Inequalities in Infant Mortality Project Briefing Paper 4

The contribution of congenital anomalies to infant mortality

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Summary

- Congenital anomalies are the second commonest cause of infant deaths in England and Wales; although the vast majority of infants born with a congenital anomaly will survive. There are many different congenital anomalies and the cause of most is not known. In any single year infant deaths due to congenital anomalies are associated with over 150 different causes. Congenital anomalies contribute about one third of the extra infant deaths experienced by the routine and manual socio-economic groups compared with the population as a whole.
- The *primary prevention* of congenital anomalies requires delivery of high quality universal pre-pregnancy and pregnancy care for women in general together with optimisation of management before conception for specific women at higher risk of anomalies, e.g. diabetics. The availability of genetic services is essential for couples with a family history or past history of pregnancies affected by congenital anomalies, particularly due to specific genetic conditions. Some sections of the population are at increased risk of particular genetic conditions and as a consequence *infant mortality rates* due to congenital anomalies may be higher in some areas compared with England and Wales overall.
- *Secondary prevention* of congenital anomalies is achieved through prenatal screening and diagnosis followed by the offer of termination of pregnancies affected by major anomalies. Because termination of pregnancy is the only option for many congenital anomalies *secondary prevention* is not universally acceptable.
- *Infant mortality rates* due to congenital anomalies are strongly influenced by prenatal screening and diagnosis, and uptake of termination of pregnancy. However, it is important to note that many of the anomalies subject to *primary and secondary prevention* would not in any case have resulted in an infant death and thus their prevention, although of great importance because of the associated morbidity and disability, will not necessarily impact on the *infant mortality rate*.

1 Introduction

Congenital anomalies are the second commonest cause of infant deaths in the United Kingdom. This briefing paper is the final in a series of four papers commissioned by the Department of Health as part of a project to evaluate the evidence base of interventions to reduce infant mortality and inequalities in the *infant mortality rate*.[1,2,3] The aim of this paper is to provide a background to the evidence review process by examining the contribution of congenital anomalies to the *infant mortality rate*; inequalities in the rate; the role of prevention; and how variations in risk factors and uptake of preventive strategies might affect the *infant mortality rate* associated with congenital anomalies. Definitions of terms used in this paper are given in the glossary at the end.

2 Congenital anomalies

2.1 Definitions

Congenital anomalies, congenital abnormalities, birth defects and congenital malformations are all terms used to describe developmental disorders of the *embryo* and *fetus*. There are several hundred separate anomalies which fall under these headings including structural, functional, metabolic and hereditary conditions. However, there is no single universally accepted system of classification of anomalies or indeed a single agreed definition of what constitutes a congenital anomaly. For the purposes of this paper we will use the term congenital anomalies and take this to mean an *embryonic* or *fetal* developmental

abnormality of any type, but noting that not all variations in development are anomalies as anatomical variation in humans is common.

There are four distinct types of anomalies which result from different sets of causes:[4]

- Malformations are caused by intrinsically abnormal processes during the development of the egg or the sperm, or during fertilisation. These include the anomalies that are caused by chromosomal abnormalities, for example having an extra chromosome 21 in *Down's Syndrome*, and single gene defects, for example, *campomelic syndrome*.
- Disruptions refer to defects that are caused by the interference with an originally normal developmental process. Disruptions can be caused by *teratogens* such as drugs, for example alcohol, thalidomide and warfarin; chemicals, for example polychlorinated biphenyls (PCBs); viruses, for example cytomegalovirus (CMV) and rubella; and ionising radiation, for example X-rays.
- Deformations are abnormal forms, shapes or positions of a part of the body and result from mechanical forces. For example, twins can suffer limb deformation such as clubbed foot due to the crowded uterine space.
- Dysplasia refers to the abnormal organisation of cells into tissue. The causes are generally nonspecific and as a consequence often affect several organs simultaneously.

The frequency of occurrence of congenital anomalies is usually quoted as *birth prevalence* rather than *incidence*. This is because we know that many *fetuses* affected by a congenital anomaly will miscarry, that the miscarriage may occur before the pregnancy is confirmed and even if the miscarriage is later the anomaly may not be diagnosed. The term *birth prevalence* therefore acknowledges that not all cases of congenital anomalies can be diagnosed and counted in an *incidence rate*. The denominator for the calculation of *birth prevalence* is usually taken as all births which excludes miscarriages and terminations of pregnancy.

2.2 Sources of information about congenital anomalies in England

The National Congenital Anomalies System (NCAS) was established in 1964 in the wake of the thalidomide disaster as a surveillance system intended to identify hazards such as thalidomide quickly. The system has operated by issuing monthly alerts to Directors of Public Health when there are changes in the frequency of reported anomalies as a means of highlighting possible clusters of cases[i]. *NCAS* was not established as a register intended to ascertain all cases of congenital anomalies in the population; its purpose was to concentrate on identifying changes in the frequency of occurrence of reports of anomalies rather than estimating the *birth prevalence* of conditions. It is only in those areas where a regional congenital anomaly register supplies data to *NCAS* that robust *birth prevalence* estimates can be derived from *NCAS* data.[5]

A further limitation of increasing importance in the context of prenatal screening and diagnosis and the impact on the *infant mortality rate* is that *NCAS* does not collect information about pregnancies affected by a congenital anomaly that are terminated. For conditions with a high rate of prenatal detection and termination, for example *neural tube defects* (NTDs), this leads to a substantial under-ascertainment of cases and means that if, for example, *primary prevention* of NTDs through folate fortification of flour is introduced in the UK, as it has been elsewhere, *NCAS* will not be able to provide useful data for the evaluation of the effects of fortification.

