Congenital Anomaly Register & Information Service for Wales

caris review

including 1998-2006 data

inside...

NHS WALES GIG CYMRU

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CARIS, the Congenital Anomaly Register and Information Service for Wales, is based at Singleton Hospital, Swansea. It is funded by the Welsh Assembly Government and is part of NHS Wales.

Foreword

Welcome to the 2006 CARIS annual review. This year our special articles focus on risk factors for congenital anomalies.

Detailed data tables are available from the CARIS website on www.wales.nhs.uk/caris

Once again, we would like to express our appreciation to all contributing professionals for their continuing support for the register.

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The CARIS team at the 2006 South Wales Annual Meeting.

We are (left to right) Val Vye, Helen Jenkins, Judith Greenacre, Margery Morgan and David Tucker.

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

What is CARIS?

CARIS aims to provide reliable data on congenital anomalies in Wales. These data are used to assess:

- **patterns of anomalies in Wales**
- **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 is 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 are reported via warning cards, reporting forms and data exchanges. CARIS co-ordinators in each trust are responsible for much of the clinical reporting (details available from our website).

In the CARIS office, data are collated, information is coded and quality carefully checked. The data are then available for feedback to clinicians – paediatricians, ultrasonographers, midwives, etc. We also supply information to the National Assembly for Wales, EUROCAT, International Clearing House for Birth Defects and the Office for National Statistics (National Congenital Anomaly System) for surveillance.

We cannot overemphasise the importance we give to data confidentiality. We operate a strict security and confidentiality policy and have gained support under Section 60 of the Health and Social Care Act 2001.

This is renewed annually and means that the register can continue collecting and analysing data.

CARIS has set up an Expert Advisory Group to advise on future developments and monitor progress of the register.

Over 37,000 recorded pregnancies occur in Wales each year. Of these, about three quarters are registered as live or still births, 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 13 consultant obstetric units and 13 midwifery led units. The majority of births take place in these units. However, a significant number of births to Welsh mothers occur in English hospitals. Good links with congenital anomaly registers that border Wales (Mersey, West Midlands and the South West of England) remain important. Clinical reporting is invaluable in identifying cases to CARIS, particularly those babies who:

– die but do not have a post mortem

– survive and have anomalies not requiring immediate specialist help.

Clinical reporting also gives details such as expected date of delivery that can be difficult to obtain from other sources.

Diagnostic services, particularly ultra sound and pathology, can alert us to a case or give valuable further information. Regional specialist services, including cytogenetics, can help by providing more details of the anomalies involved. We also link to other databases, such as PROTOS (Cardiff), RadIS (Radiology information system), the All Wales Perinatal Survey and the National Community Child Health Database (NCCHD).

Key points on congenital anomalies in Wales 1998-2006

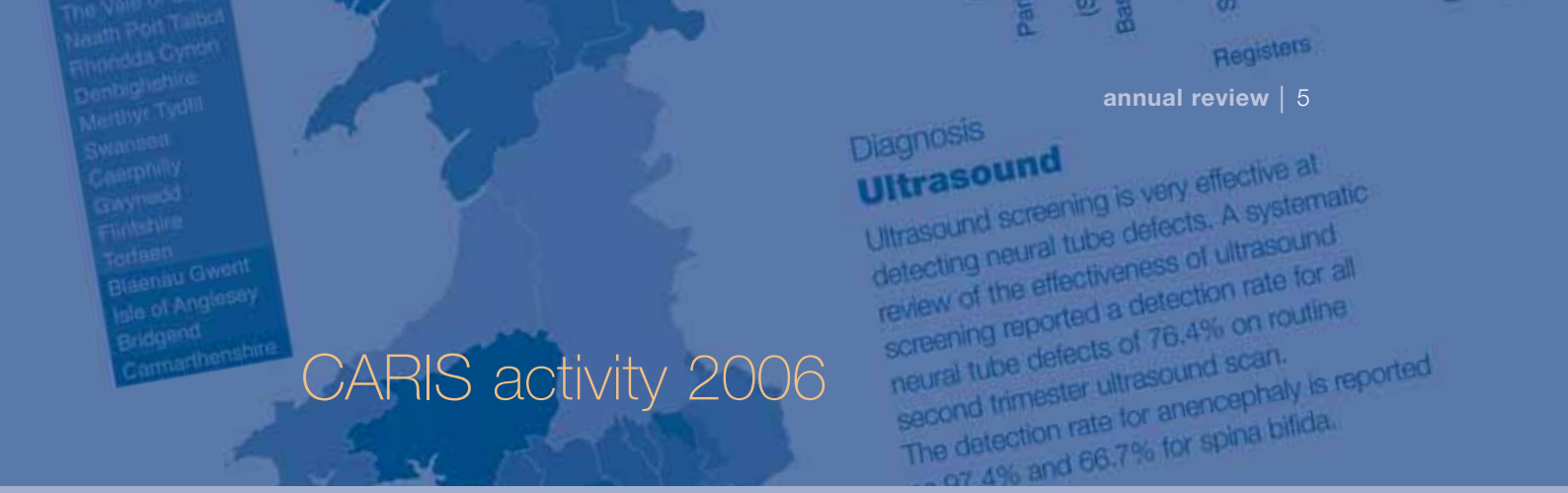
- 13,878 cases with confirmed congenital anomalies have been reported to CARIS with pregnancy ending between 1st January 1998 and the 31st December 2006. These include live births, stillbirths, terminations of pregnancy for congenital anomalies and miscarriages (although reporting of miscarriages will inevitably be incomplete). This means that the provisional gross* rate of known pregnancies affected by congenital anomaly is about 4.8% At the time of writing this report, delays in the publication of birth data for 2006 from the Office for National Statistics (ONS) mean that we have been unable to use the normal data sources to calculate rates. Analysis this year has been undertaken by the National Public Health Service Information and Analysis Team (HIAT). HIAT has estimated the number of births from other ONS sources. At this stage the rates must be regarded as provisional, although it is unlikely that the rates at national level will be very different from those published in this report.
- Eighty five percent of cases were live born. The percentage of all live born babies affected by congenital anomalies is 4.0%. CARIS makes every effort to ensure that babies who die during the first year of life are identified. According to our records, over 96% of live born babies with a congenital anomaly survived to the end of their first year of life. In over half of cases only one birth defect was recorded. In about 11% of cases an underlying chromosomal disorder was identified that could account for many of the physical anomalies. The remainder of cases had multiple anomalies of varying levels of complexity.

*The gross rate includes all cases of anomaly recorded as miscarriages, terminations of pregnancy, live and stillborn babies

- When analyses can be completed using ONS birth data, it is expected that, marked variations in congenital anomaly rates will again be seen around Wales, with apparently much higher rates for Swansea and Neath Port Talbot compared to other areas. Some of this variation remains due to continuing differences in reporting practices across Wales (see Reporting of anomalies in Wales: CARIS Review 2003). The areas with highest rates tend to have better survival rates for live born babies. This may again reflect better reporting of cases in infancy, allowing more survivors to be added to the numbers from better reporting areas. A further study of variations in rates will be undertaken in association with the NPHS during 2007/2008 and we hope to be able to report again on this in our next review.
- Rates for many anomalies in Wales appear relatively high when compared to other areas of Britain and Europe. This was also discussed in detail in the 2003 CARIS review. We still suspect that good reporting in Wales accounts for a large part of these differences and this year will again review the situation in detail. Data tables and a more detailed commentary are available on the CARIS website.

