NEURAL TUBE DEFECTS

Introduction

Neural tube defects (NTDs) have their origin very early in pregnancy. A localised thickening of embryonic cells known as the neural plate is observable approximately 18 days after conception. This elongates and develops a central groove and then the edges of the groove fold to produce the neural tube. The neural tube closes at around day 25 at the cranial end and at around day 27 at the sacral end [1]. The walls of the neural tube thicken to produce the brain and spinal cord. The closed neural tube stimulates the development of the bony structures of the vertebral column and skull. Neural tube defects are the malformations that occur when the neural tube fails to close and the bone fails to form above an unclosed region of the neural tube [2]. Defects may occur anywhere along the neural axis. Cranial defects include anencephaly (a lethal defect) and the rarer conditions encephalocele. Defects elsewhere in the neural tube result in spina bifida.

Spina bifida occulta is a common and often asymptomatic anomaly in which there is a midline defect in the vertebral bodies without protrusion of the spinal cord or meninges. When the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum a meningomyelocele is formed. These defects are mostly well covered with skin. They require surgical correction but the spinal cord is usually normal and the prognosis is good [3]. The most severe form of neural tube defect is myelomeningocele where there is protrusion of central nervous system tissue through the defect in the vertebral column. This condition most commonly occurs in the lumbosacral region (75% of cases) where it is associated motor and sensory disabilities in the lower limbs and bowel and bladder dysfunction [4]. Surgery in the newborn period allows most children with myelomeningocele to survive and most survivors have normal intelligence (>70%). Many can walk with assistive devices when they are young but ambulation becomes more difficult with age and increasing body mass. The most life-threatening aspect of the condition long term is renal dysfunction as a result of a neurogenic bladder [3].

Since the publication of the results of the MRC international multicentre randomised controlled trial of periconceptional folic acid supplementation in 1991 [5] it has been accepted that folic acid supplementation can prevent up to two thirds of NTDs [1]. In many countries, including the U.S., Canada and Australia, there is mandatory fortification of staple foods (flours) with folic acid [6]. In New Zealand voluntary fortification of certain foods (cereal products, bread and fruit juice) with folic acid is permitted and folic acid supplementation for women planning a pregnancy is recommended. The Ministry of Health recommends that women at low risk of having a child with an NTD take 800µg of folic acid daily for at least four weeks prior to conception and for 12 weeks after. High risk women, including those who have previously had a pregnancy affected by a NTD, those who have a family history of NTD in their own or their partner's family, those with insulin dependent diabetes and those taking medications known to affect folate metabolism (including the anti-epileptic drugs valproate and carbamazepine) are recommended to take 5mg of folic acid daily over the same period. Subsidised 800 µg and 5mg folic acid tablets are available over the counter from pharmacies [7,8].

The following section uses the National Minimum Dataset to review the number of babies born with neural tube defects. The section concludes with a brief review of policy documents and evidence-based reviews which are relevant to their prevention.

Data Source and Methods

Definition

1. Number of central nervous system anomalies identified at birth (by anomaly type)

2. Number of babies with neural tube defects (NTD) identified at birth

Data Source

1. National Minimum Dataset

Numerator: Hospital admissions with event type = birth and a nervous system anomaly (ICD-10 Q00–07) listed in any of the first 15 diagnoses.

For this indicator, the unit of analysis is the number of nervous system anomalies rather than the numbers of babies, as some babies have more than one anomaly. Specific anomalies include: Anencephaly (Q00), Encephalocele (Q01), Microcephaly (Q02), Congenital Hydrocephalus (Q03), Other Brain Malformations (Q04), Spina Bifida (Q05), Other Spinal Cord Malformations (Q06), Other CNS Malformations (Q07).

2. National Minimum Dataset

Numerator: Hospital admissions with event type = birth and a neural tube defect listed in any of the first 15 diagnoses.