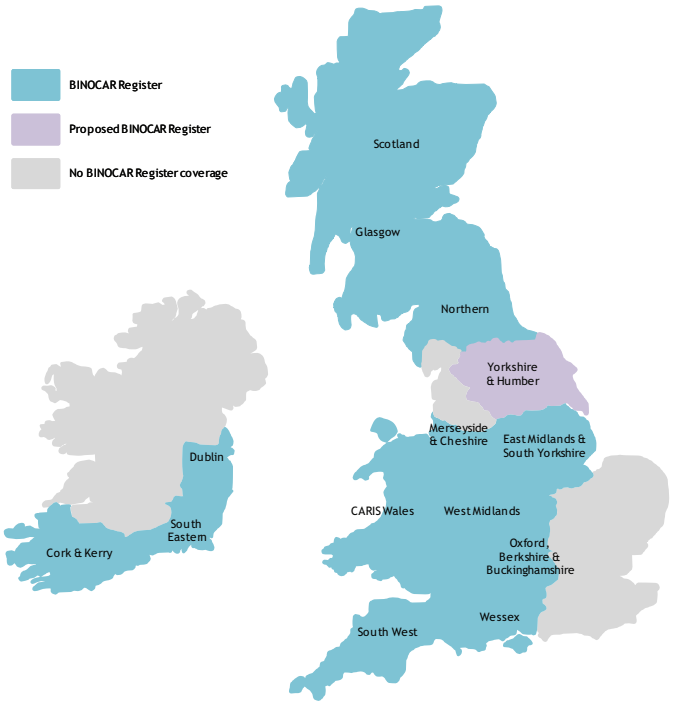
The problems with *NCAS* data may, however, be of limited concern in the future since the whole of the *NCAS* system is currently under review (consultation closed March 2010) with the proposal that data collection will cease and a final report will be issued in 2009/2010. Whilst a legacy data system will be retained subsequent data collection will cease. Discussions about how to provide surveillance data and alerts of potential clusters in the short and longer term are in progress with the relevant members of the British Isles Network of Congenital Anomalies Registers (*BINOCAR*).[6]

Congenital Anomalies Registers are highly organised systems for collecting data about congenital anomalies with the purpose of identifying all the cases of congenital anomalies in geographically defined populations. Most Registers in the UK collect information about anomalies diagnosed prenatally, and those diagnosed in the newborn and early childhood in specific designated geographical regions.[7] In the UK the network of regional congenital anomalies registers is represented by *BINOCAR* (Figure 1).[6] The regional congenital anomalies registers are now the only source of population-based congenital anomalies data in the UK able to: support on-going audit and evaluation of the national prenatal screening and diagnosis programme; provide routine prevalence and trend information about anomalies; and the only means to systematically identify and investigate potential clusters of cases.

i NCAS ceased issuing alerts in mid-2009 and NCAS has subsequently closed completely.

Geographically the *BINOCAR* registers cover much of the area of England, however, mainly because of the concentration of births in the East, London and the South East of England and the lack of registers in those areas, only about 50% of births in England are born in areas served by a *BINOCAR* register. Two of the registers are however, at risk with funding in place only to March 2011: Congenital Anomalies Register for Oxfordshire, Berkshire and Buckinghamshire (*CAROBB*)[i] and the Northern Congenital Anomalies Survey (*NorCAS*).[ii] Whereas, a new register is proposed for Yorkshire and Humber (*YHCAR*).

Figure 1. BINOCAR Registers Map[6]*



* A BINOCAR register operates in Glasgow; information about congenital anomalies in the rest of Scotland is collected by routine data systems and provided by the Information Services Division, NHS Services Scotland

2.3 Frequency of occurrence of congenital anomalies

The lack of agreement about the definition of congenital anomalies means that the comparison of the *birth prevalence* of anomalies is problematic as inclusion and exclusion criteria vary between different data sources. Furthermore some registers have historically concentrated on prenatally and neonatally diagnosed conditions[10] whereas others in different parts of the world have included anomalies diagnosed from pregnancy into childhood, for example to age 6 years in Western Australia.[11] Variations in *birth prevalence* estimates may also arise depending upon whether or not figures relating to pregnancies terminated because of fetal congenital anomalies (*TOPFA*) are included. Variations in methods of ascertainment are also important. Passive systems of case notification tend to identify fewer cases compared with more active ascertainment.[7] As a consequence of all these differences estimates of *birth prevalence* vary from place to place. However, apart from a small number of specific anomalies, any differences in prevalence are thought largely to be due to methodological differences rather than true differences in underlying population *incidence*.

About 3% of *fetuses* and newborns are diagnosed with a congenital anomaly in the UK each year[10,12] either before or soon after birth; this includes *fetuses* which are terminated because of the presence of a congenital anomaly (*TOPFA*). This means that in 2008 when there were 712,328 *live births* and *stillbirths* in England and Wales over 21,000 were affected by a congenital anomaly diagnosed before or around birth.

