Epidemiology of Neural Tube Defects

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Summary: Neural tube defects (NTDs)—malformations secondary to abnormal neural tube closure between the third and fourth weeks of gestational age—have a complex and imperfectly understood etiology in which both genetic and environmental factors appear to be involved. A number of specific chromosomal or single-gene disorders, presumably not affected by environmental influences, are associated with the development of NTDs, but such syndromal cases account for a small proportion of NTDs in live-born infants. Analysis of recurrence patterns within families and of twin-concordance data provides evidence of a genetic influence in nonsyndromal cases, but factors such as socioeconomic status and geographic area (independent of race or ethnicity) are also associated with variations in the incidence of NTDs. The prevalence at birth of both anencephaly and spina bifida has decreased, but the advent of antenatal diagnosis and elective termination of affected pregnancies has undermined the reliability of birth prevalence rate as an estimate of incidence. Some occupational and other exposures, including maternal use of antiepileptic drugs (AEDs), are associated with increased risk for NTDs. Among women who have had an NTD-affected pregnancy, recurrence risk is markedly higher than the risk for a first NTD-affected pregnancy in the general population. There is strong evidence, overall, for a protective effect of adequate folate consumption. In some high-risk groups, however, such as women taking AEDs, folate supplementation has not been proven to reduce NTD risk. Key Words: Neural tube defects—Anencephaly—Spina bifida—Folate.

Neural tube defects (NTDs) are malformations secondary to abnormal neural tube closure that occur between the third and fourth weeks of gestational age. They result in structural defects that occur anywhere along the neuroaxis from the developing brain to the sacrum and often result in the exposure of neural tissue.

CLASSIFICATION OF NTDs

Classically, NTDs have been divided into two main groups: (a) defects affecting cranial structures, such as anencephaly and encephalocele; and (b) defects involving spinal structures (spina bifida). Groupings based on these gross anatomic findings are readily differentiated even in the smallest of neonates. Of the two groups, the cranial malformations are the more clinically obvious and are often incompatible with life. Spina bifida, on the other hand, can range from a severe, obvious, open defect to one that is less easily recognized, making the characteristics of the defects in this group very variable and, ultimately, difficult to uniformly define.

The mechanisms of embryonic closure of the neural tube are discussed elsewhere in this supplement. Additional investigation into the embryonic mechanisms for normal and abnormal neural tube formation is clearly needed.

Newer classification schemes for the NTDs may not be exact, but attempts to group these malformations by more exact localizations within the neuroaxis rather than by gross anatomic characteristics have already proved useful clinically. In British Columbia, Hall et al. (1) found that the recurrence rate after index cases with upper NTDs (above T12) was significantly higher than that found in families with index cases with lower NTDs (T11 and below) (3.3% vs. 0.7%). The recurrence rate after an index case with a lower NTD was not statistically different from the baseline population risk (1). However, if NTDs were divided into groups based solely on gross anatomic criteria (anencephaly versus spina bifida), differences in their recurrence rates were obscured (2).

GENETIC INFLUENCES ON NTD OCCURRENCE

Chromosomal and genetic syndromes

On the whole, NTDs are currently considered to be a “complex” genetic disorder, meaning that both genetic and environmental factors can be shown to play a role in causation (3). While gene–environment interaction may be important for the occurrence of NTDs overall, there are several specific syndromes that are clearly associated...
with chromosomal or single-gene disorders (Table 1) (4). Presumably, these syndromal cases are not affected by external environmental influences and constitute an unmodifiable base NTD prevalence.

One of the primary problems, from an epidemiologic standpoint, is the absence of estimates of the proportion of all NTDs that these cases comprise. Despite the existence of a wide range of genetic syndromes associated with NTDs, the actual proportion of the total cases that these syndromes represent is probably quite small. If one considers the cases included in most epidemiologic studies—that is, live births and, at times, stillbirths—the impact of chromosomal syndromes is probably quite small. In studies of abortuses and fetuses with central nervous system (CNS) malformations or with NTDs, a high proportion (40–100%) demonstrated chromosomal abnormalities, but none of the cases from a series of live or stillborn infants demonstrated abnormalities (Table 2) (5–8). It seems likely that few of the chromosomally abnormal cases come to term. It should be emphasized here that while the syndromic cases of NTDs may have identifiable genetic causes, many of the nonsyndromal cases may also have an as-yet-unidentified primary genetic etiology.