For this indicator, the unit of analysis is the number of babies with one or more NTDs rather than the numbers of NTDs. Specific NTDs include: Anencephaly (Q00), Encephalocele (Q01), and Spina Bifida (Q05).

Denominator: All Hospital Admissions with event type = birth.

Notes on Interpretation

Note: This analysis includes all admissions recorded in the National Minimum Dataset (NMDS) where the Event Type was listed as Birth. In the NMDS only one birth event is allowed per NHI number, with admissions for babies born prior to hospital admission, or readmitted shortly after discharge being listed as a routine inpatient event. Thus the analysis does not include babies born prior to hospital admission, babies born at home, or babies whose NTD was overlooked at the time of discharge, but who re-presented shortly thereafter.

New Zealand Distribution and Trends

New Zealand Distribution

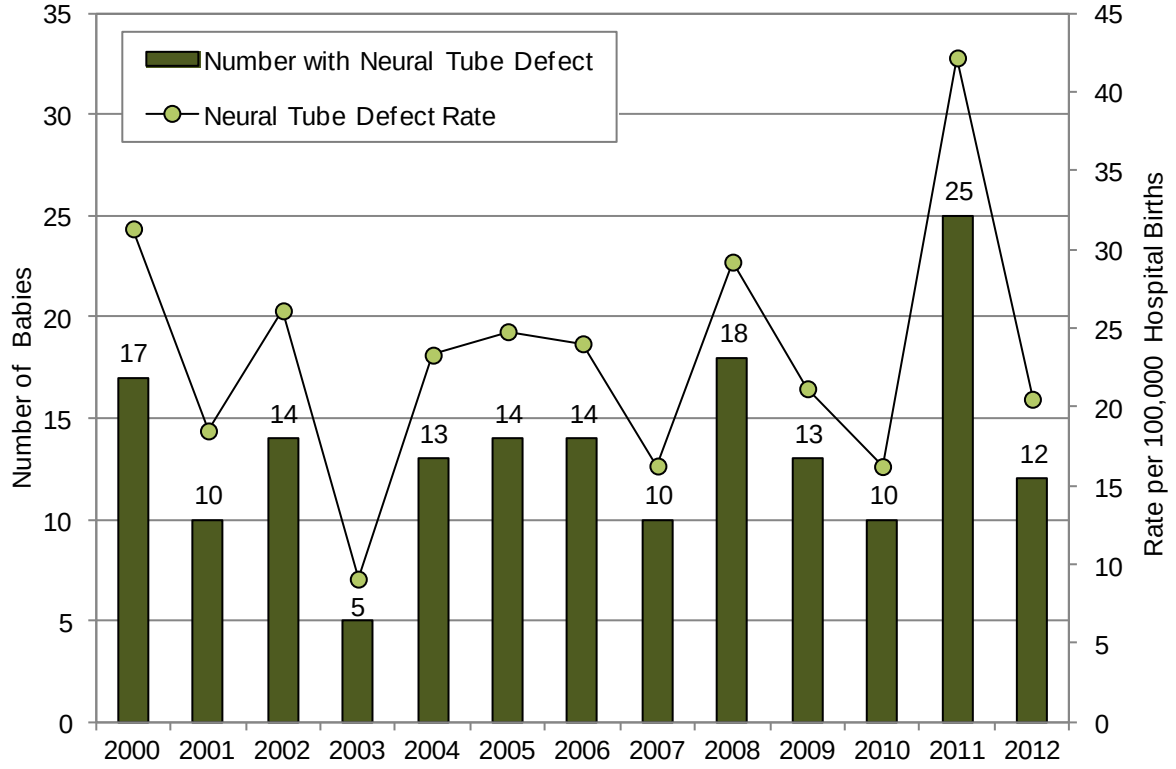
In New Zealand during 2008–2012, 79 neural tube defects (NTDs) were identified at the time of birth (anencephaly (n=13), encephalocele (n=13), spina bifida (n=53)), with on average 16 NTDs being identified per year. NTDs accounted for 17.8% of all nervous system anomalies identified during this period. Note: The unit of analysis is the number of NTDs, rather than the number of babies with one or more NTD (**Table 1**).