3 Contribution of congenital anomalies to infant deaths

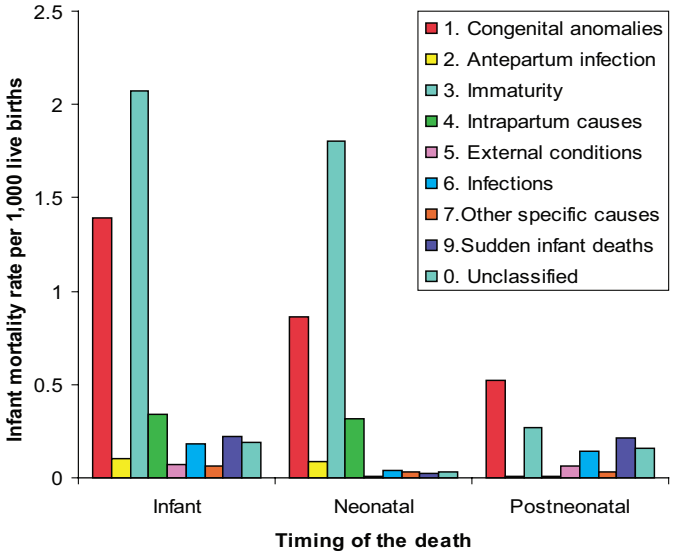
3.1 National statistics

Since the introduction of the current *stillbirth* and neonatal death certificate in 1986 it has not been possible to directly compare the causes of neonatal deaths with the causes of postneonatal deaths.[1] This is because, in contrast to deaths in general (including postneonatal deaths), no single underlying cause of death is recorded for neonatal deaths. As a consequence, the Office for National Statistics (ONS) developed a hierarchical classification which allows both *neonatal* and *postneonatal* deaths to be assigned to a specific category based on the likely timing of the damage leading to the death (see glossary for the definition of the *ONS cause of death* classification algorithm). The causes of death given in Figure 2 are shown in the hierarchical order of the *ONS cause* groups.

i CAROBB website available at: http://www.npeu.ox.ac.uk/carobb [Accessed April 2010]

ii NorCAS website available at: http://www.nepho.org.uk/rmso/surveys/congenital [Accessed April 2010]

Figure 2. ONS cause group-specific mortality rates by timing of the death*, England and Wales, 2007[13]



*Neonatal deaths – deaths occurring under 4 weeks of age
Post-neonatal deaths - deaths occurring from 4 weeks to one year of age
Infant deaths – deaths occurring before one year of age

Congenital anomalies are the second commonest cause of infant deaths overall with a rate in 2007 of 1.39 per 1,000 *live births*; and they are the leading cause of deaths in the postneonatal period at 0.52 per 1,000 *live births*.[13]

3.2 The proportion of infants with a congenital anomaly who die

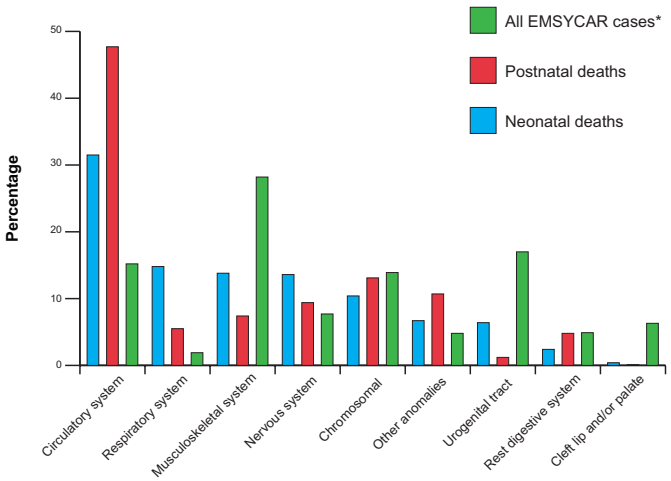
The vast majority of pregnancies and births affected by a congenital anomaly survive and do not result in a *stillbirth* or infant death. In 2007 957 infant deaths and 557 *stillbirths* were ascribed to congenital anomalies. That is, of the 3% of pregnancies and infants diagnosed with an anomaly only 7% of them resulted in a *stillbirth* or infant death; 93% of affected cases survived birth and infancy. Furthermore the risk of *stillbirth*, neonatal death and later deaths varies between different anomalies.

3.3 Congenital anomalies which result in an infant death

Mortality associated with congenital anomalies varies enormously depending upon the particular anomaly. For example anencephaly (failure of the development of the skull and brain) is incompatible with life. The vast majority of *fetuses* affected by anencephaly are either detected prenatally and the pregnancy is terminated, or the baby is stillborn.

Figure 3 illustrates the distribution of neonatal and postneonatal deaths in England and Wales 2002 to 2005 where the main cause of death was a congenital anomaly, by the system affected. Figure 3 also shows the distribution of **all** cases congenital anomalies taken from the East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR).[12] This illustrates the difference in the proportion of actual cases of different types of anomalies compared with the proportion of deaths from the different anomalies. Note that the distributions are shown as proportions of deaths and proportions of cases by category of anomaly; there are many more actual cases than deaths.

Figure 3. Distribution of causes of neonatal and postneonatal deaths from congenital anomalies (2002 to 2005)[13] and the distribution of all congenital anomalies cases from the East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR) (births 1997 to 2001)[12] *



*Note – the figures given are percentages of deaths and percentages of cases. There are about 14 times more cases of congenital anomalies than deaths due to anomalies

The commonest anomalies affect the musculoskeletal and urogenital system, although these are relatively uncommon causes of death. Whereas, the commonest causes of death from anomalies are due to anomalies affecting the circulatory system (mainly the heart) which are only the third commonest cause of anomalies overall.

Many different anomalies are responsible for these deaths as illustrated by the detailed neonatal death information provided in routine ONS publications. In 2007 there were 482 neonatal deaths for which the main cause was a congenital anomaly[13] with 165 different congenital anomalies recorded as the main cause of death. Furthermore, the 165 different categories included several which are defined as 'other' which includes a series of separate conditions so that the 165 is an underestimate of the very wide range of different anomalies associated with neonatal mortality.