**Table 1. Genetic syndromes associated with NTDs**

<table>
<thead>
<tr>
<th>Mode of inheritance</th>
<th>Number of reported syndromes associated with NTDs</th>
<th>Associated NTD type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal</td>
<td>26</td>
<td>Anencephaly, spina bifida, meningocele, encephalocele, craniorachischisis</td>
</tr>
<tr>
<td>Single-gene disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>7</td>
<td>Anencephaly, spina bifida, meningocele, myelomeningocele</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>20</td>
<td>Anencephaly, spina bifida, meningocele, encephalocele, myelomeningocele</td>
</tr>
<tr>
<td>Autosomal, not otherwise specifieda</td>
<td>2</td>
<td>Encephalocele</td>
</tr>
<tr>
<td>Sex-linked</td>
<td>5</td>
<td>Anencephaly, spina bifida, meningocele</td>
</tr>
</tbody>
</table>

*NTD, neural tube defect.*

*aThe exact inheritance patterns of a few of the more recently proposed disorders have yet to be identified (3, 4).*

### Evidence for genetic influence among nonsyndromal NTDs

The epidemiologic evidence supporting a genetic influence on the occurrence of nonsyndromal NTDs comes from two sources: the analysis of recurrence patterns within families and the analysis of concordance data in twins.

#### NTD recurrence within families

There are several factors specific to the analysis of NTDs (and other similar congenital defects) that hamper the analysis of familial cases. These include low parent-to-child transmission due to decreased reproductive abilities in affected cases, increased risk of spontaneous abortion in mothers who have had an NTD-affected pregnancy, high perinatal mortality, and the recent increase in the number of elective terminations of NTD-affected pregnancies. Despite these factors, a clear increase in NTD occurrence within families can be discerned (9–11). Several authors have published complex segregation analyses based on large data sets from different populations with no definitive conclusion.

Studies on large families with recurrent NTDs have reported an excess of affected family members on the maternal side compared with the paternal side. However, only one of these studies attempted to correct for the recognized difference between the completeness of maternal and paternal recall (12,13).

#### Concordance within twin pairs

In the NTD twin studies published to date, the zygosity of the twin pairs is unknown, making exact conclusions about concordance difficult. Instead, twin pairs are usually divided into groups based on whether the twins are like-sexed or unlike-sexed, and these categories are used as surrogate markers for zygosity. In their synthesis of pooled data, Elwood et al. (2) found that the difference in concordance rates between like-sexed and unlike-sexed twins was larger for spina bifida than for anencephaly, but the difference was statistically significant only for all NTDs combined (like-sexed, 7.7 vs. unlike-sexed, 4.0).

**Table 2. Survivorship of chromosomally anomalous fetuses with an NTD**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population studied</th>
<th>Number (% chromosomally abnormal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al., 1976 (5)</td>
<td>Stillborn and live-born infants with NTDs</td>
<td>0/17 (0%)</td>
</tr>
<tr>
<td>Creasy and Alberman, 1976 (6)</td>
<td>Spontaneous abortuses with CNS malformations</td>
<td>10/25 (40%)</td>
</tr>
<tr>
<td></td>
<td>Spontaneous abortuses without CNS malformations</td>
<td>71/544 (13%)</td>
</tr>
<tr>
<td>Byrne and Warburton, 1986 (7)</td>
<td>Spontaneous abortuses with NTDs</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>McFadden and Kalousek, 1989 (8)</td>
<td>Spontaneous aborted embryos with NTDs</td>
<td>26/33 (79%)</td>
</tr>
</tbody>
</table>

*NTD, neural tube defect; CNS, central nervous system.*
PREVALENCE OF NTDS

Measurement of NTD prevalence

Many congenital malformations, including NTDs, occur very early in embryonic development. This makes the calculation of incidence nearly impossible. Creasy and Alberman (6) performed a large study in London, a region with a fairly high NTD prevalence at birth. Based on the rates of NTDs found within a group of spontaneously aborted fetuses, they estimated that the prevalence of NTDs (anencephaly or spina bifida) at 8 weeks’ gestation (an estimate of true incidence) was 5.3 per 1,000 population. The concurrent prevalence of NTDs at birth was 2.8 per 1,000. A similar study of spontaneously aborted fetuses in Northern Ireland estimated the prevalence of NTDs at 8 weeks to be 10.8 per 1,000, compared with the birth prevalence of 7.1 per 1,000 (14).