Table 1. Nervous System Anomalies Evident at Birth, New Zealand 2008–2012

Nervous System Anomaly	Number: Total 2008−2012	Number: Annual Average	Anomalies per 100,000 Births*
New Zealand			
Anencephaly (NTD)	13	2.6	4.30
Encephalocele (NTD)	13	2.6	4.30
Microcephaly	61	12.2	20.18
Congenital Hydrocephalus	77	15.4	25.47
Other Brain Malformations	190	38.0	62.85
Spina Bifida (NTD)	53	10.6	17.53
Other Spinal Cord Malformations	14	2.8	4.63
Other CNS Malformations	24	4.8	7.94
Total Malformations of the Nervous System	445	89.0	147.20

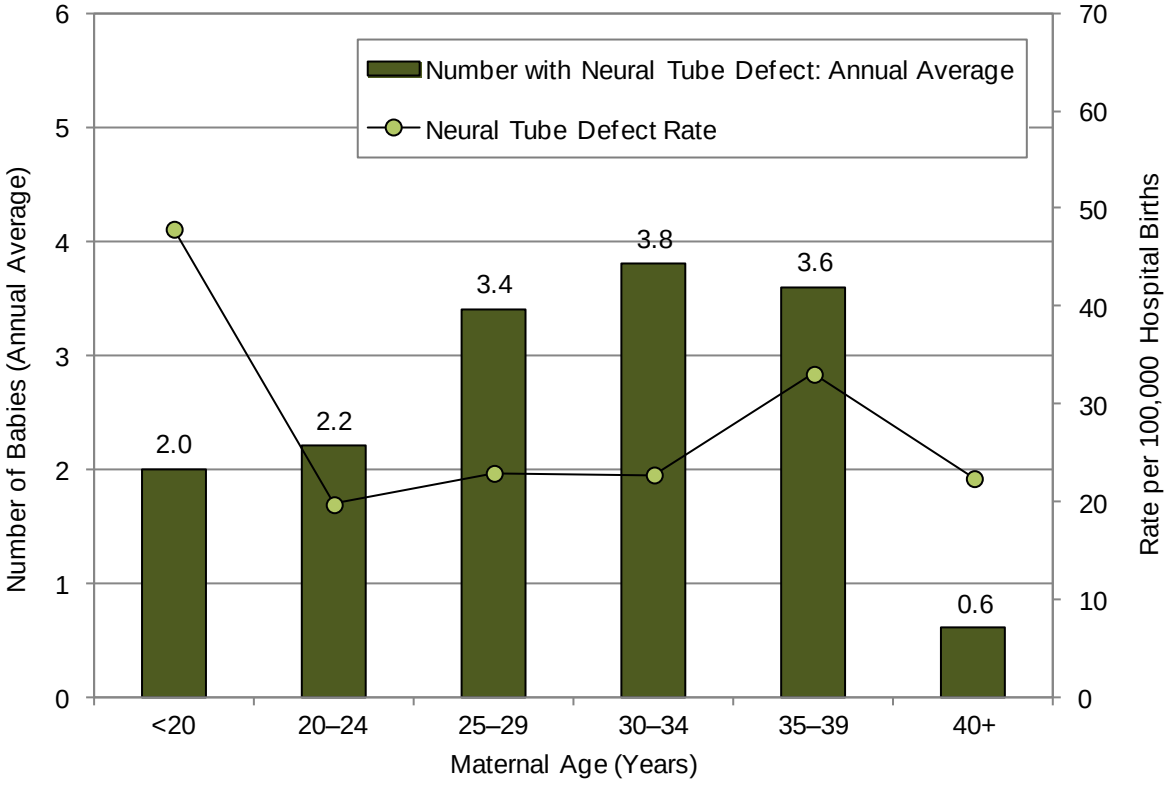
Source: National Minimum Dataset: Numerator: Hospitalisations with event type = birth and a nervous system anomaly in any of first 15 diagnoses; Denominator: Hospitalisations with event type = birth; Note: *Anomalies per 100,000 births = number of anomalies rather than number of babies, as some babies have more than one anomaly; NTD denotes neural tube defect