Summary

- Provisional gross* rates of congenital anomalies reported is 4.8%.
- 85% of cases are live born.
- 96% of live born cases survive to the end of their first year.
- Heart and circulatory defects are the largest single group.
- Variations in rates are again expected to be seen around Wales.
- Congenital anomaly rates in Wales are often apparently higher than for other areas of Europe or Britain.



CARIS activity 2006

The team has been involved with projects in Wales, the United Kingdom and internationally.

Wales

- Throughout 2006, we were involved in ongoing work with other agencies to monitor and investigate record levels of babies with gastroschisis, born across Wales. No clear pattern or reason for the increase could be discerned. We work closely with academic colleagues and the National Public Health Service for Wales to undertake enhanced data collection on all new cases of gastroschisis, to try and learn more about this condition.
- In our review last year we identified apparently high rates of neural tube defects in Carmarthenshire. We have contributed to a further investigation during 2006 / 2007. A review by Dr Ann John (National Public Health Service) has been presented to Carmarthenshire Local Health Board. This indicates that no specific problem could be identified in the Carmarthenshire area and that the high rate appears to be a chance finding. CARIS will continue to monitor levels of neural tube defects on behalf of Carmarthenshire LHB.
- CARIS continued to collaborate with Antenatal Screening Wales, supporting development of the new antenatal ultrasound module of RadIS (radiology information system) and providing information on the antenatal diagnosis of congenital heart defects. We have also supported the development of a population based ultrasound soft marker study.
- CARIS has established good links with the Children's Kidney Centre, University Hospital of Wales, Cardiff.
- We contributed to a study day on antenatal diagnosis of cleft lip and palate, held by the South Wales and South West Managed Clinical Network for Cleft Lip and Palate.
- Annual meetings were held in Wrexham and Abergavenny. The focus was on anomalies of the central nervous system.

United Kingdom

- CARIS is an active member of the British Isles Network of Congenital Anomaly Registers (BINOCAR) executive group. At the scientific meeting in Bristol we presented posters on hypospadias and craniosynostosis.
- David Tucker has chaired the BINOCAR clinical coding working group which developed a coding framework to help achieve consistency in coding of congenital anomalies across the UK.

International

- CARIS presented Welsh data on craniosynostosis at the International Clearing House of Birth Defects Surveillance and Research (ICBDSR) conference in Uppsala, Sweden. We submit enhanced anonymised data to the ICBDSR rare diseases programme.
- CARIS presented information on the usefulness of inpatient (PEDW) data to congenital anomaly registers at the European Collaboration of Congenital Anomaly Registers (EUROCAT) Leaders meeting in Graz, Austria.
- We contributed to a WHO worldwide study on orofacial clefting.

Websites

- www.binocar.org
- www.eurocat.ulster.ac.uk
- www.icbdsr.org

Congenital anomalies: causes and mechanisms

CARIS describes congenital anomalies as involving a structural, metabolic, endocrine or genetic defect, present in the fetus / baby at the end of pregnancy.

Having a child with a serious abnormality can be a traumatic event for many couples. They may blame themselves in some way for the defect or may wonder if other factors in the environment may have caused the anomaly to arise.

However, parents are not to blame in any way for the great majority of birth defects. Indeed, no one may be at fault for what may represent a tragic accident.

The exact cause of most birth defects is unknown. For some anomalies, the reasons that it has developed are clearer – for example an inherited genetic defect or anomalies arising from congenital rubella syndrome. In other cases, the reasons that anomalies occur are not clearly understood but have been linked to various underlying 'risk factors'. In these situations, the underlying causes are often complex, involving interactions between genetic factors that predispose individuals towards having a birth defect and environmental factors that actually trigger the occurrence of the abnormality. Other factors such as smoking may also increase the risk of defects occurring.

Mechanisms leading to structural defects

Structural congenital anomalies can be divided into four groups that can help give clues about how the anomaly developed. This can be useful for both parents and clinicians. Although this can help explain how the defect developed, it does not necessarily explain why events occurred in one pregnancy rather than another.

Malformation	- poor formation of fetal tissue
Deformation	- unusual forces on normal tissue
Disruption	- breakdown of normal tissue
Dysplasia	- abnormal organisation of cells into tissues

Malformation

The development of an organ is abnormal from the beginning e.g. if fertilisation results in a chromosomal anomaly such as Trisomy 21 (Down Syndrome), organs such as the heart or brain can develop abnormally from the outset.

Deformation

Mechanical forces cause an abnormal form, shape or position of part of the baby e.g. talipes equinovarus (club foot) caused by oligohydramnios (reduced amount of amniotic fluid).

Disruption

A normal development process is broken down or interfered with by some external factor e.g. exposure to teratogens such as drugs or viruses (teratogenesis). A classic example of this is the limb reduction defects that developed in babies of mothers who took the drug thalidomide during early pregnancy.

