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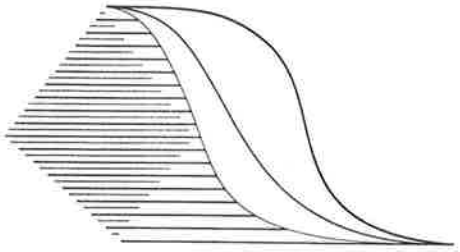

REDUCING BIRTH DEFECTS IN POPULATIONS

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Reducing Birth Defects in Populations

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Reducing Birth Defects in Populations

Executive Summary

Birth defects occur in populations in 3-5% of births. All those birth defects due to chromosomal errors, hundreds of those due to single genes and many of those due to unknown or multifactorial cause can be detected prenatally. However, it is not feasible to test all pregnancies for all of these causes, and it cannot be predicted which pregnant women are more likely to be carrying a fetus with a birth defect except in a few instances, namely:

- Down syndrome (1.5 per 1,000 births)
- Neural tube defect (1-3 per 1,000 births)
- A previous history in the family of a particular defect
- A history in a sub-population of a high birth incidence of a particular gene-caused defect.

Carefully developed programs focused on these four situations may bring benefits to a population, because it allows families to avoid the suffering involved in having a severely handicapped child. It may also be cost effective, since the treatment and ongoing care of such individuals is so expensive, and most couples opt for pregnancy termination.

Another potential approach is to use ultrasound to look for structural defects in all pregnant women. It is not yet possible to say accurately how much routine ultrasound screening of all pregnancies would contribute. However, in the present state of knowledge, it has not been demonstrated that it is possible to dramatically decrease the population birth incidence of defects by such a prenatal diagnosis program, although a decrease of perhaps 20% may be feasible. Estimation is complicated by the facts that 15% of cases identified by ultrasound to have severe defects either spontaneously abort or die before birth, and that 20% of individuals with defects detected are in fact found not to be affected at birth.

Modelling of projected numbers of how many women would be screen positive and require counselling, and of how many will then have diagnostic testing, is an essential step in planning realistically for the facilities, equipment, and number of trained personnel required. Pilot projects

to assess the feasibility of implementation are essential as the administration and management of services and their implementation at regional and local levels is complex. Not only personnel to provide ultrasound screening testing, but personnel able to provide confirmatory diagnostic cytogenetic, biochemical, and molecular genetic services would have to be in place. Related laboratory and ultrasound equipment and space must be budgetted and planned for.

The resources required to provide counselling sufficient for informed consent are very substantial. Although much can be done to make a program efficient - information brochures in simple understandable language, group counselling, and T.V. or video information sessions, inevitably large numbers of individual counselling sessions will be needed in a population-wide program. The limitations of screening tests need to be explained to women, as screening simply divides them into a low and a high risk group. For example, for every 30 women identified by nuchal translucency ultrasound screening as eligible for an invasive diagnostic procedure, only one of them will be found to have a fetus with Down syndrome at that procedure. Women should be aware of this before choosing to undergo the initial ultrasound screen.

Outcomes should be monitored in order to see if the program is achieving its goals, and a population-based system to record and classify birth defects and terminations done for defect detection would have to be put in place to enable outcomes to be tracked.

Even if a program is projected to be cost-beneficial, it would be foolhardy to institute it without carefully monitored and adequately funded stages being reached. Not only funding for personnel with expertise is needed, but time for recruitment and training of them is necessary. Unless it is undertaken in a carefully planned, monitored and staged way, a population-based birth defects reduction program is likely to bring harm and anxiety rather than benefit.

What are birth defects?

It is not easy to define precisely a birth defect, but a working definition is a gross anatomic developmental anomaly present at birth or found during the first year of life. Under this definition,

infections that result in abnormalities, tumours, genetic syndromes, or metabolic derangements that show anatomic anomalies are included.

Some birth defects have a genetic basis, at either the chromosomal or the gene level, others are the result of environmental factors that interfere with normal development of the fetus, such as rubella infection or radiation exposure. Many birth defects are multifactorial due to interaction between genetic and environmental factors. However, a substantial proportion is of unknown cause, as the following table shows:

The Causes of Birth Defects[1]

Cause	% of infants
Chromosomal	10.1
Single-gene	17.6
Multifactorial	23.0
Unknown	43.2
Teratogens	3.2
Uterine factors	2.5
Twinning	0.4

What proportion of individuals has birth defects?