The congenital anomalies which result in an infant death are those which meet the following conditions:

They are:

- Not universally lethal during pregnancy
  and
- Have a high risk of early death either due to the anomaly itself or the complications of treatment
  and
  - Are NOT detectable (or have a low detection rate) through screening during pregnancy
    Or
  - Are detectable through prenatal screening but there is poor access to screening, or low uptake of screening, or termination of pregnancy tends not to be taken-up

The group of anomalies which best illustrates this typology is the heart anomalies group. There are over 80 individual heart anomalies described in the *ICD10 classification system*, including several categories of 'other' in which many individual, rarer anomalies may be classified. Unless they form part of a syndrome, heart defects tend not to result in *stillbirth*. The overall prenatal detection rate for cardiac anomalies is relatively low at about 35-40%[10] and even with the sophisticated surgery now available the complex cardiac anomalies generally have a relatively high risk of infant death.

3.4 Variations in infant mortality due to congenital anomalies

Variations in *infant mortality rates* due to congenital anomalies between different groups in the population arise under the two sets of conditions outlined in Figure 4.

The typology outlined in Figure 4 makes explicit the points (*) at which interventions might theoretically be put in place to reduce variations between groups in the rate of infant deaths due to congenital anomalies.

The two main points for intervention to reduce variation are first the underlying **aetiological risk**, and second in the **access to screening**. A third potential point is in differential **uptake of screening** for which there may be variation due to lack of information. However, even assuming that full information is given to all women, variations in choice about prenatal screening between different groups of women are likely to remain.[15] These are very personal choices mainly relating to termination of pregnancy for which there may be strong cultural, moral and religious influences, and different views of what is regarded as a 'good' reproductive outcome.

There is a fourth potential intervention point if there is **differential access to treatment** once a baby with a congenital anomaly is born. In the context of the NHS any variations in access and quality of treatment, where they exist, are likely to be geographical rather than based

Figure 4. Conditions under which variations in *infant mortality rates* due to congenital anomalies might arise between different groups in the population

Conditions 1:

- There are NO variations between groups in the underlying risk of the anomalies; *incidence* is the same
  and
- The anomalies are not universally lethal during pregnancy
  and
- The anomalies have a high risk of early death due to the anomalies or the complications of treatment
  and
- The anomalies are detectable through prenatal screening BUT there is differential screening access (*), or differential screening uptake, or differential uptake of termination of pregnancy (*TOPFA*)

Conditions 2:

- There ARE variations between groups in the underlying risk (*) of the anomalies resulting in differences in incidence
  and
- The anomalies are not universally lethal during pregnancy
  and
- The anomalies have a high risk of early death due to the anomalies or the complications of treatment
  and
  - The anomalies are NOT detectable (or have a low detection rate) through prenatal screening
    Or
  - The anomalies are detectable through prenatal screening BUT there is differential screening access (*), or differential screening uptake, or uptake of termination of pregnancy (*TOPFA*)

(*) Points at which it may be possible to introduce interventions to reduce variations in infant mortality due to congenital anomalies between different groups in the population

on individual patient characteristics. However, providing information to parents to enable them to make fully informed treatment choices in relation to complex high risk procedures may be particularly difficult for some groups, for example, where English is not their first language.

To intervene on the underlying risk of anomalies (*primary prevention*) requires knowledge of potentially modifiable risk factors, the means to modify the risk factors and the widespread uptake of those interventions. Risk factors for congenital anomalies are discussed later.

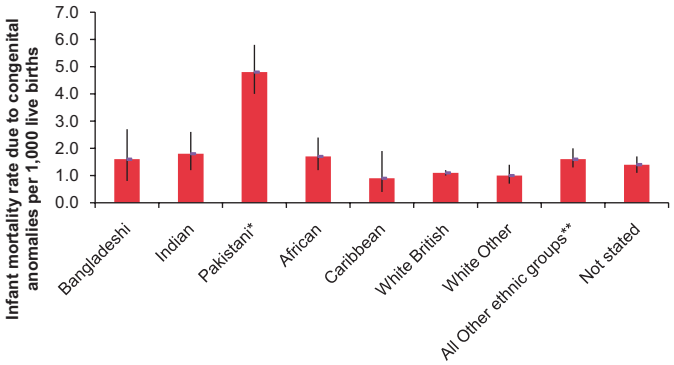
To intervene on access to prenatal screening (*secondary prevention*) requires an understanding of variations and barriers to access. However, even if screening access is universally equal, and there is some evidence that this is not the case,[15] there may nevertheless be groups in the population who choose not to take up prenatal screening and diagnosis[15] or, where they take up prenatal screening and diagnosis they may act on a 'positive' result by choosing to continue with their pregnancy and parent their child as an alternative to choosing to terminate the pregnancy.

3.5 Evidence of variations between groups in infant mortality rates due to congenital anomalies

The available national data relating to congenital anomaly deaths only allows examination of a small number of different groups in the population. Figure 5 illustrates differences in the rate of infant death by the ethnic group of the mother and highlights the statistically significantly four-fold higher risk of infant death from congenital anomalies faced by babies born to mothers of Pakistani origin compared with all the other groups listed. This higher risk represents about 90 extra deaths per year in the infants born to Pakistani mothers in England and Wales over the number of deaths that would have been expected in this group had they experienced the same *infant mortality rate* as White British mothers.

Babies born to mothers from 'other' ethnic groups are also at a statistically significantly higher risk of infant death compared with infant born to White British mothers of about 45%. This represents an excess of about 25 deaths per year compared with the number that would have been expected had they experienced the same *infant mortality rate* as White British mothers.