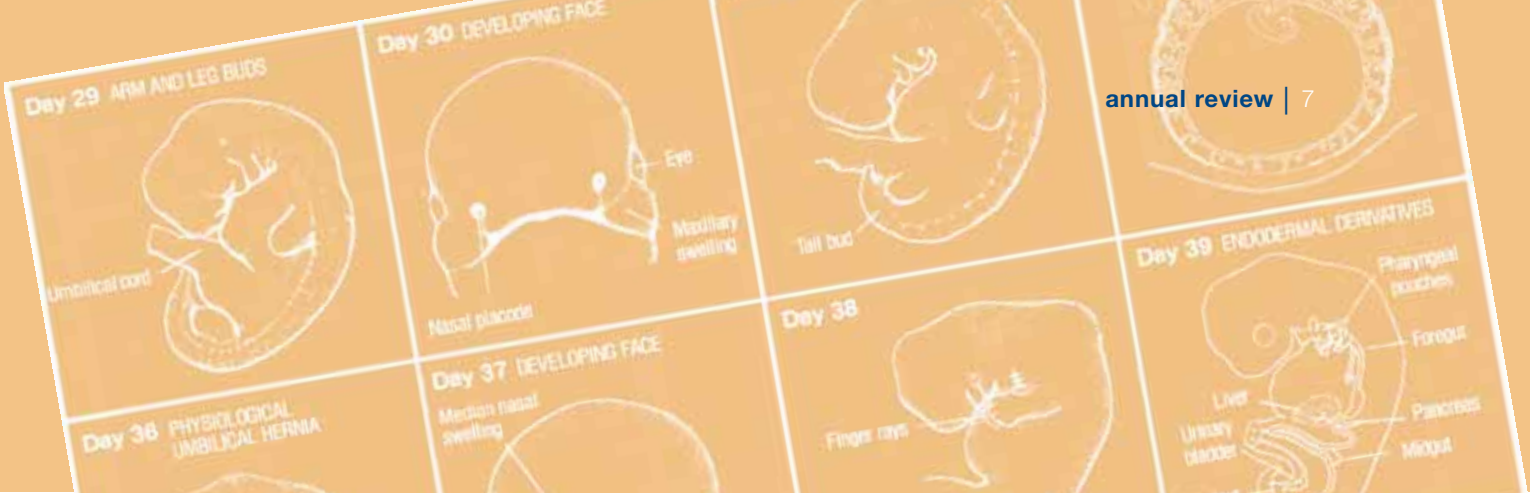
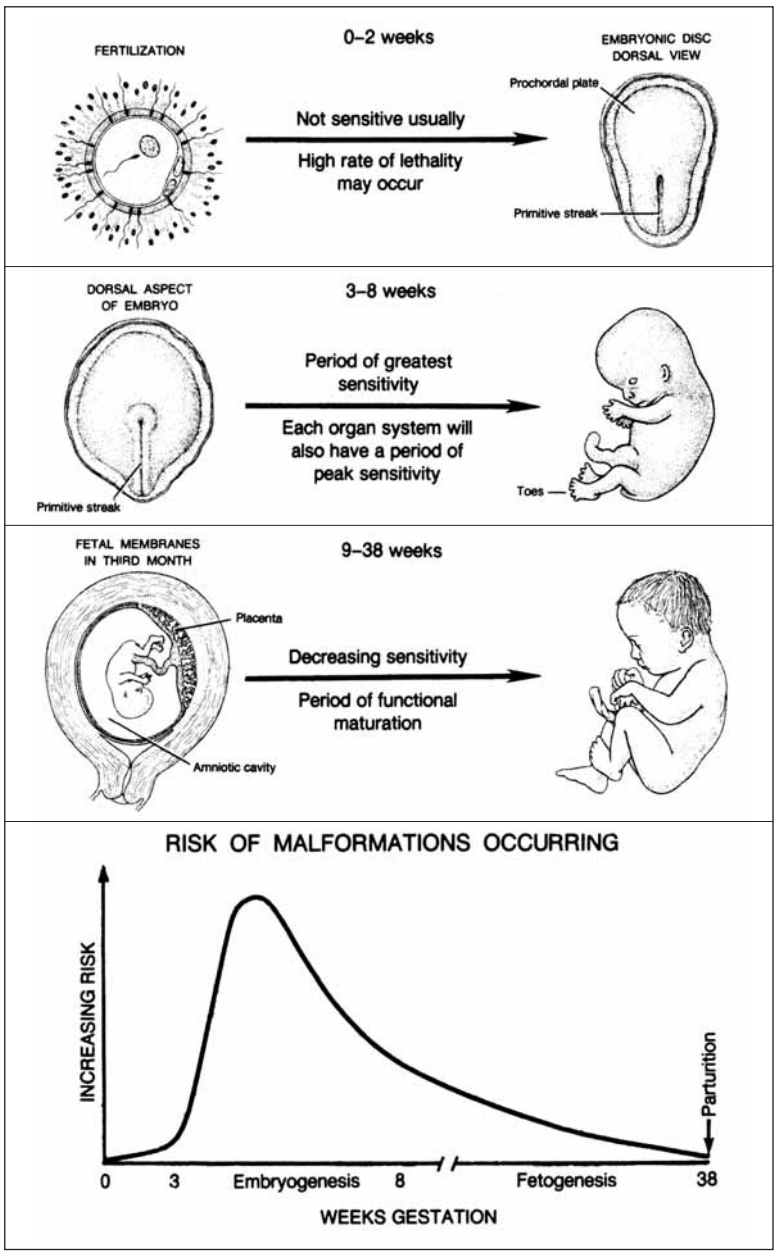


figure 1: embryonic development in days.



Reproduced with permission of the authors T W Sadler PhD :
Langman's Medical Embryology (10th edition 2006) : Lippincott Williams & Wilkins

Dysplasia

This involves abnormal organization of cells into tissues e.g. congenital ectodermal dysplasia, which presents as abnormalities of hair, nails, teeth, or skin.

Teratogenesis

Maternal exposure to certain agents can cause developmental disruption to the embryo. It is most sensitive at the times of rapid differentiation of body tissues into organs.

The three important principles of teratogenesis are:

- Critical periods of development
- Dosage of the drug or chemical
- Genotype of the embryo

Critical periods of human development

The most important period in development is when cell differentiation and morphogenesis are at their peak. Figure 1 shows the changing risk of malformations as pregnancy develops. During the first two weeks the embryo is not usually susceptible to teratogens. At this stage a teratogen either damages all or most if its cells resulting in death, or damages only a few cells allowing the embryo to develop without birth defects.

In Figure 2, the red time periods denote highly sensitive stages when major defects may be produced (e.g. amelia – absence of limbs). The yellow time periods show less sensitive stages of development when minor defects may be induced (e.g. hypoplastic thumb).

This embryological timetable can be helpful when considering the cause of birth defects but timewise it can only indicate that a teratogen has disrupted development sometime before the end of the critical period.

Dosage of the drug or chemical

For a drug to be considered a human teratogen, a dose response relationship has to be shown. This means that the greater the exposure of a drug during pregnancy the more severe the fetal abnormality.

Genotype of embryo

The genotype of an embryo determines whether a teratogenic agent will disrupt its development. Anti-epileptic drugs, which are known teratogens, can cause congenital anomalies in some but not all exposed embryos. Phenytoin can cause serious problems – fetal hydantoin syndrome – in 5 to 10% of embryos and milder associated anomalies in about 30%. More than half of the exposed embryos are unaffected.