Figures from different studies on this question can be expected to differ from one another due to differing study definitions of birth defect, different methods of case detection, and differing time periods over which individuals are ascertained. For example, in some studies every consecutive newborn is examined by a trained observer, in other studies notifications of birth defects are taken from birth certificates. However, in all populations that have been examined with good methodology, the overall proportion of affected liveborns is about the same. The following table shows the range in some large studies:-

Reference		Time Period	Births	% with Birth Defects
2	Hungary	1970-75	1,001,631	3.24
3	Birmingham England	1964-84	334,389	2.87
• 4	United States	1959-65	53,257	5.75
5	Western Australia	1980-97	437,255	5.2
6	Australia	1981-94	3,370,000	1.6
7	3 Canadian Provinces	1979-81	538,241	3.84
8	3 Canadian Provinces	1991-93	631,299	3.85
* 9	British Columbia	1952-83	1,169,873	3.6
* 10	British Columbia	1974-83	387,705	5.3
11	Norway	1967-89	371,933	2.5

* These were live births, not total births.
• This sample was examined several times and followed to 1 year.
In summary, approximately 3-5% of all individuals born have a significant birth defect.

What are the most common birth defects?

Although birth defects as a group are frequent, many particular birth defects are individually rare, and even those that occur most often are uncommon. (12) Those birth defects that occur more often than 1 in 1,000 births are shown in the table below:

Approximate Rate of Common Birth Defects *

	Neural tube defects	1 - 2	per 1,000 births
Heart	(Venticular septal defects	1 - 2	per 1,000 births
Defects	(Atrial septal defects	1 - 1.5	per 1,000 births
	(Patent Ductus Arteriosus	1 - 1.5	per 1,000 births
	Down syndrome	1 - 1.5	per 1,000 births
	Cleft lip ± palate	1 - 2	per 1,000 births
	Congenital inguinal hernia	2	per 1,000 births
	Pyloric stenosis	1 - 2	per 1,000 births
	Hypospadias	2 - 4	per 1,000 births
	Congenital dislocated hip	2 - 4	per 1,000 births
	Club foot	2	per 1,000 births

* Compiled from numerous large population-based studies

Many birth defects are not seriously handicapping, and some can be treated after birth by surgery, examples from the above table are pyloric stenosis, inguinal hernia, hypospadias, and cleft lip. However, it would be desirable to prevent them from occurring; and there is no effective treatment for many other birth defects, so the only approach for these is prevention.

Can birth defects be prevented from occurring?

It is not understood why most birth defects occur, and so the great majority of them cannot be prevented from happening. A common birth defect that is an exception to this is neural tube defects (NTD). These are defects in closure of the nervous system which result in anencephaly and/or spina bifida. Infants with anencephaly do not survive, whereas those with spina bifida often do, and have serious handicaps. It is now known that an increase in folic acid consumption by all pregnant women will result in preventing over half of such defects from occurring,(13, 14, 15) and it reduces other defects somewhat as well. It is probable that the only way of ensuring all women of child-bearing age increase their intake of folic acid sufficiently is to fortify staple foods, as even in developed countries there is insufficient intake of folic acid by most pregnant women. Food fortification is therefore an important public health preventive measure. Women who have already had an infant with NTD are at increased risk for NTD to recur (3.5%) in subsequent pregnancies, and should receive higher doses of folic acid before conception and during early pregnancy so their risk is then reduced to about 1%.

Whether a public health program of folic acid supplementation in a staple food is warranted will depend on the population birth prevalence of NTD's relative to other health problems that need resources. (16) With regard to China for example, two studies of the birth prevalence of NTD's in over a million births showed that about 2.7 per 1,000 births were affected,(17, 18) but the frequency differed markedly in different regions of China, and NTD's were several times more common in rural areas.

Apart from NTD's, there are few opportunities to prevent occurrence of birth defects on a population basis, other than women having a good diet, rubella immunization in childhood, and abstaining from alcohol during pregnancy.

Can the birth incidence of defects be decreased?

Although it is not possible to prevent most birth defects from occurring, it is possible to detect some of them after they have occurred, but during pregnancy, before the birth of the affected fetus. Most couples opt for pregnancy termination if a fetus is found to have a serious birth defect; as a consequence there is a decrease in birth incidence of those particular defects in the population when prenatal diagnosis is available. (As context, it is of note that most disabilities are not due to birth defects but result from other factors such as low birth weight, prematurity, viral or bacterial diseases, birth traumas, and accidents.)

Which common birth defects can be detected prenatally?

1. Down syndrome

Individuals with Down syndrome have mental retardation and physical problems such as congenital heart defects and gastrointestinal malformations. If they survive to middle adulthood, they often develop Alzheimer disease. The diagnostic procedures of amniocentesis (19) or chorionic villus sampling (20) for this birth defect are costly and have some risk, so it is only justified to offer diagnosis if a woman is more likely to have an affected fetus. Initially women were identified as at higher risk if they were older, because occurrence of Down syndrome is related to increasing maternal age. At best this approach can only identify about 30% of Down syndrome pregnancies.