Figure 5. *Infant mortality rates* due to congenital anomalies with 95% confidence intervals, by ethnic group† per 1,000 live births for babies born in England and Wales in 2005[16]



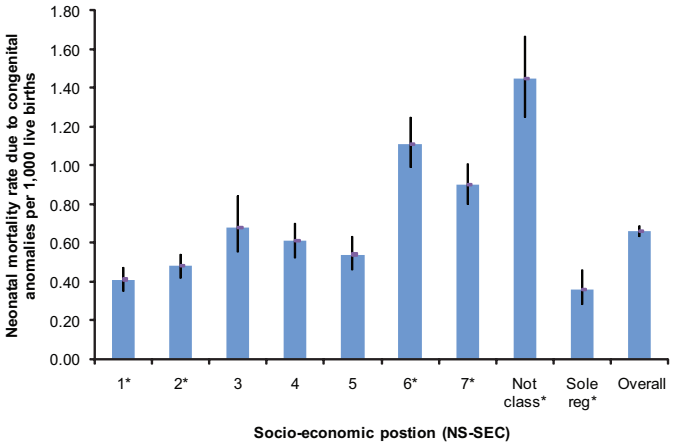
*Statistically significantly higher than all the other groups
**Statistically significantly higher than the White British group
**Chinese, Other Asian, Other Black, Other and all Mixed groups
† Ethnic group of mother derived from linkage of birth registration statistics to NHS numbers for babies (NN4B) data[1,3,16]

Figure 6 illustrates differences in the rate of neonatal death due to congenital anomalies by the socio-economic position of the neonate based on paternal occupation coding. This highlights a statistically significantly doubling in the risk of neonatal death due to congenital anomalies in the groups of babies born to fathers in the *NS-SEC* categories of 6 and 7 and those whose occupations could not be classified, compared with babies born to fathers in the *NS-SEC* groups 1-5. This higher risk represents about 88 extra deaths per year in groups 6,7 and unclassified over the number of deaths that would have been expected in this group had they experienced the same mortality rate as the infants born to fathers in the *NS-SEC* groups 1-5.

In trying to understand these differences it is important to note that the figures relating to ethnicity and socio-economic position are not independent and it is likely that some ethnic groups are more likely to have a higher or lower socio-economic position that is, these two factors confound each other. It is not possible to untangle these effects in relation to infant mortality from ONS published data because the data are only available in aggregated form. However, work undertaken by the Bradford Infant Mortality Commission demonstrated that in Bradford 88% of babies in 1996-2003 born to Pakistani mothers and 41% of babies born to white British mothers were born in the most deprived two-fifths of neighbourhoods.[17] For infant deaths overall a further analysis of the Bradford data was suggestive of an independent excess infant mortality for mothers of Pakistani origin over and above the effects of socio-

economic position. These results were not statistically significant but this was not surprising given the small numbers of deaths involved.

Figure 6. *Neonatal mortality rate* due to congenital anomalies† with 95% confidence intervals, by socio-economic position (NS-SEC) per 1,000 live births for babies born in England and Wales 2002 to 2005±



†For main cause of death
±Derived from a data download provided by ONS
*Statistically significantly different than the overall rate

3.6 The contribution of congenital anomalies to the gap in infant mortality between the routine and manual groups and the population as a whole

The aim of the infant mortality public service agreement target for infant mortality is: "...to reduce by at least 10% the gap in the mortality between the routine and manual groups and the population as a whole...."[18] Using the data provided by *ONS* for England and Wales and illustrated in Figure 6 we have estimated the excess number of infant deaths per year for the routine and manual groups in the population and have calculated the contribution of congenital anomalies to the excess. For the period 2002 to 2005 the routine and manual groups experienced, on average, 160 extra infant deaths above the number that would have been expected had they had the same *infant mortality rate* as the England and Wales population as a whole. Infant deaths due to congenital anomalies contributed about one third of this total that is, 50 of these extra deaths each year. Of note, these are average national population figures and are likely to vary across localities due to differences in the population characteristics.

4 Causes and prevention of congenital anomalies

4.1 The causes of congenital anomalies

The cause of the majority of congenital anomalies is not known.[4] There is a small number of very specific anomalies associated with particular conditions. These include, the *teratogenic* effects of particular drugs taken during pregnancy, for example, abnormal or absent limbs (phocomelia) associated with thalidomide, valproate embryopathy associated with sodium valproate treatment for epilepsy, and characteristic skeletal abnormalities associated with warfarin ingestion during pregnancy.[19] Some infectious diseases also cause characteristics anomalies, for example rubella infection contracted during pregnancy can result in the classic triad of: eye and heart anomalies with sensorineural deafness. Some women who have had a previous pregnancy affected by a congenital anomaly are at an increased risk of having a further affected pregnancy, for example the recurrence risk of *neural tube defects* (spina bifida and anencephaly) is about 5%.

Some specific anomalies are known to have a genetic origin where particular gene mutations or deletions have been identified. For example, most cases of *Apert's syndrome* are due to a spontaneous mutation affected one of two genes. The cause of the mutations is not known but when one or other mutation is present *Apert's syndrome* results. *Apert's syndrome* has an *autosomal dominant inheritance*, so that someone with *Apert's syndrome* has a 1 in 2 chance of passing the condition on to their children.