With the advent of prenatal diagnosis, a substantial proportion of women carrying fetuses with NTDs now undergo therapeutic abortion. There are few studies, but the changes over time are impressive. In 1986, therapeutic abortion was performed in 25% of all identified cases of NTD; by 1999, that proportion had doubled (15).

Prevalence at birth is a more practical measure of the frequency of NTDs in any population. Birth prevalence can be estimated from a number of sources, such as birth registries and hospital records systems, but the best estimates are those that include information on both live births and stillbirths, although these data are more difficult to acquire.

Even if a reliable estimate of NTD prevalence is made, the extensive variation in prevalence by race, geographic area, and socioeconomic status, makes a single estimate meaningless. A further difficulty relates to the dramatic time trends in prevalence, which make it necessary to take into account the time period during which the study was done.

Time trends in NTD prevalence

Over time, the prevalence at birth of both anencephaly and spina bifida has decreased dramatically. However, calculations of prevalence at birth routinely include only data from live-born and stillborn babies and often exclude data from spontaneous or elective abortions. Before the mid 1970s, the rate of NTD prevalence at birth was a reliable estimate of actual disease incidence. While the prevalence may not include a rate of spontaneous loss of NTD-affected fetuses each year, the rate of fetal loss remained relatively stable from year to year. With the advent of antenatal diagnosis and elective termination, however, the prevalence of NTDs at birth is no longer as reliable an estimate of incidence. Recent secular trend analysis is now dependent on data collection that includes all sources of NTD occurrence: live births, stillbirths, miscarriages, and elective abortions. The specific impact of antenatal diagnosis and elective termination on prevalence varies by country. Studies from Ireland are theoretically free from the impact of therapeutic abortion. Even in areas with higher proportions of NTD-affected pregnancy undergoing abortion, such as the United States and the U.K., data on birth prevalence over the past century show similar trends for the two areas. It should be pointed out that the changes in trends antedated prenatal diagnostic procedures, so this is not the only explanation of altered frequency.

Between 1936 and the early 1960s, the birth prevalence rates of both anencephaly and spina bifida in Great Britain peaked twice (Fig. 1) (2,16–19). The first peak occurred around 1940 and the second peak in the mid to late 1950s. Since the early 1970s, the prevalence at birth of both anencephaly and spina bifida has been declining.

The trends in NTD occurrence in Scotland are similar to those seen in England and Wales: a peak in anencephaly rates occurred in the early 1940s, and a second, broad peak occurred in the late 1950s and early 1960s (Fig. 2) (2,20–22). Since the early 1970s, the prevalence at birth of both anencephaly and spina bifida has been declining.

There appears to be only one major peak in the occurrence of NTDs in Dublin, Ireland, between 1900 and the early 1980s: a broad peak that reached its maximum around 1960 (Fig. 3) (23,24). Subsequently, similar to the trends seen in England, Wales, and Scotland, the birth prevalence of NTDs in Dublin has also largely been declining.

The trends in NTD occurrence in North America are similar to those seen in Dublin, with one broad peak in the first half of the 20th century, although the timing of the peak was different (Fig. 4) (19,25,26). In Boston, Massachusetts, and in Providence, Rhode Island, peak rates of NTDs were recorded around 1930. Since then, the prevalence at birth of both anencephaly and spina bifida has been declining.

Variation by geographical area

There is geographical variation in prevalence that cannot be explained by regional differences in data collection or analytic methodology. Although ascertainment of NTD cases is limited in many countries, there are several areas for which a clear regional difference in NTD prevalence has been documented and sustained over time.

In the British Isles, a clear geographic gradient in NTD prevalence has been reported, with higher rates of NTDs at birth in the northwest and lower rates in the southeast. This gradient is seen only for NTDs and not for other congenital malformations. Within continental Europe, no clear geographic gradient has been reported, although, as a whole, rates of both anencephaly and spina bifida are higher in the British Isles than on the Continent. In Canada, consistently higher prevalence rates of NTDs have been reported in the eastern part of the country compared with the western portion.
In China, a higher prevalence of NTDs is seen in provinces north of the Yangtze River, especially near the Taihang Mountains. Rates in these northern provinces may be as much as six times those in southern provinces. Similar pockets of increased prevalence have been reported in India that do not clearly fit any geographic or ethnic gradient (2).

