Congenital anomalies: Overview and a brief report on promising new research

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Background

The release of Australian research earlier this month showing that potentially millions of babies can be prevented from miscarriage and neural tube and other congenital defects, through dietary interventions, has prompted us to provide a brief report on these results in the hope that the early dissemination of this information can be used by family doctors to reduce the burden of congenital anomalies for regional children and their families. Currently and prior to these new research results, approximately 50% of all congenital anomalies have not been able to be linked to a specific cause, though there are known genetic, environmental and other risk factors for many such defects. We have provided the outline of this new research and a review of current knowledge in the hope that it provides some insights into unidentified causes.

Introduction and Overview

Congenital anomalies are intrauterine malformations of the foetus and may occur at any time during development. In developed countries where foetal and maternal screening is often conducted they may be discovered early; without such screening they are usually discovered via miscarriage or at birth. The prevalence of congenital anomalies and its pattern of distribution is different globally and regionally, being affected by a variety of factors, be they physiological, socio-economic, genetic or environmental. Global distribution of congenital anomalies has been shown in Figure 1.

Key facts

• Globally, an estimated 303,000 babies die every year within the first month of life due to congenital anomalies.

• Those babies who survive with congenital anomalies, can have lifelong disability.

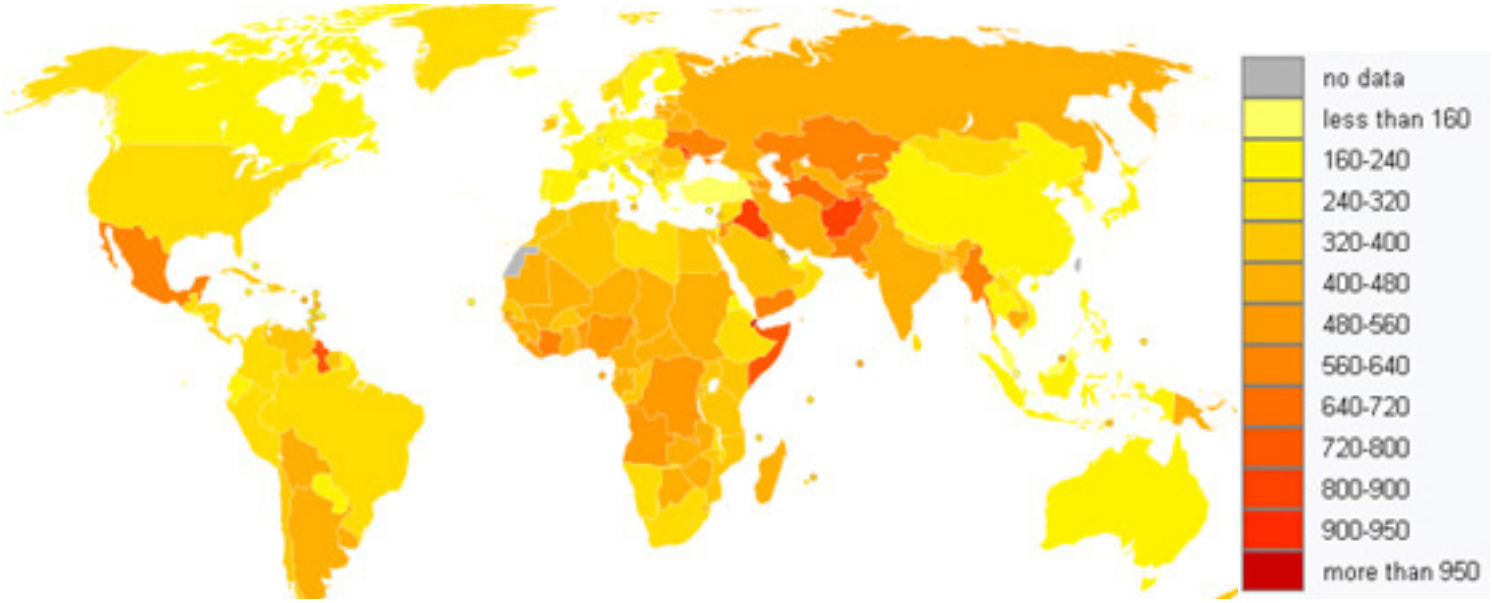
• Some disabled children are abandoned at birth due to stigma and economic burden on poor families.