Figure 1. Babies with Neural Tube Defects Evident at Birth, New Zealand Hospital Births 2000–2012



Source: National Minimum Dataset: Numerator: Hospitalisations with event type = birth and a neural tube defect listed in any of first 15 diagnoses; Denominator: All hospitalisations with event type = birth; Note: Rate per 100,000 refers to number of babies with one or more neural tube defects

Figure 2. Babies with Neural Tube Defects Evident at Birth by Maternal Age, New Zealand Hospital Births 2008–2012



Source: National Minimum Dataset: Numerator: Hospitalisations with event type = birth and a neural tube defect listed in any of first 15 diagnoses; Denominator: All hospitalisations with event type = birth; Note: Rate per 100,000 refers to number of babies with one or more neural tube defects

New Zealand Trends

In New Zealand during 2000–2012, on average 13.5 babies per year had one or more neural tube defects identified at the time of birth. Large year to year variations (possibly as a result of small numbers) made trends in NTD rates difficult to interpret (**Figure 1**).

Distribution by Maternal Age

In New Zealand during 2008–2012, the babies of teenage mothers had the highest neural tube defect rates, although in most cases differences between the babies of teenage and older mothers did not reach statistical significance. In contrast, mothers aged 30–34 years had the largest actual number of babies born with a NTD (as a result of the higher number of overall births in this age group (**Figure 2**, **Table 2**)).

Distribution by Prioritised Ethnicity, NZDep Index Decile and Gender

In New Zealand during 2008–2012, there were no *significant* ethnic, socioeconomic (as measured by NZDep06 quintile) or gender differences in the proportion of babies born with a neural tube defect. The highest rates however, were seen amongst Pacific babies, the babies of teenage mothers, and those born into the most deprived (NZDep06 deciles 9–10) areas (**Table 2**).

Table 2. Babies with Neural Tube Defects Evident at Birth by Ethnicity, NZ Deprivation Index Decile, Gender and Maternal Age, New Zealand Hospital Births 2008–2012

Variable	Number of Babies: Annual Average	Rate per 100,000 Births	Rate Ratio	95% CI
Neural Tube Defects				
Prioritised Ethnicity				
Māori	4.2	31.48	1.45	0.85–2.48
Pacific	2.4	35.40	1.63	0.85–3.13
European/Other	7.2	21.71	1.00	
Asian/Indian	1.6	23.39	1.08	0.50–2.32
NZ Deprivation Index				
Deciles 1–2	2.0	23.57	1.00	
Deciles 3–4	2.0	22.18	0.94	0.39–2.26
Deciles 5–6	3.2	28.41	1.21	0.55–2.66
Deciles 7–8	2.8	19.85	0.84	0.37–1.90
Deciles 9–10	5.4	30.83	1.31	0.63–2.70
Gender				
Female	7.0	23.81	1.00	
Male	8.6	27.68	1.16	0.74–1.82
Maternal Age				
<20 Years	2.0	47.91	1.00	
20–24 Years	2.2	19.70	0.41	0.17–0.97
25–29 Years	3.4	22.91	0.48	0.22–1.04
30–34 Years	3.8	22.74	0.47	0.22–1.02
35–39 Years	3.6	33.05	0.69	0.32–1.49
40+ Years	0.6	22.37	0.47	0.13–1.70

Source: National Minimum Dataset: Numerator: Hospitalisations with event type = birth and a neural tube defect listed in any of first 15 diagnoses; Denominator: All hospitalisations with event type = birth; Note: Rate Ratios are unadjusted; Rate per 100,000 refers to number of babies with one or more neural tube defects

South Island DHBs Distribution

South Island DHBs Distribution

In the South Island DHBs (combined) during 2008–2012, 5 cases of spina bifida and 4 of anencephaly/encephalocele were identified at the time of birth, with these accounting for 8.9% of all nervous system anomalies during this period (**Table 4**). The proportion of babies with one or more NTDs identified at birth in Canterbury was not *significantly* different form the New Zealand rate, although in the remaining DHBs numbers were too small to make any meaningful comparisons with the New Zealand rate (**Table 3**).

