates published by EUROCAT (based on over 6 million births around Europe) but these differences are not statistically significant.
The CARIS rate for Wales is 1 case of cleft lip in 1299 live births.

CARIS data supports published figures in that:

- 110/164 (67%) of cases of cleft lip were associated with cleft palate
- 110/164 (67%) of cleft lip cases were male (compared with 52% of all births in Wales)
- The presence of anomalies was suggested antenatally in 80/164 (49%) of cases.

Against the published figures, CARIS data showed a higher than expected rate of additional birth defects (41% of cases).

Cleft lip and cleft palate	Liveborn cases per 10,000 livebirths (95%CIs)	Cases that are liveborn/stillborn/ TOP/fetal deaths (20+ weeks gestation) per 10000 live & stillbirths (95%CIs)
CARIS data 1998-2002 (156,000 births)	7.7 (6.4-9.1)	9.5 (8.0-11.0)
EUROCAT data 1995 - 1999 (6 million births)	7.4	8.5

Isolated cleft palate

What do we know from the literature?

- Isolated cleft palate is less common than cleft lip, and is diagnosed in about 1 per 2000 live births.
- Diagnosis may not be made at birth if the cleft is small and at the back of the palate. Diagnosed rates by the age of 5 are therefore approximately twice that at birth.
- Girls are more often affected than boys.
- Other birth defects are found in 50% of cases.
- The condition itself remains difficult to identify antenatally although other associated anomalies may be picked up through ultrasound scanning.
- Isolated cleft palate is not associated with maternal use of antiepileptic drugs.

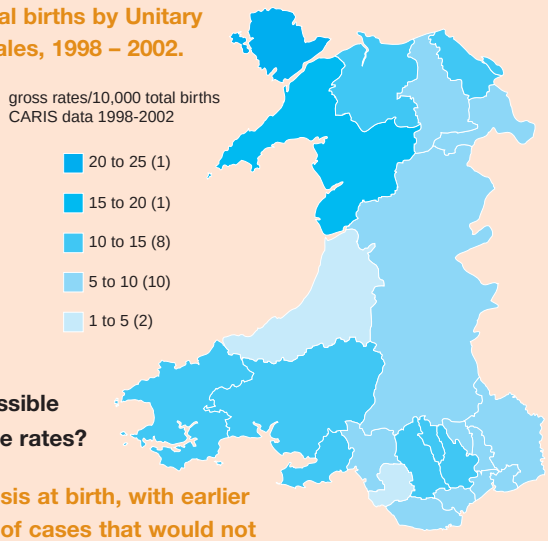
The picture in Wales

CARIS data for isolated cleft palate in Wales give a rate of 1:1429 livebirths. Rates are significantly higher than the most recent figures available from EUROCAT.

Rates are generally higher on the western side of Wales, with the highest in the North West (although these are not statistically significantly higher than for Wales as a whole).

Figure 9

Gross rates of isolated cleft palate/10000 total births by Unitary Authorities in Wales, 1998 – 2002.



What are the possible reasons for these rates?

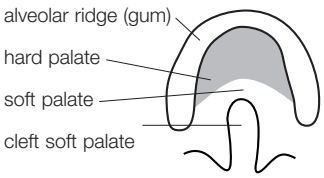
- **Better diagnosis at birth, with earlier identification of cases that would not normally be picked up until later in childhood.**

  Data from the Register in Mainz in Germany show high rates for cleft palate, similar to Wales. We know that an intensive infant surveillance programme is used there, ensuring that the majority of cases are picked up early. It is possible that the apparent excess of cases in Wales could be due to better early detection of palate defects, especially those affecting the soft palate. (This is the type most difficult to diagnose early on).