• Such disability also therefore becomes an economic burden on society.

• The most common and most severe of congenital anomalies are heart defects, neural tube defects and Down syndrome.

• It is estimated that about 94% of severe congenital anomalies occur in low- and middle-income countries. (1)

Figure 1: Global distribution of congenital anomalies (2012) (1)



Causes and Risk factors

Most severe congenital anomalies occur in low- and middle-income countries (1).

The following summarises the major causes:

1. Diet and appropriate nutrition
Being born in a low income or developing nation can have an immediate effect on risk factors not only through malnourishment of the mother and consequently the foetus, but also lack of dietary requirements and inability to afford supplements.

1a. Folate
An adequate intake of folate in the peri-conceptional period has the capacity to prevent 70 per cent of all cases of Neural Tube Defects (NTD). Those women planning pregnancy are therefore in a position to avoid such defects by ensuring adequate supplies in their diet. For women unable to purchase folate supplements it is readily found in green leafy vegetables. The growing and eating of such vegetables is a cost effective way of avoiding NTD.

Neural tube defects include spina bifida, encephalocoele and anencephaly, and result from failure of the spinal cord or brain to develop normally during early foetal development. Less than 40 per cent of those affected survive to birth. People born with an NTD, especially those with spina bifida, will experience lifelong disability.

Pregnancy guidelines recommend that women of childbearing age take in 0.5mg of folic acid for at least one month before pregnancy and three months into the pregnancy. Women who are at high risk of having a baby with an NTD include those where a parent-to-be has spina bifida, has had a previous child with an NTD, has a close relative with an NTD, or where the woman has been treated for epilepsy. These women should take ten times the minimal dose (5mg of folic acid daily one month before pregnancy and three months into the pregnancy) (2).

1b. Vitamin requirements
Vitamin A deficiency may cause blindness while excessive vitamin A intake during pregnancy may affect the normal development of an embryo or foetus.

Risk of Vitamin D deficiency can be found in those with low exposure to sunlight (this may include Muslim women whose attire can prevent adequate sunlight exposure), in women with dark skin, and those with a pre pregnancy BMI ≥ 40. Vitamin D deficiency leads to a higher risk of pregnancy complications such as gestational diabetes, preeclampsia, preterm birth, and low birth weight (3).

The new Australian study outlined below shows that lack of Vitamin B may be the cause of many of the 50% of unexplained congenital anomalies.

The obvious conclusion from these studies is that pregnant women need to have a varied diet that covers all food groups, vitamins and minerals, to allow the foetus to gain all it needs for proper development. This obviates the necessity of nutritional guidelines and prenatal care being made available to all pregnant women globally.

2. Pre-natal care
Prenatal care should not only include guidelines as to a healthy diet for mother and foetus, but also the monitoring of foetal growth and mother's health; for example, for cases of gestational diabetes, eclampsia and pre eclampsia . Mothers in low socio-economic areas may receive no pre-natal care at all, as well as be subject to a wider range of causative factors. In some developed countries the foetus or mother is screened for congenital and genetic disorders and aborted if found to be affected or a genetic carrier.

3. Vaccination, Infection and disease
A number of maternal diseases are known to cause congenital anomalies with the most common being syphilis and rubella. Rubella vaccination of women and girls occurs in most developed nations but is a more prevalent cause of

congenital anomalies in low- and middle-income countries. More recently, the effect of in utero exposure to Zika virus has been reported and has had devastating congenital defects, such as severe microcephaly, subcortical calcification, congenital contractures and hypertonia, and is now prevalent in a wide range of countries that host the mosquito carrier (4).

4. Environmental risks

While there can be a wide range of environmental dangers to the developing foetus, such as infections and disease prevalence, maternal exposure to certain pesticides, chemicals, and medications (including traditional herbal mixtures), alcohol, tobacco and radiation during pregnancy, increases the risk of congenital anomalies. Working or living near, or in, waste sites, smelters or mines may also be a risk factor (1). These risk factors are more common in low and middle income countries.

5. Genetic factors

These can be inherited conditions such as anophthalmos, microphthalmos, coloboma, congenital cataract, infantile glaucoma, and neuro-ophthalmic lesions as examples.

