PREVALENCE OF NEURAL TUBE DEFECTS IN ILLINOIS, 1989-2002

Illinois Department of Public Health
Division of Epidemiologic Studies

April 2004

ACKNOWLEDGMENTS

This report was possible because of the special efforts of many individuals and organizations. Particular thanks are due to the following APORS staff:

Carol Strainis, Quality Control Specialist/Trainer
Terrie Wyatt, Hospital Liaison

Kelly Easton, APORS Data Entry
Marjorie Higgins, Medical Coder/Editor

Roosevelt Lance, APORS Field Abstractor
Dorothy McIntire, APORS Field Abstractor
Patricia Rassi, APORS Field Abstractor

Support

This publication was supported by a grant (cooperative agreement number U50/CCU523303-02) from the U.S. Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

Suggested Citation

Fornoff JE, Egler T, Shen T. Prevalence of Neural Tube Defects in Illinois 1989-2002. Epidemiological Report Series 04:02 Springfield, IL: Illinois Department of Public Health, April 2004.

PREVALENCE OF NEURAL TUBE DEFECTS IN ILLINOIS, 1989-2002

TABLE OF CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

INTRODUCTION

Adverse pregnancy outcomes are recorded by the Illinois Department of Public Health (IDPH) for infants with neural tube defects, other congenital anomalies (birth defects) and other serious neonatal conditions. Each year in Illinois, IDPH's Adverse Pregnancy Outcomes Reporting System (APORS) obtains information on thousands of such births throughout the state. Information about congenital anomalies identified in newborn infants was first collected statewide by APORS in 1989.

This information is collected for two major reasons. First, infants with a birth defect often need special services to help assure that they reach their full potential. These babies, therefore, are referred to the Illinois Department of Human Services for follow-up services. Second, the data are collected for surveillance purposes. These may include describing disease patterns, tracking trends, conducting cluster investigations, and developing education and intervention strategies.

APORS is the most complete source of data on birth defects that exists in Illinois. All Illinois hospitals are mandated to report infants with congenital anomalies who are born to Illinois women. (Perinatal centers in St. Louis, Missouri, voluntarily participate.) It is a passive surveillance system because reports are sent to IDPH rather than APORS staff going to hospitals to identify children with birth defects. Such passive systems are likely to underestimate birth defect rates. The Trust for America's Health gave APORS a rating of B because of this lack of active surveillance activities. (Only eight states received an A rating.)

Since 1996, a number of projects have been carried out to identify cases and birth defects that have not been reported to APORS using the passive surveillance mechanism described above. These measures do not constitute a systematic active surveillance system, but are important elements of such a system. These projects are described in Table 1 below. More information is available from APORS.

Table 1. Projects to identify cases and birth defects

Birth years	Study Title	Purpose
1996-1997	Out to One Year Study	Identify birth defects diagnosed in the first year of life, after the newborn hospital stay
1999-2002	Active Casefinding	Identify major birth defects diagnosed in the first year of life at large Chicago hospitals, after the newborn hospital stay
2000	Hospital Discharge Study	Identify birth defects noted in the hospital newborn stay discharge record, but not reported to APORS
1999-2002	Very Low Birth Weight Studies	Identify children not reported to APORS, but with low birth weights or low APGAR scores recorded on their birth certificate

APORS casefinding is an ongoing process; children with birth defects identified during the newborn stay but not reported to APORS are added for previous years whenever they are found. This report presents a report of neural tube defect rates among newborns and infants up to 1 year of age from 1989 to 2002.

METHODS

Calculation and interpretation of rates and confidence intervals

Annual incidence rates (per 10,000 live births) for neural tube defects identified during the newborn hospital stay or associated with a fetal death were calculated as

$$10{,}000 \times \frac{\text{number of infants with selected congenital anomaly}}{\text{number of live births}}$$

The numbers of live births were obtained from the master birth files provided by the Department's Center for Health Statistics.