Table 3. Babies with Neural Tube Defects Evident at Birth, South Island DHBs vs. New Zealand Hospital Births 2008–2012

DHB/Area	Number: Total 2008−2012	Number: Annual Average	Rate per 100,000	Rate Ratio	95% CI
Neural Tube Defects					
Nelson Marlborough	<3	s	s	s	s
South Canterbury	<3	s	s	s	s
Canterbury	4	0.8	13.18	0.51	0.19–1.40
West Coast	<3	s	s	s	s
Otago	<3	s	s	s	s
Southland	<3	s	s	s	s
New Zealand	78	15.6	25.80	1.00	

Source: National Minimum Dataset: Numerator: Hospitalisations with event type = birth and a neural tube defect listed in any of first 15 diagnoses; Denominator: All hospitalisations with event type = birth; Note: Rate per 100,000 refers to number of babies with one or more neural tube defects; Rate Ratios are compared to New Zealand rates and have not been adjusted for population demographics; s: suppressed due to small numbers

Table 4. Nervous System Anomalies Evident at Birth, South Island DHBs Hospital Births 2008–2012

Nervous System Anomaly	Number: Total 2008−2012	Number: Annual Average	Number of Anomalies per 100,000 Births*
Nelson Marlborough			
Brain Malformations	6	1.2	76.48
Spina Bifida (NTD) and Other CNS Malformations	<3	s	s
Total Malformations of the Nervous System	8	1.6	101.98
South Canterbury			
Microcephaly	<3	s	s
Congenital Hydrocephalus	<3	s	s
Other Brain Malformations	4	0.8	128.74
Spina Bifida (NTD)	<3	s	s
Other CNS Malformations	<3	s	s
Total Malformations of the Nervous System	11	2.2	354.04
Canterbury			
Anencephaly (NTD)	3	0.6	9.89
Microcephaly	6	1.2	19.77
Congenital Hydrocephalus	15	3.0	49.43
Other Brain Malformations	34	6.8	112.05
Spina Bifida (NTD)	<3	s	s
Other CNS Malformations	<3	s	s
Total Malformations of the Nervous System	61	12.2	201.03
West Coast			
Congenital Hydrocephalus	<3	s	s
Other Brain Malformations	<3	s	s
Spina Bifida (NTD)	<3	s	s
Total Malformations of the Nervous System	4	0.8	217.40
Otago			
Microcephaly	<3	s	s
Congenital Hydrocephalus	<3	s	s
Other Brain Malformations	3	0.6	31.31
Spina Bifida (NTD)	<3	s	s
Total Malformations of the Nervous System	7	1.4	73.06
Southland			
Encephalocele (NTD)	<3	s	s
Congenital Hydrocephalus	5	1.0	65.37
Other Brain Malformations	3	0.6	39.22
Spinal Cord Malformations	<3	s	s
Total Malformations of the Nervous System	10	2.0	130.73

Source: National Minimum Dataset: Numerator: Hospitalisations with event type = birth and a nervous system anomaly in any of first 15 diagnoses; Denominator: Hospitalisations with event type = birth; Note: *Anomalies per 100,000 births = number of anomalies rather than number of babies, as some babies have more than one anomaly; s: suppressed due to small numbers

Local Policy Documents and Evidence-Based Reviews Relevant to Neural Tube Defects

In New Zealand there are a number of policy documents relevant to the prevention or diagnosis of neural tube defects. These are summarized in **Table 5**, along with a range of reviews which consider these issues in the overseas context. In addition, **Table 16** (Local Policy Documents and Evidence-Based Reviews Relevant to Antenatal and Newborn Screening) on **Page 81** considers publications relevant to antenatal and newborn screening, while **Table 32** (Local Policy Documents and Evidence-Based Reviews Relevant to Congenital Anomalies) on **Page 105** considers congenital anomalies collectively.