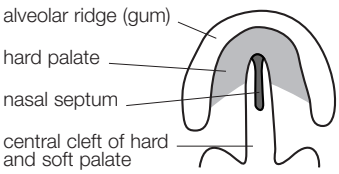
Isolated cleft palate	Liveborn cases per 10,000 livebirths (95%CIs)	Cases that are liveborn/stillborn/ TOP/fetal deaths (20+ weeks gestation) per 10000 live & stillbirths (95%CIs)
CARIS data 1998-2002 (156,000 births)	7.2 (6.4-9.1)	9.0 (8.0-11.0)
EUROCAT data 1995 - 1999 (6 million births)	4.7	5.3

Partial clefts of palate

Roof of mouth with cleft soft palate

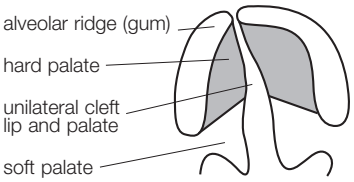


Roof of mouth with central cleft of hard and soft palate

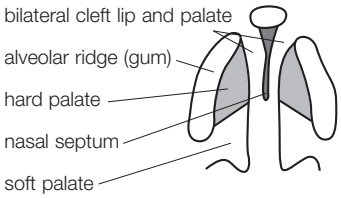


Complete clefts of lip and palate

Roof of mouth with unilateral cleft lip and palate



Roof of mouth with bilateral cleft lip and palate



With only 5 years of data, numbers for the different types of cleft palate remain small and difficult to interpret. Interestingly, for North Wales, 35% of cases of isolated cleft palate are recorded as affecting only the soft palate – a higher proportion than for Wales as a whole (28%). Identification rates beyond the first year of life are not readily available to complete the picture.

- **Misreporting of high arched palates (a normal variation) as central clefts.** There is no evidence of misreporting. The pattern of central clefts around Wales does not show an excess in the North West of the country.
- **A true excess in isolated cleft palate in Wales.** If this is the case, genetic and/or environmental factors may play a part. Certainly this would fit with the picture in Finland, where there are clearly demarcated areas with high rates of cleft palate, thought to be related to patterns of migration in the past.

Apart from the higher rates, CARIS data also showed that

- 52% of cases are female (compared to 49% of all births in Wales).
- 74% of cases are associated with other congenital anomalies – as for cleft lip, this is higher than might be expected from the literature.
- For central cleft palate, 83% of cases were associated with other anomalies (cases with this type of cleft are known to have higher levels of additional defects).
- The presence of anomalies was suggested antenatally in 42/154 (27%) of cases.

Syndromes associated with clefting

Underlying syndromes were identified in 29/164 (18%) of cases of cleft lip and 60/154 (39%) of cases of isolated cleft palate.

Where information is available on the type of isolated cleft palate, syndromes were identified in:

- 19/45 (42%) cases of central cleft
- 7/17 (41%) cases of hard and soft cleft
- 15/43 (35%) cases of soft palate cleft

Pierre Robin syndrome is the most common underlying syndrome, affecting 29/318 cases. Smith Lemli Opitz syndrome was found in 6 cases. Although not a true syndrome, congenital constriction bands were found in 6 cases.

Chromosomal disorders were present in 26/164 (16%) cases of cleft lip and 28/154 (18%) cases of cleft palate alone. The types of chromosomal disorder found include

- 22 cases trisomy 13 (Patau syndrome)
- 12 cases triploidy/polyploidy
- 8 cases trisomy 18 (Edward syndrome)
- 4 cases sex chromosome anomalies
- 2 cases trisomy 21 (Down Syndrome)
- 10 cases other chromosomal defects

Other anomalies

Underlying chromosomal disorders account for many of the anomalies associated with orofacial clefting. The graph illustrates the frequency of various broad groups of anomalies in all cases of cleft lip/palate reported to CARIS, and also indicates whether they are associated with an underlying chromosomal defect. Interestingly, about half are not associated with chromosomal anomalies.

Musculoskeletal anomalies are the largest group associated with orofacial clefts. Over half of these relate to other anomalies of the skull, face and neck. Common limb anomalies include poly/syndactyly, limb reduction defects and non postural talipes. Cardiac septal defects account for three quarters of the heart defects.