Occurrence of a specific birth defect is assumed to be a rare event, therefore following a Poisson distribution. Exact confidence intervals were calculated for each rate (Armitage and Berry, page 134). Where there were a large number of birth defect cases, the confidence interval is narrow, indicating that the rate is stable. Where there were few birth defect cases, the confidence interval becomes very wide, indicating that the rate is not very stable and a small change in the number of infants born with the specific birth defect could result in a large change in the rate.

To compare two rates, it is important to look not just at their values, but also their confidence intervals. As a conservative approximation, if two confidence intervals overlap, then there is no evidence that the two rates are really different. If two confidence intervals do not overlap, then the rates are said to be statistically different. In this report, 95 percent confidence intervals are used; where the confidence intervals do not overlap, the rates are statistically different at the 5 percent level ($p < 0.05$).

Analysis of trends

Trends in Illinois neural tube defect rates were modeled using a log-linear regression model (which is appropriate for data following a Poisson distribution). Analyses were performed using the Joinpoint Regression Program (Version 2.7, September 2003, National Cancer Institute). This software compares a linear model with a single slope to linear models with different slopes joined by one or more join-points. The model tests whether the slope(s) are significantly different from 0 (whether there is a change over time) and whether any change in slope between two segments is statistically significant.

Multiple comparisons

Since this report examines a large number of risk factors for neural tube defects, the corresponding statistical tests were subject to the "multiple comparison problem." For a given birth defect, the observed rate is an estimate of the true birth defect rate in the population. When two rates from different times or groups are compared, statisticians will assert that the observed rates are evidence of the groups having differing birth defect rates, if the observed rates are so different that the chance of them coming from the same underlying population is less than 5 percent. The 5 percent type I error rate, however, suggest that, when 100 comparisons are made, five, on average, will provide statistical evidence that there are two true differing rates, when in fact there is no difference between the two groups. Therefore, as more comparisons are made, more may be statistically significant, just by chance. In this report, no explicit corrections of the multiple comparison problem were made; instead, exact probabilities are reported when discussing trends. The smaller the reported probability, the more likely the difference is not simply the result of chance.

Impact of miscarriage and elective termination on estimated rates of neural tube defects

APORS collects information about live births and fetal deaths (infants delivered after at least 20 weeks gestation). No data are available to APORS about miscarriages (infants delivered before 20 weeks, sometimes even without the mother's knowledge) or about elective abortions. There is evidence that very few of chromosomally abnormal cases of neural tube defects come to term (Frey and Hauser). Forrester *et al.* showed that, in Hawaii, including electively terminated cases in the calculation of anencephaly, spina bifida and encephalocele increased the estimate of prevalence by 260, 41 and 82 percent respectively.

In an earlier study (Cragan *et al.*), rates of anencephaly and spina bifida for six surveillance programs were calculated with and without cases that were electively terminated. For anencephaly, the percentage of cases terminated ranged from 20 percent to 69 percent, leading to increases in prevalence estimates of between 28 percent and 275 percent. For spina bifida, the percentage of cases terminated ranged from 3 percent to 29 percent, leading to increased prevalence estimates of between 2 percent and 43 percent.

Forrester and Merz also have examined the number of early fetal deaths (gestational age unknown or less than 20 weeks and the result of a spontaneous abortion, missed abortion or miscarriage). Early fetal deaths made up 4.5 percent of the anencephaly cases and 2.2 precent of the encephalocele cases. These rates are probably underestimates of the true rates since not all early fetal deaths are recognized by the mother, a fetus may not be available for examination, or it may be difficult to recognize a birth defect in the very early stages of development.

In 2002, there were almost 47,000 induced abortions in Illinois (IDPH Center for Health Statistics) and 180,555 live births. Using the percentages of missed cases from Cragan *et al.*, and Forrester and Merz, APORS data may be underestimating the rate of anencephaly by as much as 75 percent. Estimates of spina bifida rates would be affected less markedly, but still significantly, by the lack of information about cases among elective terminations and early fetal deaths.