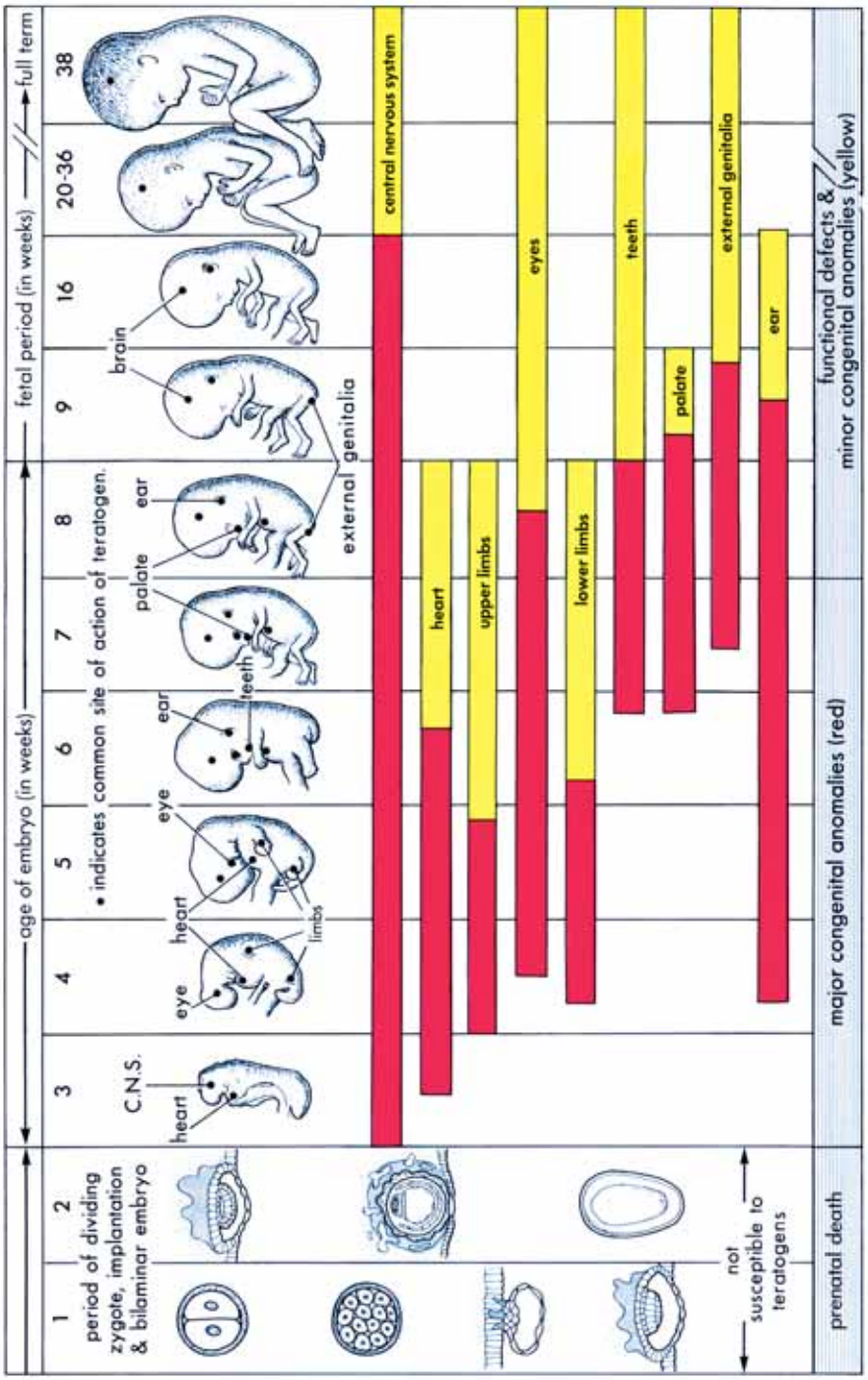
Studying causes of congenital anomalies

Information about the ways congenital anomalies arise can be gained in two ways:

Laboratory animal or in vitro studies

These are used to test new drugs or chemicals to see if they cause birth defects in laboratory animals. Of course, there is no guarantee that results obtained from animal studies will accurately predict likely effects in humans.

figure 2: critical periods in human development.



Reproduced with kind permission of the authors K L Moore and T V N Persaud from their book The Developing Human (5th edition 1993) : Saunders Philadelphia

Congenital anomalies: causes and mechanisms

Epidemiological studies

These are used to describe the pattern of birth defects seen in human populations. Studies increase in complexity from simple case studies, in which the features of one or two cases are described, to large scale case control and / or cohort studies where larger groups of 'cases' with the condition are compared with normal 'controls' to identify key differences between the two groups.

Studying causes of birth defects can be extremely challenging. Particular issues arise in relation to:

- Getting a good history about relevant maternal medications, lifestyle factors or environmental exposures. Problems can arise in remembering exactly what took place and when, as information is usually obtained several weeks or months after events took place.
- Identifying and quantifying exposures. This involves considering not only where a mother has lived, but also where she works, her hobbies, where she takes older children to school, etc. All of these different environments could be relevant.
- Estimating the timing of any potential exposures. Most chemicals that affect human development do so in a critical window of embryonic life. For example, some children exposed to thalidomide during the third to sixth week of pregnancy often developed severe limb reduction defects. However, if the drug was taken later on in pregnancy, it had no demonstrable adverse effect.
- Separating out the individual contribution of factors that predispose to the occurrence of birth defects. For example, women living in more affluent areas tend to smoke less and be older when they have their babies. Chromosomal disorders tend to be more common in this group of women. Studies are therefore required to assess the contribution not only of maternal age, but also of smoking and relative affluence to the development of these anomalies.
- Distinguishing between factors that definitely *cause* an anomaly to arise and factors that are *associated* with the underlying cause. Distinguishing between causation and association is a complex but very important area of study, in order to determine effective action to try and prevent anomalies arising.
- Taking account of small numbers of cases. Where numbers of cases are small, one or two new cases can cause apparently profound variations in rates between areas or over time. Some agents have been shown to increase the risk of birth defects moderately rather than dramatically. The risk following exposure is often only slightly raised and it can be difficult to be sure that the effects seen are not due to chance, especially where the number of affected cases is relatively small.

- **Differences in the quality of reporting over time or between areas can give a false impression.** Variations in reporting can suggest dramatic rises or falls in rates of anomalies. Rises can suggest the presence of sudden clusters of cases. Similarly, poor reporting can mask an otherwise identifiable rise in cases of a particular congenital anomaly where public health action is required. Collecting high quality data through congenital anomaly registers such as CARIS over many years is one way of building up good data that allows study of mild or moderate effects of environmental agents on the development of congenital anomalies.

Risk factors for congenital anomalies

Risk factors for congenital anomalies can be classified in many different ways, for example:

- Pre-existing parental factors, including maternal age, maternal medical conditions, socio economic status and genetic factors.
- Exposures to the fetus during pregnancy, including lifestyle factors, drug exposures and environmental exposures.

In this report we have considered some common examples from these groups.

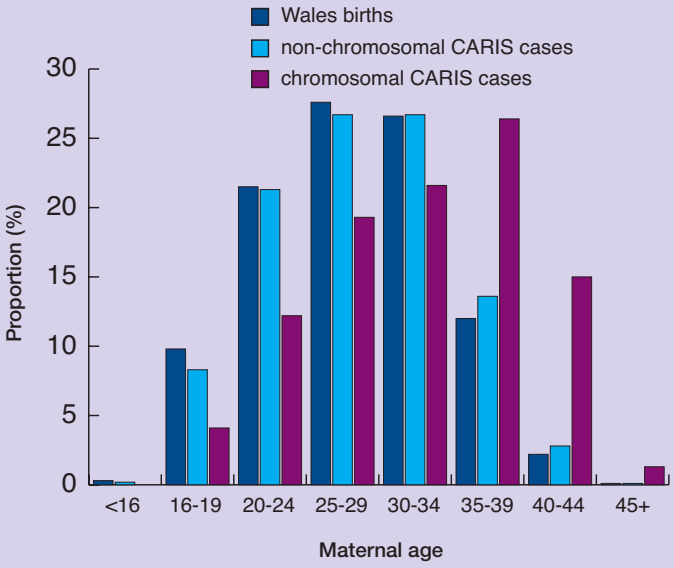
Maternal Age

Most research on congenital anomalies and maternal age has focused on the strong association between advanced maternal age and chromosomal defects. Looking at congenital anomalies across the age distribution, a J shaped curve is seen[1]. This means that women aged between 20 and 29 had the lowest prevalence of anomalies, teenagers had an intermediate prevalence and women more than 40 years old having the highest prevalence.

Rates of congenital anomaly reported to CARIS by maternal age group are shown in Figure 3. More detailed information for individual anomaly groups are available from the CARIS website.