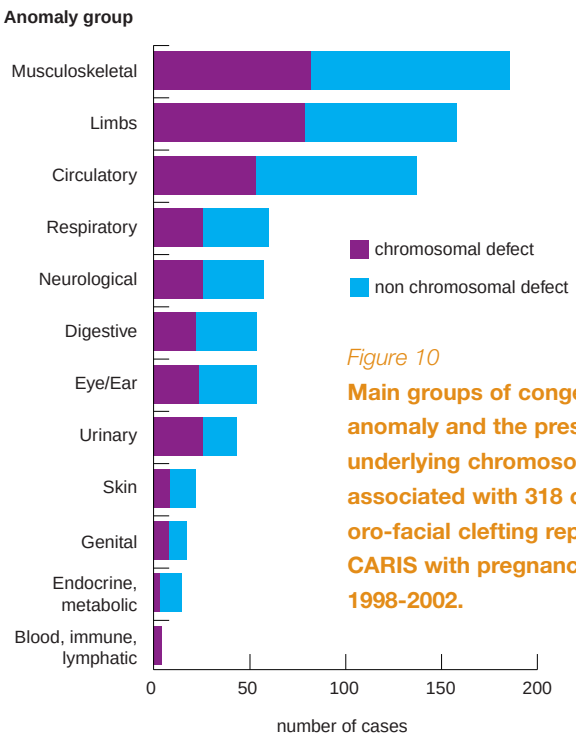


Figure 10

Main groups of congenital anomaly and the presence of an underlying chromosomal defect, associated with 318 cases of oro-facial clefting reported to CARIS with pregnancy ending 1998-2002.

Outcome+survival

Overall, 73% of cases of cleft lip and/or palate were liveborn and of these, 94% survived their first year of life (just over two thirds of all cases reported). Within these figures, the survival outcome for cases of isolated cleft palate was slightly poorer than for cases involving cleft lip, although these differences are not statistically significant.

The presence of an underlying chromosomal defect has a major impact on outcome.

- For cases involving cleft lip:
  - liveborn rates were 31% with an underlying chromosomal disorder but 86% without.
  - for liveborn cases, 1/5 cases with a chromosomal defect (20%) survived to 1 year of age, compared to 115/117 (98%) without.
- For cases of isolated cleft palate:
  - liveborn rates were 39% with an underlying chromosomal disorder and 79% without.
  - for liveborn cases, 6/11 cases with a chromosomal defect (55%) survived to 1 year of age, compared to 97/100 (97%) without.

Sex chromosome problems

Every human cell has 22 pairs of chromosomes plus a pair of sex chromosomes, making 46 chromosomes altogether. Females have an XX pair of sex chromosomes whilst males have an XY pair. Problems in the production or fertilisation of human sex cells can result in sex chromosome abnormalities. The commonest problems involve missing or extra chromosomes.

Having an extra sex chromosome is actually a fairly common event. It's often unnoticed because the effect of an extra X or Y does not lead to the same severe consequences as an extra chromosome in the other pairs (as in Down or Edward syndrome). However, extra sex chromosomes can increases the chance of physical abnormality or learning disability and may be associated with later fertility problems.

With the exception of Turner syndrome, antenatal detection of a sex chromosome anomaly in a fetus or baby is often a chance finding, perhaps as a result of antenatal testing. When the situation arises, it can pose challenging issues for parents and staff alike as problems need to be discussed and decisions made about the future.

Turner syndrome

Turner syndrome involves a lack of one X chromosome in a female, giving a total number of 45 chromosomes instead of the normal 46. The lost chromosome is usually from the father. Advanced paternal age is associated with the condition.

Some key features of the syndrome are shown in the box.

Turner syndrome

Chromosomes:	45 XO
Occurrence:	1/3000-5000 live females
Phenotypic sex:	Female
Gonads:	Streak ovaries
Fertility:	Very low
Intelligence:	Usually normal
Other features	• Neck webbing • Short stature • Aortic coarctation • Auto immune conditions
Treatment:	• Oestrogen from puberty • Growth hormone

The prevalence in liveborn females varies between 1 in 3000 to 5000 livebirths, although it isn't clear how much this has been affected by improvements in antenatal detection.

The miscarriage rate is reported to be very high with over 95% of cases lost in early pregnancy. 10% of all miscarriages in the first 12 weeks may be due to Turner syndrome.

70 cases were reported to CARIS from 1998-2002, giving a gross rate* in Wales of 9.1 per 10,000 female births. Of the 70 cases, 17 (24%) were fetal losses, reflecting the known high miscarriage rate. Pregnancy was terminated in 37 (53%) cases and 16 (23%) were liveborn. This means that in Wales over the past 5 years, 1 in 4782 liveborn girls have been affected by Turner syndrome, in keeping with expected levels. Of the 16 liveborn cases, 14 (88%) were still alive at the end of the first year of life.