Regardless of the pattern of inheritance, genetic conditions associated with a high *infant mortality rate*, for example, *campomelic syndrome* generally occur sporadically because affected infants tend not to survive. However, a couple who has had a child affected by a genetic condition are likely in any subsequent pregnancy to have an increased risk of having a further affected child and will require genetic counselling. Depending upon the condition, in subsequent pregnancies prenatal diagnosis through amniocentesis and the termination of an affected pregnancy, will be offered if an appropriate genetic test is available. *Pre-implantation genetic diagnosis* may also be appropriate if couples are willing and able to undergo in vitro fertilisation (IVF) treatment. By identifying and transferring only unaffected *embryos*, *pre-implantation genetic diagnosis* avoids the need for termination of an affected pregnancy.

Some conditions are associated with a general increase in the risk of groups of congenital anomalies, although not associated with single specific conditions or syndromes. For example, pregestational maternal diabetes is associated with an increase in the risk of congenital anomalies overall[20] and there is evidence that gestational diabetes is associated with a similar two fold increase in the risk of anomalies overall.[21] While cardiac, skeletal and central nervous system anomalies are the most common, diabetes-associated anomalies usually involve one or more organs. Whilst the exact mechanism is unclear hyperglycaemia is thought to be the primary *teratogen* causing, in particular, cardiac anomalies.[20] As a consequence the NICE guidance for diabetic women during pregnancy recommends that women with diabetes who are planning to become pregnant should be told that "establishing good glycaemic controls before conception and continuing this throughout the pregnancy will reduce the risk of miscarriage, congenital malformation, *stillbirth* and neonatal death."[22]

Women who are obese are also at an increased risk of a range of congenital anomalies, including cardiovascular anomalies, neural tube defects, cleft palate, hydrocephaly and limb reduction defects.[23] Again, the causal mechanism(s) underlying these associations is unclear. Obesity and diabetes share common metabolic abnormalities including hyperglycaemia and insulin resistance and undiagnosed diabetes and hyperglycaemia are possible explanations for the increased risk of congenital anomalies in the offspring of obese women. Nevertheless, whilst the evidence is conflicting there does appear to be an independent risk of obesity above that associated with diagnosed diabetes.[23] A role for nutritional deficiencies associated with obesity, including reduced folate levels, has also been postulated.

Further generally non-specific risk factors for congenital anomalies include maternal age, cigarette smoking, alcohol and drug use. The risks of anomalies in general and chromosomal anomalies in particular increase with increasing maternal age; there is also growing evidence of the effects of older paternal age on the risk of dominant gene mutations, for example, *Apert's syndrome*. There are some specific exceptions to the increase in risk with maternal age, for example the risk of *gastroschisis* is inversely related to maternal age with the peak *birth prevalence* in women <25yrs. The risk of *gastroschisis* is also increased with use of recreational drugs, particularly those with a vasoconstrictive action, for example, cocaine, amphetamines and ecstasy.[24]

The role of *consanguinity* as a risk factor for congenital anomalies and infant death is complex and studies in the past often failed to account for socio-economic circumstances and other important confounders.[25] Data from Pakistan, in the early 1990s where 61% of marriages were between first (50%) and second cousins (11%), enabled adjustment for socio-economic and other factors. Against a background *infant mortality rate* of 99 per 1,000 *live births*, infants of first cousins had a 42% increased risk of death in the first year and for second cousins the increase was 24%.[25] The overall contribution of *consanguinity* to infant mortality generally and infant mortality due to congenital anomalies in the UK will inevitably be small since first and second cousin marriages are generally uncommon.[26] However, as was found in Bradford, the burden will be disproportionally borne by groups in the population where cousin marriages are more common, for example, couples of Pakistani origin (Figure 5).[17] Of note *consanguinity* is particularly associated with genetic conditions which have an *autosomal recessive* pattern of inheritance.

4.2 Primary prevention of congenital anomalies

The *primary prevention* of congenital anomalies is only possible for a very small range of specific anomalies for which there is either a known cause, or even in the absence of a clear understanding of the cause, a means of prevention has been identified. On a population level these include childhood rubella immunisation, screening and treatment for syphilis during pregnancy, periconceptional folic acid supplementation and/or folate food fortification for the prevention of neural tube defects. On an individual level, optimising the management of women at higher risk, for example, for women who are diabetic or epileptic, is the ideal approach to minimising the risks of anomalies. However, as about 40% of pregnancies in the UK are unplanned[27] this approach is not always possible even in those women at higher risk of problems in their pregnancy. Furthermore, since relatively few of the anomalies given in these examples would result in deaths in infancy, whilst the goal of reducing the risk of anomalies is important, it may have relatively little impact on the *infant mortality rate*.

4.3 Secondary prevention of congenital anomalies

There are two main methods of prenatal screening relating to congenital anomalies available in the UK. Screening for *Down's syndrome* (trisomy 21) which affects about 2.6 per 1,000 pregnancies is offered in the first or second trimesters.[28] Screening for Down's

may also detect the rather rarer conditions of *Edward's syndrome* (trisomy 18; 0.7 per 1,000 pregnancies) and *Patau's syndrome* (trisomy 13; 0.2 per 1,000 pregnancies).[28] Although *Down's syndrome* is associated with an increased risk of miscarriage or *stillbirth*, it is a rare cause of infant death and when a death does occur is it usually due to a cardiac anomaly to which infants with Down's have an increased risk. From maternal report it is estimated that about 65% of women take up the offer of screening for *Down's syndrome*.[15] Lack of universal uptake probably reflects first, a failure of universal offer of screening and the extent to which this occurs and the reasons why are unclear;[15] and second, a desire by some women not to terminate their pregnancy even if the *fetus* is affected by *Down's syndrome*. Perceptions of a 'good' reproductive outcome are very personal and influenced by many social, cultural and religious factors.