Table 5. Local Policy Documents and Evidence-Based Reviews Relevant to Neural Tube Defects

New Zealand Policy Documents, Publications and Websites
Ministry of Health. 2010. **Folate/folic acid**. http://www.health.govt.nz/our-work/preventative-health-wellness/nutrition/folate-folic-acid accessed May 2013. This web page provides information on folate and New Zealand's policy on folic acid supplementation for reducing neural tube defects. The Ministry of Health recommends that women planning to become pregnant take 800 µg of folic acid daily for at least four weeks before conception and for 12 weeks after. Women at high risk of having a baby with a NTD, including those with a previous affected pregnancy or a family history of NTD and those with some medical conditions including insulin-dependent diabetes, are recommended to take 5000 µg (5g) of folic acid for the same period. Subsidised 800 µg and 5mg folic acid tablets can be purchased over the counter from pharmacies.
Ministry of Health. 2010. **Folic Acid and Spina Bifida/Iodine and Iodine Deficiency**. Wellington: Ministry of Health. https://www.healthed.govt.nz/system/files/resource-files/HE4147_0.pdf This is a brief pamphlet for pregnant women or women planning to become pregnant about the benefits of folic acid and iodine supplement tablets.
Ministry of Health. 2010. **Eating for Healthy Pregnant Women/Ngā Kai Totika mā te Wahine Hapū**. Wellington: Ministry of Health. https://www.healthed.govt.nz/system/files/resource-files/HE1805_1.pdf Page 16 of this healthy food guideline intended for pregnant women covers the recommendations for folic acid.
Ministry of Health. 2006. **Food and Nutrition Guidelines for Healthy Pregnant and Breastfeeding Women: A background paper**. Wellington: Ministry of Health. http://www.health.govt.nz/system/files/documents/publications/food-and-nutrition-guidelines-preg-and-bfeed.pdf Pages 58–62 of this publication deal with folate. They cover background information on folate and its relationship to neural tube defects, recommended dietary intakes (RDIs) of folate equivalents, folic acid supplementation, RDIs for breastfeeding women, studies of folate intake in New Zealand, sources of folate in the diet, and practical advice.
Ministry of Health. 2003. **Improving Folate Intake in New Zealand: Policy Implications** Wellington: Ministry of Health. http://www.moh.govt.nz/notebook/nbbooks.nsf/0/19C76A786D58C8D6CC256DA4008038A6/$file/ImprovingFolate.pdf This publication provides background information on the benefits of folic acid and reviews the current policy situation (in 2003) regarding folic acid in New Zealand, Australia, Canada, the U.K. and the U.S. It considers four policy options for improving folate status in women of childbearing age: • Increasing dietary folate intake • Consumption of folic acid supplements (status quo) • Voluntary fortification of staple food products with folic acid (status quo) • Mandatory fortification of staple food products with folic acid. The key recommendations were: • An education campaign to make women aware of the benefits of increased folate consumption • Considering mandatory fortification of either bread or flour • Continuing to recommend folic acid supplements to women planning pregnancy whether fortification remains voluntary or becomes mandatory • Making 400mg folic acid tablets available to women planning pregnancy as a registered medicine • Continuing monitoring of neural tube defects, improved reporting of terminations of pregnancy to include the type of neural tube defect involved and monitoring of the folate status and folic acid intake of new Zealanders