Antenatal diagnosis

In Turner syndrome the lymphatic vessels at the back of the neck often become blocked. This causes an accumulation of fluid behind the neck called a cystic hygroma. The fluid may be more widespread and show up as generalised swelling or hydrops of the fetus. It has been estimated that up to 70% of fetuses with a cystic hygroma will turn out to have Turner syndrome.

* *including miscarriages, terminations, live and stillbirths*

Of the 70 cases of Turner syndrome reported to CARIS, 49 (70%) were detected before the 24th week of pregnancy and in 35 of these, the pregnancy was terminated. For the remaining 2 terminated cases, termination was undertaken because of other anomalies and Turner syndrome was diagnosed after the end of pregnancy.

Forty cases were reported to have a cystic hygroma (57%) and 27(39%) had hydrops/oedema on antenatal ultrasound. 8 further cases showed some enlargement of the nuchal area. Ultrasound findings suggested cardiac anomalies in 6 cases.

As the outlook in pregnancy is poor it is not surprising that in 11 of the 70 cases no fetal heart activity was seen on ultrasound scan.

Postnatal Diagnosis

Infant blood was sent for karyotype in 13 cases, the indications being clinical suspicion (3), follow up to confirm the antenatal result (3), and others including speech delay, short stature and failure to thrive.

Anomalies associated with Turner syndrome

Published reviews suggest that cardiac anomalies are seen in 15% of fetuses, coarctation of the aorta being the most common. Renal anomalies are seen less often and include hydronephrosis, renal hypoplasia and renal agenesis.

For the 70 cases reported to CARIS, 46 (66%) had some form of additional congenital anomaly, apart from cystic hygroma/hydrops. Circulatory system defects were present in 25 cases (36%), 15 of which involved problems in the development of the aorta. Urinary defects were present in 14 cases (20%). Poor lung development was another common feature, particularly in fetal losses.

Klinefelter syndrome

Klinefelter syndrome originates at an early stage of cell division when an error in splitting of the parental sex chromosomes results in an extra X chromosome in the fetus, either from the mother or father. The risk increases with maternal age.

This is one of the commoner chromosomal abnormalities with a reported prevalence rate of between 1 in 500 to 800 liveborn males. However, the majority of cases are not diagnosed for several years and sometimes the condition may never be recognised.

For the years 1998 – 2002, 14 cases of Klinefelter syndrome have been reported to CARIS. Nine of these were liveborn so that about 1 in 9,000 liveborn boys in Wales were known to be affected. Comparing this to the generally accepted rate, it is likely that 9/10 cases of Klinefelters are unrecognised during the first year of life. Five cases were terminated, one of whom also had Edward syndrome. All 9 liveborn cases survived to the end of their first year.

Other Sex Chromosome Anomalies

31 further cases were reported to CARIS including triple X syndrome (7 cases) and XYY syndrome (7 cases). The majority of these (25) were liveborn and most were known to have survived their first year.

	Triple X syndrome	XYY syndrome
Chromosomes:	47 XXX	47 XYY
Occurrence:	1 /1200 liveborn females	1 /1000 liveborn males
Phenotypic sex:	Female	Male
Gonads:	Normal	Normal
Fertility:	Normal	Normal
Intelligence:	Usually reduced	Usually normal
Other features	• Tall stature • Learning difficulties • Possible early menopause	• Tall stature • Learning difficulties • Possible severe acne
Treatment:	None	None

Klinefelter syndrome

Chromosomes:	47 XXY
Occurrence:	1/500-800 male livebirths
Phenotypic sex:	Male
Gonads:	Atrophic testes
Fertility:	Infertile
Intelligence:	Normal/Slightly reduced
Other features	• Poor facial hair • Tall stature • Gynaecomastia
Treatment:	• Testosterone from puberty

The presence of the extra X chromosome has a feminising effect on an otherwise male child, leading to many of the typical features of the condition. Infertility and learning difficulties are two of the more significant consequences.