Maternal age is strongly linked to other factors that are associated with congenital anomalies, such as smoking and socioeconomic deprivation. CARIS has asked the NPHS to look at the association between some of these factors in greater detail during 2007/2008.

figure 3: rates of congenital anomaly reported to CARIS, by maternal age group, 1998 - 2005



[1] Croen and Shaw. Young maternal age and congenital malformations: a population based study 1995. Am J Public Health; 85:710-713

Older mothers

It is well known that the likelihood of chromosomal abnormalities in the embryo increases significantly with maternal age. The older a mother is at the time of conception the more likely it is that the genetic material in her eggs have accumulated mutations that the embryo might inherit. CARIS works closely with the National Down Syndrome Cytogenetic Register who have made the following estimations of the increasing risk of Down Syndrome with maternal age.

Mother's age when she gives birth (in years)	Approximate chance of having a baby with Down syndrome
20	1:1477
25	1:1340
30	1:938
35	1:353
40	1:86
45	1:36

From the National Down Syndrome Cytogenetic Register 2002

Younger mothers

The incidence of teenage pregnancy varies greatly between countries in the developed world. For the period 1998-2002 10.4% of mothers were under 20 years of age in Wales; (1.2% in Northern Netherlands)[2].

Most teenage pregnancies are unplanned and are more common in teenagers from more deprived areas. Teenage pregnancy is associated with higher rates of maternal smoking, alcohol misuse, use of recreational drugs, a poor diet and greater risk of sexually transmitted diseases. Antenatal services may not be utilised fully. These are all factors likely to increase the risk of congenital anomalies occurring or not being detected at an early stage in pregnancy.

A recent study in the USA looked at 5 million births from women under the age of 35. They compared the prevalence of congenital anomalies in babies born to mothers aged between 13 and 19 years old with those aged from 20 to 34 years. They found that teenage pregnancy increases the risk of congenital anomalies in the central nervous system with anomalies other than neural tube defects, gastrointestinal anomalies mainly omphalocoele/ gastroschisis and musculoskeletal anomalies which were mainly cleft lip/palate and digital anomalies[3]. CARIS data are able to show the marked association between gastroschisis and younger maternal age, with over 75% of cases occurring in mothers under the age of 25.

[2] Loane et al. Increasing prevalence of gastroschisis in Europe 1980 - 2002 : a phenomenon restricted to younger mothers? Paediatric and Perinatal Epidemiology 2007; 21: 363-369

[3] Chen et al. Teenage pregnancy and congenital anomalies: which system is vulnerable? Human Reproduction 2007; 22 6: 1730-1735

Risk factors for congenital anomalies

Maternal medical conditions

Certain maternal conditions put the fetus at greater risk of developing anomalies, either because of the effects of the condition itself or as a result of exposure to drugs needed to control the disease. Common conditions include maternal diabetes and epilepsy.

Diabetes in pregnancy

Poor control of blood glucose in the early part of pregnancy is thought to contribute to an increased risk of congenital anomaly. Studies have shown that the congenital anomaly rates among babies born to diabetic mothers are about 2-3 times that for non diabetic mothers[4]. This holds true for both Type 1 and Type 2 diabetes. Caudal regression / sacral agenesis is a classic but rare abnormality described in babies of insulin dependent diabetic mothers. Defects of the heart and nervous system are more commonly seen.

In order to reduce the chances of congenital anomalies occurring in babies of diabetic mothers:

- Pre-conceptual care is very important to help achieve good glycaemic control, and ensure that folic acid is commenced (5mg daily).
- Once pregnancy is confirmed, metformin (an oral hypoglycaemic agent) should be stopped. Other drugs that are not recommended in pregnancy but are often taken by diabetic women should also be stopped or changed. These include statins and ACE inhibitors.
- Ensure excellent glycaemic control in pregnancy with close diabetic, dietetic and obstetric supervision.
- Specialist ultrasound (if available) is advised at the fetal anomaly scan, because of the increased risk of congenital anomalies.

For those where diabetic status is available, 1.6% of mothers reported to CARIS are known to be diabetic. The Welsh Health Survey suggests that the prevalence of diabetes in the general population of women of child bearing age is 1-2%.

Specific anomalies associated with higher rates of maternal diabetes recorded by CARIS include:

- Cardiomyopathy – 5 cases in diabetic mothers of 38 cases reported (13.2%)
- Encephalocele – 5 cases in diabetic mothers of 44 cases reported (11.4%)
- Pulmonary artery stenosis – 12 cases in diabetic mothers of 159 cases reported (7.5%)

(Numbers of cases are small and should be interpreted with caution).

Blood glucose meter

[4] CEMACH. Diabetes in pregnancy: are we providing the best care? 2007

Epilepsy in pregnancy[5]

Epilepsy affects about 1 in 250 mothers expecting a baby and is the most common neurological disorder affecting pregnancy. The congenital anomaly rate can be as high as 8-9% in treated epileptics.

The risk of teratogenesis in untreated epilepsy is thought to be low but seizures in pregnancy may be associated with an increased anomaly rate and adverse developmental outcome.

Studies of the more established drugs including sodium valproate, phenobarbitone, phenytoin and carbamazepine have shown a two to threefold increase in the major malformation rate. Sodium valproate seems to be the most teratogenic. Polytherapy using a combination of drugs is also associated with an increased rate of congenital anomaly. Single drug therapy is preferred. Over the last 15 years a newer anti-epileptic drug, lamotrigine has been used in teenagers and women of childbearing age. The effects on pregnancy are being carefully monitored by the drug manufacturer and the UK Epilepsy and Pregnancy Register. Initial results appear encouraging in terms of a lower risk of associated congenital anomalies.

As many of the drugs used in the treatment of epilepsy are folate antagonists, it is not surprising that the major anomalies that occur in treated epileptics include neural tube defects, congenital heart defects, and orofacial defects.

Supplementation with 5mg folic acid daily is recommended preconceptually to 12 weeks.

Of those where details have been reported to CARIS, 1.5% of mothers are treated epileptics (131 cases). Of these 131 pregnancies, 72 (55%) are recorded as single drug usage and 12 (9%) as polytherapy. For these mothers, anti-epileptics were taken in the following proportions:

sodium valproate – 55.1%

carbamazapine – 22.4%

lamotrigine 18.0%

phenytoin 3.4%

In epileptic mothers the following anomalies appear more frequently than for non epileptic mothers of babies with congenital anomalies:

- Spina bifida 13 / 155 cases (8.4%)
- Agenesis of lung 3 / 41 cases (7.3%)
- Cardiomyopathy 2 / 32 cases (6.3%)

[5] Further reading:
Managing Epilepsy in Pregnancy, 2006 Women's Health MIMS
UK Epilepsy and Pregnancy Register www.epilepsyandpregnancy.co.uk
James, Steer, Weiner, Gonik. High Risk Pregnancy - Saunders 1997

Risk factors for congenital anomalies

Maternal exposures during pregnancy

In this section we consider some common lifestyle factors and maternal medications that are associated with congenital anomalies.