**Migration studies**

When populations with high risk migrate away from the British Isles, they do not keep their high risk for NTDs, suggesting that other factors besides ethnicity are at work. When ethnic groups with low NTD prevalence (e.g., Africans or Asians) migrate, they tend to maintain their low rates, as a group, even if they have migrated to a region with higher regional prevalence.

**Race/ethnicity**

The possibility of variation in NTD prevalence by ethnicity was first raised as an attempt to explain the geographic variation seen within the British Isles. It was postulated that populations of Irish, Scottish, or Welsh descent might have intrinsically higher risks for NTDs, thus explaining the increased prevalence of NTDs seen in regions densely populated with these people. In the United States, it is clear that Hispanics have a higher risk for NTDs than other ethnic groups, whereas the risk among African Americans is low. The Hispanic excess persists after control for other NTD risk factors such as diabetes and obesity (27,28).

**MATERNAL FACTORS AFFECTING NTD PREVALENCE**

**Age**

The effect of maternal age on risk of NTDs is generally considered to be small. When an association with age can be found, risk tends to be elevated in older or very young mothers.
Parity
The effect of maternal parity on NTD risk is probably stronger than that of maternal age. Studies have shown both a “modest risk in mothers of parity three or more” and an increased risk in primiparous mothers (2). Mills et al. (29) found no association between the risk of an NTD-affected pregnancy and markers of maternal fertility or use of various treatments for infertility. No clear biological explanation has been found for these associations.

Previous pregnancy wastage
An association between NTDs and previous spontaneous abortions has been noted in several studies (27). In the California birth defects registry, NTDs were more likely to follow previous completed term pregnancies and short intervals between pregnancies (30).

Multiple gestation
The relationship between NTDs and multiple gestations is complex and has not yet been completely elucidated. There is some evidence to suggest that the process of twinning itself may be associated with a higher risk for NTDs (31,32). More recent evidence linking twinning and the occurrence of NTDs has also been published, although the degree of association found between the two entities varies by NTD type and, in multicenter studies, by center (33,34).

In a synthesis of pooled data, Elwood et al. (2) found that the prevalence of anencephaly in twins at birth was 0.99 per 1,000, significantly higher than the birth prevalence of anencephaly in singletons (0.86 per 1,000) (RR = 1.16; 95% CI, 1.02–1.3). The birth prevalence of spina bifida in twins was slightly lower, but not significantly so, than prevalence at birth of spina bifida in singletons (RR = 0.97).

Obesity
Maternal obesity and elevated body mass index have been consistently associated with an increased risk for NTDs. Body mass index >29 doubles the risk (35–37).

Maternal Illness
Maternal diabetes has long been considered a risk factor for NTDs, although the association has seldom been tested in multivariable analysis. In one study, after control for other potential confounding factors, the risk associated with diabetes was not significantly elevated (27). However, hyperinsulinemia has been found to be a significant risk factor in Hispanic women in Texas (37).

A “flu” or “cold” syndrome or a febrile illness in the first trimester has been associated with a two- to threefold increase in risk for NTDs (38–40). Heat exposure in general has been associated with an increased risk for NTDs (41). Hot-tub use in the first trimester was associated with a threefold increase in risk, and any combination of hot-tub use, febrile illness, or sauna use was associated with a sixfold increase in risk.

Parental socioeconomic status
Higher rates of NTDs have been reported in populations with lower socioeconomic status. This has been true in Europe, North America, and several other regions. A small amount of intriguing evidence suggests that a mother’s social stratum as a child is also inversely correlated with her risk of having an NTD-affected pregnancy, although this relationship may be true only in populations with high baseline risk.

Parental occupational exposures
Studies of parental occupation and the occurrence of NTDs (42–46) found increased odds ratios associated with both paternal and maternal occupations, including welding, transport, painting (paternal), cleaning, healthcare occupations (nursing, dentistry), and agriculture.

Dietary factors and other exposures
A number of factors have been examined as possible risk factors for NTDs. Smoking has consistently been protective. Alcohol and recreational drugs do not alter risk (36,47). Tea use in the period before and during the first trimester is associated with a twofold increase in risk (48). Other caffeine products do not alter risk. Excess vitamin A is a risk factor. Zinc deficiency, lead, and high levels of organic matter in drinking water have all been associated with higher NTD occurrence, but not consistently (49–52). Some drugs (including antiseizure medications) are associated with increased risk for NTDs. The relation between drug exposures, specifically antiseizure medications, and NTDs is discussed extensively elsewhere in this supplement and will not be elaborated on further here.