The second main form of universal prenatal screening is detailed second trimester ultrasound scanning usually offered between 18 to 20 completed weeks gestation and which is designed to assess fetal growth and identify structural congenital anomalies including some structural anomalies associated with chromosomal defects. Despite the fact that the consequences of detection of anomalies through this route is the same as for *Down's syndrome*, uptake of second trimester ultrasound scanning is higher than the uptake of *Down's syndrome* screening. This is possibly because many women may be unclear about the purpose of the scan and view it primarily as a source of reassurance and of pictures of their baby.[29]

Prenatal detection rates vary by anomaly (Table 1). It is important to note however, that only a relatively small proportion of these cases would contribute to the *infant mortality rate* even if they remained undetected prenatally. The main contributors to infant deaths for these selected anomalies would be a minority of the cardiac defects, the more severe cases of *congenital diaphragmatic hernia* and a minority of the chromosomal anomalies.

Table 1. Prenatal detection rates for selected isolated* congenital anomalies, data from the Congenital Anomalies Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB)2005-2008[10]

Selected isolated* anomalies	Detection rate (%)	95%CI
Neural tube defects	95%	89%-98%
Cardiac anomalies	35%	30%-42%
Cleft lip +/- palate	65%	53%-75%
Congenital diaphragmatic hernia	64%	41%-83%
Gastroschisis	100%	93%-100%
Exomphalos	90%	68%-99%
Chromosomal	56%	50%-62%

*Isolated – no other congenital anomalies present

On an individual basis couples identified as being at increased risk of genetic conditions will be offered genetic counselling and where suitable tests are available, they will be offered prenatal diagnosis through amniocentesis in a subsequent pregnancy. As discussed above *pre-implantation genetic diagnosis* may also be an option.

5 Conclusions

Congenital anomalies are the second commonest cause of infant deaths in England and Wales, although the vast majority of infants born with a congenital anomaly will survive with a near normal life expectancy. The underlying cause of most congenital anomalies is not known. There are many different congenital anomalies and in any single year infant deaths due to congenital anomalies in England and Wales are associated with over 150 different causes. Congenital anomalies contribute about one third of the extra infant deaths experienced by the routine and manual groups compared with the population as a whole.

The *primary prevention* of congenital anomalies requires many different activities and the delivery of a high standard of universal pre-pregnancy and pregnancy care for women in general together with optimisation of management before conception for specific women at higher risk of anomalies, for example, women with diabetes, epilepsy and those taking other specific drugs with *teratogenic* effects. The availability of genetic services is essential for couples with a family history or past history of pregnancies affected by congenital anomalies, particularly due to specific genetic conditions. Some sections of the population are at increased risk of particular genetic conditions and as a consequence *infant*

mortality rates due to congenital anomalies may be higher than in the population in general; genetic services will be of particular importance in these areas.

Secondary prevention of congenital anomalies is achieved through prenatal screening and diagnosis followed by the offer of termination of pregnancies affected by major anomalies. Because termination of pregnancy is the only 'therapeutic' option for many congenital anomalies *secondary prevention* is not universally acceptable.

Infant mortality rates due to congenital anomalies are strongly influenced by prenatal screening and diagnosis, and uptake of termination of pregnancy. However, it is important to note, that many of the anomalies which can be prevented through primary or secondary actions would not in any case have resulted in an infant death and thus their prevention, although of great importance because of the associated morbidity and disability, will not necessarily impact on the *infant mortality rate*.

Glossary

Apert's syndrome – a rare congenital disorder characterised by malformations of the skull, face, hands and feet which requires extensive surgery. It is almost always caused by a spontaneous gene mutation of paternal origin and the risk of Apert's syndrome increases with the age of the father.

Autosomal dominant genetic inheritance – this is the mechanism of inheritance of genetic conditions which are caused by a single gene inherited from one parent. Someone who carries the gene for an autosomal dominant condition will always be affected by the condition and each of their children will have a 1 in 2 chance of inheriting the condition.

Autosomal recessive genetic inheritance – this is the mechanism of inheritance of genetic conditions which requires a single gene from both parents to be affected in order for their child to be affected. Carriers of recessive genes are themselves not affected but if they have a child with someone who is also a carrier each child they have will have a 1 in 4 chance of being affected by the condition.

BINOCAR – British Isles Network of Congenital Anomalies Registers.

Birth prevalence – is the measure of frequency of occurrence usually used in relation to congenital anomalies. The term incidence is not used in acknowledgement of the fact that many *embryos* and *fetuses* affected by a congenital anomaly are miscarried and therefore not counted in the rate calculation. Birth prevalence is the number of new cases of congenital anomalies born (*live births* and *stillbirths*) divided by the total number of births.

Campomelic syndrome – a rare single gene defect with autosomal dominant inheritance which results in abnormalities of the bones and the cartilage of the respiratory tract. Almost without exception affected babies die in the neonatal period from respiratory complications. The characteristic bone features can be diagnosed on prenatal ultrasound. There is no treatment available, other than to provide respiratory support to babies born alive. It affects about 1 in 500,000 pregnancies.

CAROBB – Congenital Anomalies Register for Oxfordshire, Berkshire and Buckinghamshire.

Consanguinity – unions contracted between persons biologically related as second cousins or closer. This arbitrary limit has been chosen because the genetic influence in offspring from marriages between couples related to a lesser degree would usually be expected to differ only slightly from that seen in the general population. Globally, the most common form of consanguineous marriage is between first cousins, in which the spouses share 1/8 of their genes inherited from a common ancestor.