Smoking

Although recent legislation banning smoking in public places will reduce the likelihood of passive smoking by pregnant women, current data suggest that approximately 30% of women in the reproductive years are smokers[6].

The primary components of cigarette smoke are tar and nicotine. Tar contains carbon monoxide, cyanide and cadmium. Nicotine transfers readily through the placenta and passes into breast milk.

Smoking during pregnancy is a well recognised cause of intrauterine growth restriction resulting in low birth weight babies.

The accepted view has been that smoking is not associated with congenital anomalies but in 2000 a large study in the USA assessing over 3 million births found that there was a significant association between smoking and cleft lip/palate. The research group also found that the risk increased with heavier smoking habits[7].

Recent work has suggested an association between congenital digital anomalies with smoking. This included extra fingers (polydactyly), webbed fingers (syndactyly) or missing fingers (adactyly). This association worsened with heavier smoking[8].

Alcohol and Pregnancy

Both Greek and Roman mythology allude to the adverse effects of alcohol on the unborn child. Recent publications have raised public awareness and given advice about the problems caused by taking excessive alcohol during pregnancy.

Glass	A	B	C	D
Volume	125ml	125ml	250ml	250ml
Alcohol content	9%	13%	9%	13%
Units	1.1	1.5	2.3	3
Number of glasses for a binge (six units in one sitting)	5.5	4	2.5	2

Based on UK guidance on units by volume of alcohol, DoH. Published with permission from Haymarket Business Media.

Women drinking heavily in pregnancy are at greater risk of miscarriage and can put their babies at risk of congenital anomalies including fetal alcohol syndrome[9].

This term was coined to describe the pattern of anomalies seen in children of chronic alcoholic women. The syndrome has also been reported following a history of binge drinking, as defined by six drinks or more on one occasion[10]. Fetal alcohol spectrum disorder is a milder form associated with more moderate drinking. The National Organisation on Fetal Alcohol Syndrome[11] estimates there are more than 6,000 children born each year with the spectrum disorder.

[6] ASH www.ash.org.uk

[7] Chung, Kowalski, Kim et al. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. Plastic and Reconstructive Surgery 2000; 105: 485-491

[8] Man and Chang. Maternal cigarette smoking during pregnancy increases the risk of having a child with a congenital digital anomaly. Plastic and Reconstructive Surgery 2006; 117: 301-308

[9] Fetal Alcohol Spectrum Disorders – A guide for healthcare professionals BMA June 2007

[10] Alcohol and pregnancy Department of Health 2007

[11] www.nofas.org

One study has shown that major structural anomalies are three times more common in women drinking more than 35g (4.5 units) a day compared with those consuming less or none at all[12].

Alcohol readily crosses the placenta and without a mature liver or developed blood filtration system the fetus has no protection from alcohol circulating in the blood stream. As one would expect, the fetus is most susceptible to the effects of alcohol in the first trimester, the period of greatest organ development. Alcohol causes premature fetal cell death and disrupts normal cell development. This effect is most debilitating on neural development. Cells in the central nervous system experience more rapid cell death than other cells because of a lower toxicity threshold for alcohol. It also causes damage by disrupting neural development (e.g. maturation of glial cells). This affects basal ganglia, the corpus callosum, the cerebellum and hippocampus – responsible for motor and cognitive skills, learning, memory and executive functioning.
Alcohol also affects fetal behaviour in utero. This behaviour is now thought to contribute to the normal development process.

Children with fetal alcohol syndrome have smaller brains which using MRI mapping suggests a disproportionate reduction in white matter compared with grey matter Common anomalies outside the CNS that are associated with FAS include haemangiomas, cardiac septal defects, minor joint and limb abnormalities, genital anomalies and single palmar creases.

North American studies suggest the incidence of fetal alcohol syndrome is 0.6/1000 live births and the fetal alcohol spectrum disorders is 9/1000 live births. Limited English data from DH Hospital Episode Statistics recorded 128 cases of fetal alcohol syndrome in 2002-3.

The diagnosis of alcohol spectrum disorder can be confused with many genetic and malformation syndromes and is usually a diagnosis of exclusion.

Detailed reporting of alcohol intake to CARIS is limited. This makes it difficult to assess the effect of alcohol in fetal development in Wales. CARIS has details of 16 cases of fetal alcohol syndrome (0.55 per 10,000 live births) during the time period 1998-2006. This is possibly an underestimate.

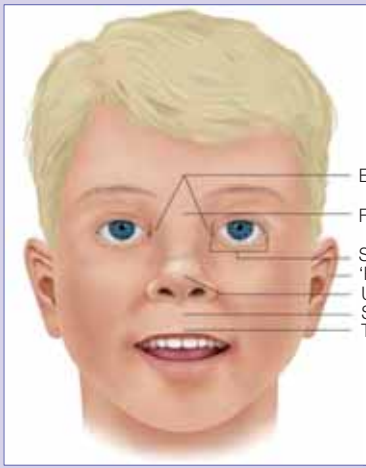
[12] Alcohol Consumption and the Outcomes of Pregnancy RCOG Statement 5 2006

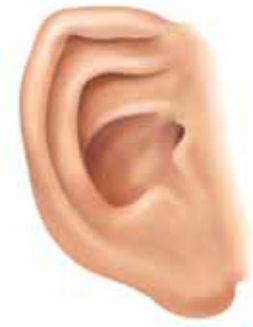
Risk factors for congenital anomalies

Diagnostic Criteria for Fetal Alcohol Syndrome

Level	Criteria
1	Confirmed maternal exposure
2	Characteristic pattern of facial anomalies (e.g. flat upper lip, flattened philtrum, flat midface)
3	Growth restriction in at least one of the following:
	Low birth weight for gestational age
	Decelerating weight over time not due to nutrition
	Disproportionately low weight to height
4	CNS neurodevelopmental anomalies with at least one of the following:
	Decreased cranial size at birth
	Structural brain anomalies (e.g. microcephaly)
	Neurological signs (e.g. impaired fine motor skills, sensorineural hearing loss)

Characteristics associated with FASD (fetal alcohol spectrum disorders)





Characteristic features of an ear of a child with fetal alcohol spectrum disorders. Note the underdeveloped upper part of the ear parallel to the ear crease below ('railroad track' appearance).

Characteristic features of hand of a child with fetal alcohol spectrum disorders. Note the curved fifth finger (clinodactyly) and the upper palmar crease that widens and ends between the second and third fingers ('hockey stick' crease).

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Obesity

Obesity is a serious health concern in the developed world and represents a risk to the expectant mother with associated increased risks of complications or maternal death.

The Confidential Enquiry into Maternal and Child Health (CEMACH)[13] reported a 10% increase in the prevalence of obesity among women aged between 25 and 34 years from 1993 to 2002.

Recently a population based study of eight states in the USA looked at mothers of babies born with congenital anomalies comparing them with mothers of healthy babies. Body mass index (weight in kilograms divided by height in metres squared) of these mothers was estimated from a maternal report of pre-pregnancy weight and height. They concluded that mothers of babies with a range of structural birth defects were more likely to be obese than the mothers of controls[14]. These defects included spina bifida, heart defects, limb reduction defects and diaphragmatic hernia. The authors raised the possibility of undiagnosed diabetes as being responsible for these associations.