In 1983 it was found that pregnancies with Down syndrome were associated with reduced levels of maternal serum alpha protein (MSAFP). This led to a new screening approach, using information on the woman's age and also serum markers to estimate the risk of having an affected fetus. The "triple test" using serum markers measures maternal serum AFP, human chorionic gonadotropin (HCG) and unconjugated oestriol (uE_3) at 16 weeks gestation. Current serum

screening of all pregnant women at 16 weeks with state of the art implementation can detect at best about 72% of Down syndrome pregnancies for a 5% false negative rate. (21) In practice most studies are somewhat lower. (22) (An incidental benefit of the Down syndrome triple screen is that it picks up pregnancies at high risk for Trisomy 18. Individuals with Trisomy 18 rarely survive, and the birth prevalence is only about 1/10 that of Down syndrome, so screening for this alone is not justified.)

A more recent approach to detection of pregnancies at increased risk of Down syndrome is to use ultrasound measurement of nuchal translucency at 10-13 weeks. This is a subcutaneous translucency between the skin and the soft tissues overlying the cervical spine. Selection of the Down syndrome high risk group for invasive diagnostic testing by this method allows the detection of about 80% of affected pregnancies (23) and also identifies a high risk of Trisomy 18. It requires about 30 invasive diagnostic procedures for identification of one affected fetus. It appears that screening for chromosomal abnormalities by ultrasound evaluation of nuchal thickness at 10-13 weeks will become the most effective screening method, and in future, this approach is likely to replace biochemical screening. However, structured training and experience of ultrasonographers with this methodology is essential for accuracy, as it is a very unreliable method in unskilled or partially skilled hands.

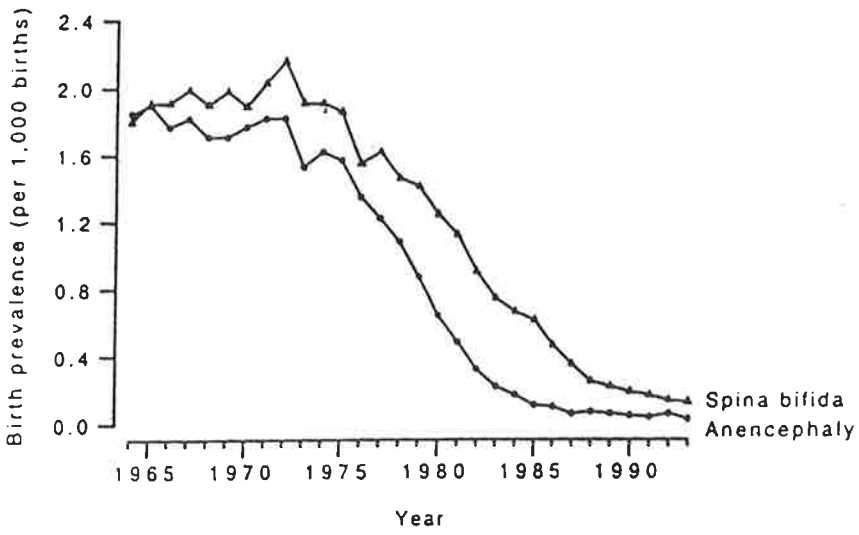
Another future approach, not feasible at present, is to use fetal cells that are shed into the maternal circulation to detect chromosome anomalies. It will not be feasible in population programs unless cheap, automated methods of cell separation and analysis become available. (24)

2. Neural Tube Defects

A second common birth defect that can be detected prenatally is neural tube defect.Women who have had an infant with neural tube defect are at increased risk for it to occur again, and as well as folic acid supplementation, should be offered screening and diagnosis. However, an approach targetted in this way will not change birth incidence in the population much, since 95% of affected pregnancies occur in women with no previous history.

Women in the general population at increased risk of neural tube defects can be identified by MSAFP screening, and then offered diagnostic testing. If serum screening alone is used as an indication for abortion, 19 out of 20 pregnancies that are terminated would be normal, so counselling and diagnostic tests, using amniocentesis or detailed expert ultrasound, are an integral part of the program. Where such integrated programs are in place, neural tube defect births have declined dramatically. Some of the decline is due to improved diet and greater folic acid supplement consumption, but most of the decline is due to screening, followed by diagnosis and selective abortion. The following figure shows one population where this has occurred.