Antenatal Diagnosis

Klinefelter syndrome is not associated with early pregnancy problems. Many cases are never diagnosed as there are no specific structural abnormalities.

Of the 14 cases in Wales, only 3 scan anomalies were reported. Interestingly, 3 mothers received Down syndrome screening results in the high risk range.

Postnatal Diagnosis

4 cases had infant blood karyotypes, the indications being congenital anomaly and developmental delay.

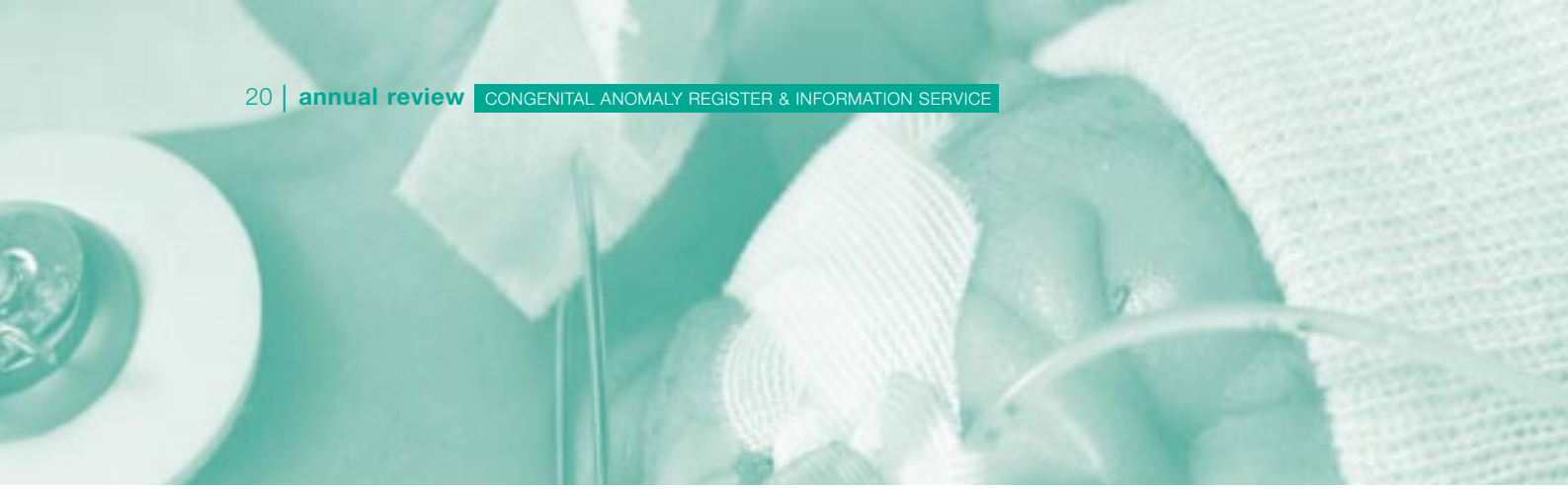
Associated Anomalies

Relatively few other anomalies were reported for cases of Klinefelter syndrome, apart from 1 case with additional chromosomal defects. Three cases were diagnosed as having cardiac septal defects.

Counselling in Sex Chromosome Anomalies

Giving parents any abnormal test result requires great care and sensitivity. Though sex chromosome anomalies appear to be quite common, clinicians may find it difficult to explain the implications of the diagnosis.

In the antenatal period the ultrasound and serum screening processes are in search of more serious conditions. After birth subtle changes in the baby such as developmental delay may prompt a request for a karyotype. A result may be negative for a serious chromosomal disorder but show a problem with the sex chromosomes. The parents deserve that this information is handled with the utmost care and it is essential to give honest informed advice.



A recent study looked at what parents were told after a prenatal diagnosis of a sex chromosome abnormality. They found great variation in how, where and who gave the information, with some examples of misleading or inaccurate counselling. Health professionals involved in this work need to be properly informed of the nature of sex chromosomal syndromes and their likely outcomes.

Abramsky L, Hall S, Levitan J, Marteau TM.
What parents are told after prenatal diagnosis of a sex chromosome abnormality: interview and questionnaire study.
BMJ (2001) 322 (7284):463-6

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