Mothers of babies born with gastroschisis were significantly less likely to be obese than mothers of controls.

Previous studies have shown a twofold increased risk of neural tube defects associated with a body mass index of greater than 29 kg/m^2. The same group[15] found that physical activity lowered the risk for neural tube defect affected pregnancies independent of maternal obesity. They also showed an increased risk of this defect with the use of diets to lose weight, fasting diets and eating disorders. It was suggested that this could be due to the decreased availability of micronutrients or the presence of ketosis which accompanies reduced food intake and fasting[16].

Body mass index data has not been recorded as part of the CARIS dataset until 2007. It is hoped to study this factor in greater detail in future years, as more data become available.

[13] Confidential Enquiry into Maternal and Child Health. Why mothers die 2000-2002, RCOG : London 2004

[14] Waller et al. Prepregancy Obesity as a Risk Factor for Structural Birth Defects. Archives of Paediatrics and Adolescent Medicine, August 2007; 161(8): 745-750

[15] Shaw et al. Risk of neural tube defect affected pregnancies among obese women. JAMA 1996; 275 : 1093-1096

[16] Carmichael et al. Dieting behaviours and risk of neural tube defects. Am J Epidemiol. 2003; 158 : 1127-1131

Risk factors for congenital anomalies

Recreational Drugs

Cocaine

Chemically known as benzoylmethylecgonine, cocaine is an alkaloid extracted from leaves of the coca plant, grown mostly in Bolivia and Peru. This drug has become more widely available in the past 20 years. It is available in two chemical forms: cocaine hydrochloride and 'crack' the pure cocaine alkaloid. Cocaine hydrochloride is taken intravenously or intranasally and crack cocaine is also smoked.

Cocaine crosses the placenta and then the blood brain barrier of the fetus. Its metabolism is considerably slower in the fetus than in adults. Research has been limited by the fact that cocaine taking mothers are more likely to take other drugs, smoke more cigarettes and use more marijuana than those who do not use cocaine[17].

Despite this, it is thought that antenatal cocaine exposure may have an impact on the visual, auditory, cardiovascular and genitourinary systems[18]. Cocaine has been linked to many anomalies including limb reduction deformities, intestinal atresia and single cardiac ventricle. These are thought to be related to vascular disruption resulting from cocaine induced vasoconstriction occurring during different periods of organogenesis. Antenatal exposure has also been found to affect the central nervous system particularly the dopamine system. Research on developing children has shown this effect when measuring neurological functioning, particularly in males and those in high risk environments.

Marijuana

This remains one of the most popular recreational psychoactive substances. Its principal psychoactive substance, delta-9-tetrahydrocannabinol, passes through the placenta and may remain in the body for 30 days before excretion, prolonging fetal exposure. Carbon monoxide levels are 5 times higher with marijuana than those produced with cigarette smoking.

There is an association with intrauterine growth restriction[19] and evidence that neonatal neurobehaviour is affected.

No clear association has been found with congenital anomalies.

Opiates

Heroin and methadone are the main opiates linked to fetal exposure. Intrauterine growth restriction is common with resulting low birth weight infants. Neonatal withdrawal syndrome is well described in these infants.

No clear pattern of congenital anomalies is associated with opiates.

Thirty-one mothers known to be taking heroin or methadone were reported to CARIS from 1998 - 2006. There is no clear pattern of anomalies. In this group there are four cases of gastroschisis. These mothers were also heavy cigarette smokers. There was also a case of fetal alcohol syndrome in this group.

[17] Schiller et al. Follow up of infants prenatally exposed to cocaine Paediatric Nursing 2005; 31 : 427-436

[18] Benderstag et al. Inhibitory motor control at five years as a function of prenatal cocaine exposure Journal of Developmental Behavioral Paediatrics 2003; 24(5) : 345-351

[19] Chiriboga and Clauia. Fetal Alcohol and Drug Effects. The Neurologist 2003; 9(6) : 267-279

Common prescription drugs

The British National Formulary advises that:

'Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus. All drugs should be avoided, if possible, during the first trimester. Drugs which have been extensively used during pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs and the smallest effective dose should be used… Few drugs have been shown conclusively to be teratogenic in man but no drug is safe beyond all doubt in pregnancy'[20].

Some common or well known risks of congenital anomaly associated with prescribed medications are[21]:

Androgens and Progestogens
– used for menstrual and libido problems
Anomalies: ambiguous external genitalia in the female fetus

Isotretinoin
– used for acne
Anomalies: craniofacial abnormalities, neural tube defects, cardiovascular defects, cleft palate, thymic aplasia

Lithium carbonate
- used for mania and depression
Anomalies: heart and great vessels

Methotrexate
– used for Crohns disease, psoriasis, rheumatic disease, malignancies, ectopic pregnancies
Anomalies: skeletal problems

Phenytoin
– used for epilepsy
Anomalies: fetal hydantoin syndrome – including microcephaly, depressed nasal bridge and phalangeal hypoplasia

Tetracycline
– used for infections and acne
Anomalies: stained teeth; hypoplasia of enamel

Thalidomide
– used for its anti inflammatory activity and in recurrent myeloma
Anomalies: abnormal limb development, facial anomalies, cardiac and kidney defects

Sodium valproate
– used for epilepsy
Anomalies: craniofacial anomalies, neural tube defects, heart and skeletal defects

Warfarin
– used for anti-coagulation
Anomalies: nasal hypoplasia, stippled epiphyses, hypoplastic phalanges, eye anomalies, mental retardation

[20] British National Formulary appendix 4
[21] Moore and Persaud. Before We Are Born – Essentials of Embryology and Birth Defects 2003; Saunders Philadelphia

Risk factors for congenital anomalies

Current controversies

Lamotrigine

This is a second generation anti epileptic drug introduced in the nineties as a suitable drug for young women. This was designed to deal with the challenge of reducing teratogenicity. The traditional anti-epileptic drugs are well known for more than doubling the risk of major congenital malformations.

So far, studies have been reassuring with no evidence to clearly point to a raised anomaly rate. Because of anxiety about a possible increase in facial clefting in North America, a large study involving congenital registers in Europe (EUROCAT group) has looked at this closely. CARIS participated in this. The results did not confirm an increased risk of facial clefts relative to other anomalies with lamotrigine exposure[22].

Continued surveillance is very important in assessing the safety of this drug.

Selective Serotonin Receptor Inhibitors (SSRIs)

Major depression is common with a lifetime risk for women being between 10 and 25%. This peaks during the childbearing years. SSRIs are frequently used antidepressant medications in general and during pregnancy. The British National Formulary recommends that they should only be used if the potential benefit outweighs the risk and says there is no evidence of teratogenicity. A recent large study from the USA has confirmed that there was not a significantly increased risk of congenital heart defects or of most other defects in association with maternal use of SSRIs. The group showed an association with anencephaly, craniosynostosis and omphalocele[23].

Metformin

This biguanide drug has been used for many years in the management of diabetes. More recently it has been used as part of the treatment for polycystic ovaries. As a result, metformin may be more likely to be inadvertently taken in early pregnancy. Some diabetologists have been using the drug for the treatment of gestational diabetes usually in the second and third trimesters. The British National Formulary recommends doctors to avoid the use of metformin in all trimesters. No evidence has shown so far an association with maternal usage of metformin and subsequent congenital anomalies but caution should be exercised.