Prevalence of neural tube defects at birth in England and Wales 1964-1993



The MSAFP test is part of the triple test for Down syndrome noted in the previous section. Such screening is not expected to detect closed spina bifida, but if performed at 16 weeks gestation, the detection rate for open spina bifida is 82% (with false positive rate of 1.9%) and it detects almost all cases of anencephaly. Women identified as at higher risk on screening are offered a diagnostic test, such as targetted ultrasound examination by an experienced radiographer. This

approach performed on women at high risk will detect well over 90% with a very low false positive rate. A less used diagnostic alternative is biochemical measurement of amniotic fluid. (25)

As more centres are able to routinely offer ultrasound by trained personnel on good equipment, it may be possible to move to this modality alone for screening, so in future biochemical screening may be phased out. It has been found in some studies that routine ultrasound screening (usually performed at 18-20 weeks) can detect about 75% of pregnancies affected by spina bifida and most cases of anencephaly.

3. Other structural birth defects

Although all chromosomal abnormalities, a wide range of structural defects and several hundred single gene defects can be diagnosed early in pregnancy, it is not feasible to test all pregnancies for all conditions. The problem is, that apart from a few situations where higher risk individuals can be identified, (Down syndrome, neural tube defects, and some single gene defects (see next section), it is usually only possible to know which condition to test for after the birth of the first affected child. Therefore, non-invasive methods that could be used in total population screening to identify pregnancies at risk for unpredicted birth defects would be useful. One such method being explored is second trimester ultrasound screening for fetal structural defects.

Owing to widely different experience levels and equipment, there is a large discrepancy in results of such screening. An overview of European experience shows a detection rate of about 28% of structural defects in geographical areas outside specialist centres.(26) Other studies have shown that although varying proportions of defects were identified, there was no difference in overall postnatal outcomes in screened and unscreened populations. In a large American trial only 17% of all abnormalities were detected prior to 24 weeks gestation. (27) Identification of defects included in the categc y congenital heart disease varies wi ·ly, with prenatal identification rates ranging from 0 to 60% being reported. (28) A recent benefit-to-cost analysis on a policy of routine ultrasound screening for fetal defects in the United States concluded that it was of uncertain net societal benefit. (29)

The costs of setting up routine ultrasound screening for all pregnant women are substantial, only a proportion of birth defects are detected, and there are false positive results which can be harmful. (30) Ancilliary diagnostic services such as cytogenetics for confirmation of abnormalities are essential. Therefore, if such a screening program is embarked on, it should be carefully piloted, include maternal counselling and informed consent, and must have demonstrated a high accuracy rate in defect detection. Other considerations are relevant. Many defects detected would not be handicapping, and a significant proportion of fetuses with major defects would have died anyway before or shortly after birth. Also relevant is that many defects detectable by routine ultrasound screening would also be picked up during ultrasound screening for Down syndrome and neural tube defects, or during "indicated" ultrasound examinations, so assessment of whether a program for structural defects is worthwhile must take place in the context of prenatal care in its entirety. (31) The great distress, anxiety, and harm from unnecessary intervention caused by the false positives found on screening a low risk population must also be taken into account.

4. Monogenic disorders

Genes have entered different sub-populations because of these populations' different histories. In some populations, particular genes may have reached such a frequency (for example by selective advantage because of resistance to malaria) that they now exhibit a significant birth prevalence of a related disease. In populations where certain genetic disorders are unusually frequent, birth prevalence data provide the justification for focused special programs to identify carriers and then offer prenatal diagnosis for high risk couples. Successful programs have virtually eliminated such diseases in some regions, and dramatically reduced their prevalence in others. For example, the births of thalassaemic children have been reduced by 60-90% in the Mediterranean area, (32) and the births of children with ßthalassaemia by 50% in Greece and Sardinia, and by 90-100% in Cyprus and Ferrara. (33, 34, 35) Similarly, sickle cell disease has been reduced by 30% in Cuba. (36) Such carefully focused screening and prenatal diagnosis programs can bring real health benefits to regions which have increased carrier rates of hereditary haemoglobin disorders, or

other monogenic defects. However, they will change very little the overall burden of the more than 5,000 single gene defects so far identified in humans.