International Guidelines and Systematic and Other Reviews
De-Regil Luz M, Fernández-Gaxiola Ana C, Dowswell T, et al. 2010. **Effects and safety of periconceptional folate supplementation for preventing birth defects**. Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD007950.pub2 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007950.pub2/abstract The benefits of folic acid supplementation for preventing neural tube defects (NTDs) are well established and the World Health Organization recommends that women take 400μg of folic acid from the time they start trying to conceive until 12 weeks of pregnancy. This review, which updates an earlier Cochrane review, assessed whether folic acid supplementation reduces NTDs and also other birth defects, including cleft palate, without adverse effects for mothers or babies. It included five RCTs, all published before 2001, (6105 women, of whom 1949 had a history of a pregnancy affected by a NTD and 4156 had not) in which women received either folic acid (alone or in combination with other vitamins and minerals) or placebo (or vitamin and mineral combinations without folic acid). Overall the results of these five trials indicated a protective effect for daily periconceptional folic acid supplementation, compared to no intervention, placebo or alternative vitamins/minerals, in reducing the risk of having a baby with an NTD (Risk ratio 0.28, 95% CI 0.15 to 0.52). In women with a previous NTD-affected pregnancy (four trials) folic acid had a significant protective effect for recurrence: (RR 0.32, 95% CI 0.17 to 0.60). In the one trial involving women with no previous history of NTDs (4156 women) there were no affected pregnancies in the supplementation group but the difference between the intervention and control groups was not a statistically significant (RR 0.08, 95% CI 0.00 to 1.33). Folic acid had no statistically significant effect on rates of cleft palate, cleft lip, congenital cardiovascular defects, miscarriages or any other birth defects. The authors concluded that folic acid does prevent NTDs but no other birth defects.
National Collaborating Centre for Women's and Children's Health. **Antenatal care: Routine care for the healthy pregnant woman**. London: RCOG Press, 2008. URL: http://www.nice.org.uk/nicemedia/live/11947/40145/40145.pdf Section 9.1 of this publication covers screening for structural anomalies and reviews studies relating to the use of ultrasound and serum screening (alpha-fetoprotein, AFP) for this purpose. There were two studies identified that investigated maternal serum alpha-fetoprotein (AFP) as a screening test for neural tube defects. One found that maternal AFP had good diagnostic value in both predicting and ruling out anomalies while the other found it to have less diagnostic value than a routine ultrasound. There was no evidence on the value and effectiveness of a combination of routine ultrasound and maternal AFP screening. A short version of this guideline can be found at: http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf
Other Relevant Publications and Websites
Wolff T, Witkop CT, Miller T, et al. 2009. **Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the U.S. Preventive Services Task Force**. Annals of Internal Medicine, 150(9), 632-9. http://annals.org/article.aspx?articleid=744474 This review searched for new evidence, published since 1996, on the benefits and harms of folic acid supplementation for women of childbearing age for the prevention of neural tube defects (NTDS), to inform the updated recommendations of the U.S. Preventive Services Taskforce. The authors identified four observational studies which reported a reduced risk of NTDs associated with supplements containing folic acid. The studies were too different in type and methodology to permit the calculation of a summary risk reduction. The authors stated that this new observational evidence supported previous evidence from RCTs and that the reported association of folic acid use with twin pregnancies may be confounded by an association with in vitro fertilisation.
The European Surveillance of Congenital Anomalies and Twins (EUROCAT). 2006. **Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe**. Newtownabbey, Northern Ireland: EUROCAT Central Registry, University of Ulster. http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-IIA.pdf http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-IIB.pdf This report is in three parts. The first part provides an overview of neural tube defects in seven chapters: Introduction, Background, The Public Health Response to Evidence Concerning the Protective Effect of Folic Acid, NTD Prevalence Rates in Europe 1980-2002,The Case for Fortification of Staple Foods in Europe, Conclusions, and References. Parts IIA and IIB have a chapter for each of the countries in EUROCAT giving information on local policy and statistics.

Note: The publications listed were identified using the search methodology outlined in Appendix 1 (Search Methods for Policy Documents and Evidence-Based Reviews)

References

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