Clomiphene

This is a drug used in the treatment of female infertility. It acts as an anti-oestrogen, occupying oestrogen receptors in the hypothalamus and interfering with the feedback mechanism. Increased follicle stimulating hormone is produced from the pituitary gland which stimulates ovulation. It is normally taken in the menstrual phase. Oestrogen levels rise and can persist for some time as records have shown clomiphene levels still present in faeces 6 weeks after ingestion.

CARIS data comparing mothers who conceived after taking clomiphene with other mothers on the register found a significant association between clomiphene usage and hypospadias in male offspring[24].

[22] Jentink et al. Does exposure to lamotrigine in pregnancy increase the risk of orofacial clefts? In press 2007

[23] Alwan et al. Use of Selective Serotonin- Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects. New England Journal of Medicine 2007; 356 (26) : 2684-2692

[24] Tucker and Morgan. Congenital Anomalies in Clomiphene Induced Pregnancies: Review from a Congenital Anomaly Register. 2007; British International Congress of Obstetrics and Gynaecology

Environmental exposures and birth defects

'Over 30,000 individual chemicals are used in industry, with a further 3000 compounds being added each year. It is impossible to test all of them on pregnant animals and much of the evidence on safety [to the fetus] depends on retrospective reports of damage to humans. The number of chemicals that are proved to be teratogenic are few'[25].

A recent review of environmental exposures and birth defects summarised the following environmental exposures linked to birth defects[26]. However, the authors stressed that many of these associations, although present, appeared to present a moderate rather than major risk (6+ fold increase in risk).

The results of epidemiological studies identifying these risks were often conflicting. The quality of the studies was variable.

Factors such as maternal smoking often appeared to present a greater risk than these environmental exposures.

The studies concentrated on structural birth defects. Other factors such as premature birth, poor fetal growth or learning difficulties were not included in the review, but may present additional effects in later life.

This list is given as an example of the wide variety of environmental exposures linked to congenital anomalies, rather than a comprehensive account of our current knowledge in this area.

Agent / Exposure	Congenital Anomaly	References quoted in review
SOLVENTS		
General solvent exposure	Heart; central nervous system; oral cleft	Tikkanen 1988; 1992 Holmberg 1979; 1980; 1982 Magee 1993 McMartin 1998
Benzene	Neural tube defects Heart	Bove 1995 Savitz 1989
Toluene	Fetal solvent syndrome Urinary tract	Hersh 1985 McDonald 1987
Chloroform and trihalomethanes	Central nervous system, oral clefts	Bove 1995
Glycol ethers	Oral cleft	Cordier 1997
Trichloroethylene	Central nervous system Heart Oral cleft	Bove 1995 Goldberg 1990
Perchloroethylene	Oral cleft	Bove 1995

[25] Chamberlain G & Morgan M. ABC of Antenatal Care (4th Edn) BMJ Books 2002

[26] Mekdeci & Schettler

Risk factors for congenital anomalies

Agent / Exposure	Congenital Anomaly	References quoted in review
METALS		
Mercury	Central nervous system	Harada 1978
Lead	Abnormal pulmonary blood vessels	Correa-Villasenor 1991
OTHER CHEMICALS		
Polychlorinated biphenyls (PCBs)	'Yusho' syndrome – skin lesions, pigmentation, eye swelling, abnormal teeth and gums, abnormal calcification in skull bones (with relatively high maternal exposures)	Schatz 1996 Rogan 1988
RESIDENTIAL OR OCCUPATIONAL FACTORS		
Maternal residential proximity to pesticide applications	Fetal death from congenital anomalies	Bell 2001
Maternal residence to hazardous waste site	Central nervous system Musculoskeletal Neural tube defect Heart Neural tube defect Heart Hypospadias Anomalies of Esophagus Abdominal wall defect	Geschwind 1993 Marshall 1997 Shaw 1992 Croen 1997 Dolk 1998
Maternal agricultural garden work	Oral cleft Neural tube defect Musculoskeletal	Nurminen 1995 Blatter 1996 Hemminki 1980
Paternal occupational pesticide exposure	Circulatory Respiratory Urogenital	Garry 1996
Paternal occupational wood preservative exposure	Eye Neural tube defect Male genital tract	Dimich-Ward 1996
Paternal occupational solvent exposure	Neural tube defect	Brender 1990

Ionising Radiation exposure

Ionising radiation is a form of energy given off in particles or rays from radioactive material, high voltage equipment, nuclear reactions and stars. Everyone is continually exposed to low levels of ionising radiation – for example from the sun, rocks, soil and emissions from radioactive material in hospitals, power plants, etc. High dose exposure may occur in controlled situations such as radiotherapy treatment for cancer. Extremely high and often uncontrolled exposures are fortunately rare, but would include the exposure following atomic bomb detonation or nuclear accidents such as those in Chernobyl. Concerns exist over the effects of all types of exposure to ionising radiation on the developing fetus.

Considerable study of the association between radiation exposure and birth defects has been undertaken, particularly in the USA through the Hanford Environmental Dose Reconstruction Project (HEDR). This was established to study possible doses and effects of radiation that people were exposed to in the Hanford area of Washington State in the period 1944 to 1992[27]. The main birth defects associated with radiation exposure are:

- Genetic defects, particularly chromosomal disorders, associated with the damage radiation causes to the genetic material of cells
- Congenital malignancies, again associated with genetic damage following high radiation exposures
- Anomalies of the CNS, particularly neural tube defects

Studies generally show however, that the risks of congenital anomalies associated with low dose exposures are relatively small.

[27] Washington State DoH. Genetic Effects and Birth Defects from Radiation Exposure. Available at www.doh.wa.gov/Hanford/publications/overview/genetic.html

Reducing the risk of congenital anomaly

In 2004, CARIS and the National Public Health Service for Wales prepared advice on behalf of the Chief Medical Officer for Wales for women in Wales before or during pregnancy, to reduce the risk of congenital anomaly in their baby[28]. Whilst this advice will not prevent all congenital anomalies from occurring, it may help reduce the risk in some cases.

Things to avoid:

- Smoking
- Alcohol
- Using recreational drugs (substance misuse)
- Unnecessary over the counter medication (seek your pharmacists advice)
- Exposure to certain infectious diseases e.g. chicken pox
- Certain occupational exposures e.g. working on a farm

Things to encourage:

- A healthy balanced diet
- Check rubella immune status before pregnancy
- Folic acid (0.4mg daily from before pregnancy starts to the end of the 12th week), to reduce the chances of the baby having a neural tube defect. Even if folic acid was not taken before conceiving it is important to start once pregnancy is confirmed, until 12 weeks. Increase dose to 5mg for high risk cases (past history of neural tube defect, diabetic, or epileptic)
- Seek the advice of your doctor before getting pregnant if you suffer from any chronic disease such as diabetes, epilepsy or if you have previously had treatment for cancer

[28] Reducing the risk of congenital anomaly. CMO Update 24 (2004)