RECURRENT OF NTDS

Once a mother has had a child with an NTD, the recurrence risks are markedly higher than reported population risks of a first NTD-affected pregnancy from the same countries during the same time period. The recurrence risk may increase after each affected pregnancy. The risk of having a third NTD-affected pregnancy after already having two has been estimated (from pooled data from the British Isles, continental Europe, North America, and Australia) to be 11.1% (95% CI, 8.5–13.6), almost tripling the recurrence risk after only one affected pregnancy in that population (4%; 95% CI, 3.7–4.3) (2). The risk of having a fourth NTD-affected pregnancy after already having had three is estimated to be 28.6% (2). In other words, with each subsequent NTD-affected pregnancy after the first, the risk of a subsequent NTD-affected pregnancy nearly triples.

PREVENTION OF NTDS: THE FOLATE STORY

Many different lines of evidence suggest the protective effect of folate consumption, including descriptive epidemiology, case-control studies, cohort studies, and
### TABLE 3. Folate studies—summary

<table>
<thead>
<tr>
<th>Study reference, location</th>
<th>Characteristic/intervention assessed</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Case-control studies</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>A. Occurrent NTDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hibbard and Smithells, 1965 (53), Liverpool</td>
<td>Postnatal serum folate levels</td>
<td>Folate deficiency: 69% of case mothers, 17% of matched controls</td>
<td></td>
</tr>
<tr>
<td>Emery et al., 1969 (54), South Africa</td>
<td>Postnatal serum folate levels</td>
<td>No differences between case and control mothers</td>
<td>Low numbers</td>
</tr>
<tr>
<td>Bower and Stanley, 1989 (55), Western Australia</td>
<td>Postnatal serum and RBC folate levels, dietary folate and supplement use</td>
<td>Statistically significant reduction in NTD occurrence with increased dietary intake of free folate and total folate</td>
<td>Protective effects also seen with intakes of fiber, calcium, vitamin C, and carotene</td>
</tr>
<tr>
<td>Molloy et al., 1985 (56), Dublin</td>
<td>Prenatal serum folate and vitamin B12 levels</td>
<td>No difference in median values or frequency distributions of either serum folate or vitamin B12 levels between cases and controls</td>
<td></td>
</tr>
<tr>
<td><strong>B. Active supplementation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winship et al., 1984 (57), England and Wales</td>
<td>Use of various supplements</td>
<td>No statistically significant associations between drug use and NTD occurrence</td>
<td>Specifically analyzed multivitamin, folate-containing agents</td>
</tr>
<tr>
<td>Mulinare et al., 1988 (58), Atlanta</td>
<td>Multivitamin use</td>
<td>Specific, periconceptional use (3 months before and 3 months after) of a multivitamin supplement was associated with a crude estimated relative risk of 0.40 (0.25–0.63) for occurrence of an NTD</td>
<td>“At this time, it is not possible to determine whether this apparently lower risk is the direct result of multivitamin use or the result of other characteristics of women who use multivitamins.”</td>
</tr>
<tr>
<td>Mills et al., 1989 (59), California and Illinois</td>
<td>Use of various supplements</td>
<td>OR (multivitamin use): Grp I: 0.95 (0.78–1.14) Grp II: 1.0 (0.83–1.20) OR (receiving RDA of folate): Grp I: 0.97 (0.79–1.18) Grp II: 0.98 (0.80–1.20)</td>
<td>No difference between NTD mothers and other groups in rates of multivitamin usage or in odds of having an NTD-affected pregnancy</td>
</tr>
<tr>
<td>Bower and Stanley, 1992 (60), Western Australia</td>
<td>Multivitamin use</td>
<td>OR (MVI 3 months preconception): Grp I: 0.69 (0.06–8.53) Grp II: 0.11 (0.01–1.33) OR (MVI during first 6 weeks): Grp I: 0.70 (0.32–1.52) Grp II: 0.74 (0.29–1.88)</td>
<td>Lower baseline prevalence in California and Illinois compared with other areas that have found positive results</td>
</tr>
<tr>
<td>Werler et al., 1993 (61), North America</td>
<td>Multivitamin and folate supplementation use</td>
<td>RR of multivitamin with folate use = 0.4 (95% CI 0.2–0.6) RR of folate supplementation use (0.4 mg most common dose) = 0.3 (95% CI 0.1–0.6)</td>
<td>Dose–response relationship present for level of dietary folate intake</td>
</tr>
<tr>
<td>Shaw et al., 1995 (62), Shaw et al., 1999 (51), California birth defects monitoring program</td>
<td>Multivitamin or folate use in the 3 months before or the 3 months after conception, and usual diet in the 3 months before conception</td>
<td>Any level of use of any folate-containing vitamin in the 3 months before conception had lower risk of an NTD-affected pregnancy (OR = 0.65, 0.45–0.94) Any level of use in the first 3 months after conception also lowered risk (OR = 0.60, 0.46–0.79)</td>
<td>Dose–response relationship with combined dietary/supplemented folate amount Reduction in risk less for Hispanic women Reduction in risk absent for college graduates</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 3. Continued