Complicating inherited genetic disorders are issues of consanguinity. This can be a primary cause where consanguinity increases the prevalence of rare genetic congenital anomalies and nearly doubles the risk for neonatal and childhood death, intellectual disability and other anomalies (5).

The high prevalence of consanguinity in some regional areas needs a thoughtful public health approach.

Prevention

Vaccination, appropriate diet, including adequate intake of folic acid or iodine through fortification of staple foods or supplementation, including the Vitamins groups discussed here, in addition to adequate prenatal care, are necessary prevention methods.

Doctors everywhere also need to be alert to viral outbreaks and higher incidence of anomalies in their patient populations, report such to health authorities and, ideally, investigate the causes (6).

Report on Australian Research

Australian researchers in a 12 year study, have recently published evidence that supplements of vitamin B-3 can prevent many miscarriages and congenital defects (7).

A team of researchers has identified a key factor behind some miscarriages and congenital malformations of the heart, spine, kidneys, and cleft palate.

The Australian study evaluated the cause of a number of abnormal embryonic developments to a deficiency in nicotinamide adenine dinucleotide (NAD), a molecule that plays a key role in metabolic regulation. NAD is involved in energy production and boosting cell survival, as well as supporting DNA repair. However, NAD production can be inhibited by some genetic factors, chronic diseases (such as diabetes), or an unhealthy diet, leading to NAD deficiency.

The study initially focused on families exhibiting a rare condition known by its acronym as "VACTERL." This condition refers to people born with at least three of the following anomalies: vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, or limb abnormalities.

The researchers found that a shortage of NAD in these families resulted in miscarriages or birth defects. They also concluded that NAD deficiency might therefore explain a wider range of miscarriage and congenital anomalies globally.

The research indicated that a relatively simple solution in preventing such disorders was ensuring required Vitamin B-3 intake. They found a key element in NAD synthesis is niacin, a vitamin B-3 complex available as a dietary supplement (7).

A sustained intake of B-3 complex supplements, the researchers suggest, can effectively prevent miscarriages and birth defects such as spina bifida and other vertebral segmentation malformations, as well as some heart and small kidney defects.

An earlier Australian study (8) found vitamin B-3 deficiencies in mothers already taking B-3 supplements. Appropriate intake of vitamin B-3 during the first trimester is a requirement for proper organ development in the developing foetus (8).

This may indicate that pregnant women require an even higher vitamin B-3 intake.

The Australian study evaluated the effect of niacin on developing embryos in a preclinical mouse model, and noted that, after the vitamin B-3 complex was appropriately introduced into the expecting mother's diet, miscarriages no longer occurred. Moreover, all the babies were born healthy, with no congenital malformations. They used genomic sequencing to identify potentially pathogenic gene variants in families in which a person had multiple congenital malformations and tested the function of the variant by using assays of in vitro enzyme activity and by quantifying metabolites in patient plasma. Variants were identified in two genes.

The researchers say that developing a test to measure levels of NAD in expecting mothers will come next. This will allow practitioners to identify which women risk miscarriage or delivering a baby with a congenital malformation, and who therefore need to take more B-3 supplements in pregnancy.

For the time being, expectant mothers should include Vitamin B-3 foods in their regular diet but only take B-3 supplements as advised by their doctors, as it is still unclear what exact doses of vitamin B-3 would help to prevent miscarriages and malformations in each case.

Overview of Niacin

The current required daily intake of Niacin (Vitamin B3) is 20mg (2).

Niacin or Vitamin B3 is an essential vitamin for human health that processes fat in the body, regulates blood sugar levels and lowers cholesterol levels. A deficiency of niacin causes symptoms of diarrhoea, dermatitis, dementia, inflammation of the mouth, amnesia, delirium, and if untreated, death. It is found in many foods (see Table 1).

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Table 1: Niacin containing foods

	Serving size	Niacin
Chicken	100 grams	7.8 milligrams
Bacon	100 grams	11 milligrams
Tuna	100 grams	5.8 milligrams
Mushrooms	100 grams	5 milligrams
Broccoli	100 grams	0.64 milligrams
Veal	100 grams	9.42 milligrams
Turkey	100 grams	11.75 milligrams
Organ meats	100 grams	Most are over 10 milligrams
Asparagus	100 grams	1 milligram
Peanuts	100 grams	12 milligrams
Coffee	1 cup	39.73 milligrams

Data Source: NHMRC (2).