Down's syndrome – is one of the more common chromosomal disorders due to having part or all of an extra chromosome number 21. It is characterised by a series of major and minor structural abnormalities, for example, a small chin, an unusually round face, a large tongue and almond shaped, widely spaced eyes. Cognitive impairment is usually present, although the extent is variable. Health concerns include a higher risk of congenital heart anomalies, recurrent ear infections, obstructive sleep apnoea, thyroid disease, leukaemia and early onset Alzheimer's disease.

Edward's syndrome – is a chromosomal disorder due to having part or all of an extra chromosome number 18. Infants have multiple anomalies affecting the heart, kidney, intestines (exomphalos). The majority of affected infants die within the first month after birth and only 10% survive to age one year. Long term survival is very uncommon.

Embryo – In humans during pregnancy, an *embryo* is the developing organism from the time of fertilisation until the end of the eighth week of gestation, following which it is called a fetus.

Exomphalos – is a defect in the abdominal wall through the umbilicus through which the intestines and other organs develop outside the abdomen. It is more commonly associated with other congenital anomalies, for example *trisomy 18*, than *gastroschisis* and as a consequence the long term outcome is less favourable than for *gastroschisis*; termination of affected pregnancies is more common.

Fetus – In humans during pregnancy, a *fetus* is the developing organism from the end of the eighth week of gestation until birth.

Gastroschisis – is a defect in the abdominal wall to one side of the umbilicus through which the intestines and other organs develop outside of the abdomen. It is rarely associated with other congenital anomalies. Surgical repair of the defect is required following birth with the majority of the infants treated having a good long-term outcome although complications can arise.

ICD10 classification system – The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is a coding of diseases and signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or diseases, as classified by the World Health Organisation.

Incidence rate – is a measure of the occurrence of new cases of a disease in a population. This is in contrast to prevalence which is a measure of both new cases and existing cases in the population. In the field of congenital anomalies the term birth prevalence is rather confusingly used to describe new cases of anomalies. Birth prevalence is used because we know that many new cases of anomalies do not survive in pregnancy long enough to be identified since they are miscarried. We therefore cannot know about all new cases of a particular anomaly.

Infant mortality rate – number of deaths at ages under one year per 1,000 *live births*.

Live birth – birth of an infant showing any signs of life regardless of gestation at birth.

National Statistics Socio-Economic Classification (NS-SEC) – a method of coding socio-economic position on the basis of occupation introduced in 2002 to replace the Standard Occupational Classification which coded occupation to the Registrar General's Social Class. *NS-SEC* has a series of analytical classes which are nominal in the extended 14 operational categories form and which become ordinal when collapsed into the three-class version. Infant mortality statistics are published using the eight-class analytical version:

1.1 Large employers and higher managerial
1.2 Higher professional
2 Lower managerial and professional
3 Intermediate
4 Small employer and own-account workers
5 Lower supervisory and technical
6 Semi-routine
7 Routine
8 Never worked and long-term unemployed
Unclassifiable

NCAS – National Congenital Anomalies System for England and Wales.

Neonatal mortality rate – number of deaths at ages under four weeks per 1,000 *live births*.

NorCAS – Nothern Congenital Abnormality Survey.

NS-SEC – see *National Statistics Socio-Economic Classification* above.

Neural tube defects – a group of conditions caused by the failure of closure of the neural tube during embryonic development during the first 28 days after fertilisation. The neural tube forms the brain and spine and the type of neural tube defect which occurs depends upon where on the spine or brain the failure to close occurs. If it affects the brain a condition called anencephaly results where the brain fails to develop; a condition incompatible with life. When it affects the spine, spina bifida results and its effects depend upon where on the spine the defect occurs; the higher up the more serious the effect and the more complications that result.

ONS cause (of death) groups hierarchical classification – a classification system developed to enable comparison of neonatal and post-neonatal deaths following a change in deaths certificates for neonatal deaths and stillbirths whereby a single underlying cause of death was no longer assigned. This system allows the death to be assigned hierarchically to a specific category based on the likely timing of the damage leading to the death:

Before the onset of labour
11. Congenital anomalies
12. Antepartum infections
13. Immaturity related conditions

In or shortly after labour
14. Asphyxia, anoxia or trauma

Postnatal
15. External conditions
16. Infections
17. Other specific conditions

9. Sudden infant deaths

Unclassified

0. Other conditions

Patau's syndrome – is a chromosomal disorder due to having part or all of an extra chromosome number 13. Infants have multiple anomalies affecting the heart, kidney, and other organs including neurological effects. Stillbirth is common and the majority of affected infants die within the first month after birth.

Postneonatal mortality rate – number of deaths at 28 days and over but under one year per 1,000 *live births*

Pre-implantation genetic diagnosis –requires in vitro fertilisation (IVF) following which a single cell is removed from the developing embryos to test for specific genetic conditions. Only unaffected embryos are then transferred to the uterus. It is only available for genetic conditions where a diagnostic test can be performed.

Primary prevention – actions taken to avoid disease or injury occurring in the first place. Examples of primary prevention include vaccination against infectious diseases.

Secondary prevention – actions taken to identify and treat an illness or injury early on in its development with the aim of stopping or reversing the problem. Examples include screening for diseases which can then be treated earlier than would usually be the case.

Stillbirth – birth of an infant at ≥24 weeks gestation showing no signs of life.

Teratogen – any agent which causes abnormalities of embryonic or fetal development, examples include specific drugs (eg thalidomide), X-rays and some viruses (eg rubella).

TOPFA – termination of pregnancy for fetal anomaly. TOPFA is offered following prenatal diagnosis of major congenital anomalies.

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