<table>
<thead>
<tr>
<th>Study reference, location</th>
<th>Characteristic/intervention assessed</th>
<th>Results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>B. Recurrent NTDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schorah et al., 1983 (63), Leeds</td>
<td>Postnatal levels of multiple vitamins</td>
<td>More women who had had an NTD-affected pregnancy had low RBC folate and WBC vitamin C levels during a subsequent pregnancy</td>
<td></td>
</tr>
<tr>
<td>Yates et al., 1987 (64), Scotland</td>
<td>Postnatal levels of multiple vitamins</td>
<td>RBC folate levels 33% lower in mothers who had had two or more NTD-affected pregnancies vs. controls</td>
<td>RBC folate was the only nutrient level to show a significant difference</td>
</tr>
</tbody>
</table>

II. Cohort studies

A. Occurrent NTDs

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Characteristic/intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milunsky et al., 1989 (65), Massachusetts</td>
<td>Vitamin and/or folate supplementation</td>
<td>Protective effect found for multivitamins with folate during the first 6 weeks of pregnancy compared with women who had never used MVIs – RR 0.27 (0.12–0.59)</td>
</tr>
<tr>
<td>Laurence et al., 1981 (69), Laurence et al., 1983 (70), South Wales</td>
<td>Folate supplementation (4 mg)</td>
<td>No recurrences in group of compliant mothers</td>
</tr>
</tbody>
</table>

B. Recurrent NTDs

III. Nonrandomized interventional studies

A. Occurrent NTDs

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Characteristic/intervention</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Smithells et al., 1980 (66), Smithells et al., 1981 (67), Smithells et al., 1983 (68), U.K. multicenter</td>
<td>Level of PNV supplementation</td>
<td>First report (1980): RR of 0.12 in mothers who were fully supplemented, compared with unsupplemented mothers</td>
</tr>
<tr>
<td>Laurence et al., 1981 (69), Laurence et al., 1983 (70), South Wales</td>
<td>Folate supplementation (4 mg)</td>
<td>No recurrences in group of compliant mothers</td>
</tr>
</tbody>
</table>

B. Recurrent NTDs

Smithells et al., 1980 (66), Smithells et al., 1981 (67), Smithells et al., 1983 (68), U.K. multicenter

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<tr>
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IV. Randomized interventional studies

A. Occurrent NTDs

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Characteristic/intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czeizel and Dudas, 1992 (73), Czeizel et al., 1994 (74), Hungary</td>
<td>Two supplementation regimes: (a) one multivitamin with 0.8 mg of folate, or (b) trace-element supplement Folate 0.4 mg</td>
<td>Fewer NTDs in vitamin supplemented group (0 vs. 6); difference statistically significant</td>
</tr>
<tr>
<td>Berry et al., 1999 (71), Berry and Li 2002 (72), China</td>
<td>Four supplementation regimes: (a) folic acid and minerals; (b) folic acid, other vitamins and minerals; (c) minerals only; and (d) other vitamins and minerals Folate dose: 4 mg</td>
<td>RR of folate supplementation = 0.28 (95% CI 0.12–0.71)</td>
</tr>
</tbody>
</table>