5. Other indications for prenatal diagnosis

As noted previously, most birth defects occur in an unpredictable way. However, once a couple has had an affected child, an assessment needs to be made as to the likelihood of recurrence in that family, and this will differ a great deal depending on the cause. Some defects are due to new dominant mutations (for example - achondroplasia) so that there is little likelihood of recurrence in future sibs, but the affected individual has a 50% chance of having affected offspring. Other defects may be autosomal recessively inherited, with a recurrence risk of 25% in sibs. Chromosomal rearrangements may be sporadic with little risk of recurrence, or be inherited. An exposure during pregnancy may have been responsible and have little chance of recurring. The essential point is that an assessment of recurrence risk is complex and should be made by a highly trained person (clinical geneticist). There are numerous sources that may be used to help in this risk estimation. (37) For many common birth defects, the best prediction is from empiric risk figures based on the observed frequency of recurrence in large studies. The approximate risk is usually in the range of 3-5% for the defect to recur. If two or more relatives are affected with a multifactorial birth defect (for example, cleft lip and palate, or congenital heart disease) the risk in future is higher than this. If a precise diagnosis is reached after assessment, specific prenatal diagnosis will often be feasible, and future births of affected individuals avoidable.

What overall decrease in birth defects can be expected?

An important question is what decrease in birth defects can be expected to result if all the programs of screening and prenatal diagnosis described above are put in place. In evaluating the impact of such programs, it should be taken into account that a proportion of individuals identified as having defects by ultrasound during pregnancy will not in fact be affected at birth - this is about 20% in a recent large study. (38) In that same study, 15% of cases with severe defects either spontaneously aborted or died before birth. This too decreases the impact of the program. In addition, liveborn infants with anencephaly do not survive long, so avoiding births of

these infants brings less benefit. If certain assumptions are made, the greatest decrease that is likely with present technology can be very roughly estimated as shown in the following table:

	Birth incidence/1,000 births		
	Current	Possible with screening	% decrease
Down syndrome	1.2	0.3	75
Anencephaly	1.7	0.1	95
Spina bifida	0.9	0.2	75
Structural and other defects	25 - 45	20 - 36	20
All Defects	30 - 50	21 - 37	c.25

However, the above estimate is based on an assumption that routine ultrasound screening will result in a decrease of births of infants with defects by about 20%. Such a decrease has not yet been demonstrated in large population-based service delivery systems. The ability to decrease structural defects even by 20 to 25% may therefore be an over-estimate. In addition, those infants without major detectable structural defects, but who have dysmorphic features and mental retardation or other function defects which become apparent over some months, will not be detected. Even though from a population perspective the 3-5% birth prevalence is, for example unlikely to be reduced to less than 2-4%, that does not mean that such programs are not worth doing. Properly delivered and funded prenatal programs help families avoid the suffering and society avoid the costs entailed in having severely handicapped children.

Some individuals in any population can be identified as at increased risk to have children with serious chromosomal or multifactorially determined diseases. Effective treatment for most of these is not currently possible. Although this situation exists for only a proportion of people, in societies which can afford it, it would be uncaring not to provide access to prenatal diagnosis for these individuals.(39) Providing specific prenatal carrier detection and prenatal testing programs will also bring benefit when offered to populations with particular cultural or geographic histories that have left them with an increased prevalence of a particular gene which causes severe disease in its homozygous state - for example, the gene for Tay-Sachs disease in Ashkenazim, and

thalassemias in Mediterranean populations. This group of people only have the option of avoiding having affected children if a program of genetic prenatal diagnosis is available, or if they do not reproduce.

Since the treatment and care of individuals with major birth defects is so costly, (40) and in practice most couples opt to terminate, it is likely that carefully planned programs will be cost effective. However, cost-benefit analyses will vary even between regions within a country, and must take into account the regional epidemiology of genetic disease and birth defects. A given program may be economically justified in some areas, or for some ethnic groups (for example where neural tube defects are common), but not where the birth prevalence is low. A population-based system to record and classify birth defects that occur in the population, as well as a record system on terminations after defect detection, are necessary if data to permit evaluation of the outcomes of prenatal programs are to be available.

The situation with regard to ultrasound screening of all pregnancies for fetal defects is not yet clear. There are major costs and harms possible, as well as substantial benefit. Pilot programs are needed with careful assessment as they evolve. Well-defined prenatal screening and diagnostic programs delivered with informed consent may bring health benefits to a population. However their use should be viewed in the context of the particular needs and situations of different regions and populations. They should not be a priority for example, where a safe water supply, or lack of immunization programs are a concern.

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19. Amniocentesis is obtaining amniotic fluid by aspirating through a hollow needle inserted through the abdominal wall into the uterus. It is done under ultrasound guidance at about 15-16 weeks gestation. Maternal complications and fetal injury are rare. There is a risk of pregnancy loss of about 0.5%.

20. Chorionic villus sampling is removing by aspiration a small amount of the membrane surrounding the fetus using a catheter. Usually done around 10-12 weeks gestation.

21. Using a fourth marker, inhibin A will give a slightly better detection rate.

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