B. Recurrent NTDs

MRC trial, 1991 (75), multicountry, multicenter study

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<thead>
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<tbody>
<tr>
<td>Czeizel and Dudas, 1992 (73), Czeizel et al., 1994 (74), Hungary</td>
<td>Two supplementation regimes: (a) one multivitamin with 0.8 mg of folate, or (b) trace-element supplement Folate 0.4 mg</td>
<td>Fewer NTDs in vitamin supplemented group (0 vs. 6); difference statistically significant</td>
</tr>
<tr>
<td>Berry et al., 1999 (71), Berry and Li 2002 (72), China</td>
<td>Four supplementation regimes: (a) folic acid and minerals; (b) folic acid, other vitamins and minerals; (c) minerals only; and (d) other vitamins and minerals Folate dose: 4 mg</td>
<td>RR of folate supplementation = 0.28 (95% CI 0.12–0.71)</td>
</tr>
</tbody>
</table>

NTD, neural tube defect; RBC, red blood cell; MCAs, major congenital abnormalities; Grp, group; OR, odds ratio; RDA, recommended daily allowance; MVI, multivitamin; RR, relative risk! WBC, white blood cell; PNV, prenatal vitamin.
randomized and nonrandomized intervention studies (Table 3) (51, 53–75). While a majority of studies have shown a protective effect of folate supplementation, some have failed to demonstrate an effect. Only one definitive study of folate and vitamin supplementation in NTD occurrence has been published to date. This was a randomized trial done in Hungary (73,74). In this study, women were randomized to take either a multivitamin with 0.8 mg of folate preconceptionally or a basic mineral supplement. The prevalence of all malformations was reduced by half in the folate and vitamin group when compared with those receiving mineral supplementation. There were no NTDs in the vitamin- and folate-supplemented group.

In a randomized trial of prevention of recurrent NTDs, folate reduced the risk by 75%, whereas multivitamins alone were associated with a 20% reduction in recurrence (75). A recent study in China in which women were randomized to a group allowed to purchase folate preconceptionally demonstrated, in high-risk areas, a reduction in NTD occurrence (compared with a presumably nonsupplemented group) with less dramatic effects in lower-risk areas (71). Although educational or socioeconomic factors may bias the results in the Chinese study, the evidence for a protective role of folate is strong.

**HOW TO MAKE SURE WOMEN RECEIVE SUFFICIENT FOLATE**

Educational interventions

Educational programs were the first intervention to be initiated in both the United States and Canada, and this is the intervention currently being used in most other countries. In follow-up studies, folate use has been shown to increase among educated women and women of higher socioeconomic status but not necessarily among higher-risk groups as a result of these interventions (76). In Canada, a recent study showed no evidence of a reduction of NTDs during the period when educational programs were being carried out (15).

Folate fortification

An attempt to increase the daily folate intake for all women of childbearing age through supplementation in the food chain has been mandated in both the United States and Canada. Since 1998, folate supplementation in fortified cereal grains has been required. The objective has been to obtain an average daily dose of 0.4 mg of folate. While folate levels in women of childbearing age have increased overall, the increase has been less dramatic among high-risk groups, such as those with low socioeconomic status and Mexican Americans (77–80). On a population level, data from the United States have demonstrated a 31% reduction in spina bifida and a 16% reduction in anencephaly between January 1998 and December 1999 when compared with the birth prevalence from January 1995 through December 1996 (81). However, for the most part, the U.S. data are not adjusted for prenatal diagnosis and early pregnancy termination. More complete data are available from two Canadian studies in which data for elective pregnancy terminations, stillbirths, and live births were all included. The first study reported an increase in NTD prevalence in the period during which educational campaigns were being implemented (which the authors attributed to increased screening) and a 50% reduction in the prevalence of NTDs after the institution of folate supplementation (15). In a similar study in Nova Scotia, Canada, a > 50% reduction in NTD prevalence was observed (82).

There is evidence for lack of efficacy of folate supplementation in increasing folate levels and reducing NTD risk among some high-risk groups, such as obese women and Hispanic women (65,77,79). There is no evidence that folate supplementation influences the frequency of NTDs in other high-risk groups, such as women with epilepsy taking antiseizure medication. In fact, there are case reports of NTDs despite adequate supplementation (see the article by Mark Yerby in this supplement, pages 33–40).

**CONCLUSIONS**

The epidemiology of NTDs is complex. They remain among the most frequent and the most devastating congenital abnormalities. There are many clues to their etiology, and there is some evidence for a preventive intervention, folate supplementation, that may be effective for some individuals at risk. Many of the data are as yet unexplained, such as the dramatic temporal trends observed worldwide, the dramatic difference in birth prevalence in people of presumed similar genetic backgrounds (as is seen in China), and the effects of migration. The heterogeneity of the protective effect of folate needs exploration.

**REFERENCES**