DESCRIPTION OF NEURAL TUBE DEFECTS

Neural tube defects are a group of very serious birth defects that arise when the neural tube fails properly to develop into the brain and spinal cord during the first month of pregnancy. The main types of neural tube defects (NTDs) are described below. The corresponding codes from the International Classification of Diseases – Ninth Revision Clinical Modification (ICD-9-CM) also are provided.

Anencephaly (ICD-9-CM 740.*)

Anencephaly (ICD-9-CM 740.0) occurs when the cephalic end of the neural tube fails to close, resulting in the absence of a major portion of the brain, skull and scalp. Many infants with anencephaly are delivered stillborn; those born alive are usually blind, deaf, unconscious and unable to feel pain. If the infant is not stillborn, then he or she will usually die within a few hours or days after birth.

When the anencephaly extends down onto the neck, exposing a thin and flattened spinal cord, the condition is known as craniorachischisis (ICD-9-CM 740.1). In some infants, in addition to the anencephaly and the spinal defects, the baby's head is bent backwards, so that the face looks upwards; generally the neck is absent. This condition is called iniencephaly (ICD-9-CM 740.2). The affected infant tends to be short, with a disproportionately large head.

Spina bifida (ICD-9-CM 741.*)

Spina bifida is a condition where one or more of the spine's veterbrae does not develop properly. The impact on the baby depends on the degree to which the spinal cord is involved. Spina bifida can be broken down into two categories:

1. Open (the severest form)
   i. Myelomeningocele, in which the spinal cord and its protective covering (the meninges) protrude from an opening in the spine
   ii. Meningocele in which the spinal cord develops normally but the meninges protrude from a spinal opening

   In these cases, the deformity may remain covered by the meninges (cystica), or it may be open to the environment (aperta).

2. Closed (occulta, the mildest form.)
   One or more vertebrae are malformed and covered by a layer of skin.

Infants born with any form of spina bifida may have damage to the nerves and spinal cord. The degree of damage will depend on the type and location of the defect. Although a spinal opening can be surgically repaired shortly after birth, any nerve damage is permanent, resulting in varying degrees of paralysis of the lower limbs. In addition to physical and mobility difficulties, most individuals have some form of learning disability. Spina bifida also may cause bowel and bladder complications, and many children with spina bifida have excessive accumulation of cerebrospinal fluid in the brain (hydrocephalus). With proper care, most children with spina bifida live well into adulthood.

Encephalocele (ICD-9-CM 742.0)
Encephaloceles are sac-like protrusions of the brain and the membranes that cover it through openings in the skull; they are often accompanied by craniofacial abnormalities or other brain malformations. As with spina bifida, the encephalocele may contain just the meninges, or also contain brain tissue. The prognosis for a baby with an encephalocele varies depending on the type of brain tissue involved, the location of the sacs and the accompanying brain malformations. Encephalocele may cause, or be associated with hydrocephalus, paralysis of the arms and legs, an abnormally small head, uncoordinated movement of the voluntary muscles, developmental delay, vision problems, mental and growth retardation, and seizures. Some affected children may have normal intelligence.

CAUSES OF NEURAL TUBE DEFECTS

The causes of neural tube defects are difficult to study. Two children with similar neural tube defects may have developed them through a completely different etiology. There are four major categories of known causes of neural tube defects:

- genetic disorders (either hereditary or arising during conception)
- exposure to an environmental chemical (for example, medications or solvents)
- maternal illness during pregnancy, exposing her baby to high temperatures and/or to viral or bacterial infection
- lack of necessary nutrients

The stage of fetal development at the time of exposure to one of the latter three causes is critical. Because neural tube development takes place in the first month of pregnancy, exposure would have to occur during this time period to give rise to a defect.

Genetic disorders
While some neural tube defects may arise as a result of gene-environment interaction, there are a number of identified syndromes that also can give rise to neural tube defects. Frey and Hauser identified 60 syndromes that have a neural tube defect component together with other birth defects. Each of the different types of neural tube defects may arise as a result of one or more of these syndromes. There is also evidence that non-syndromal neural tube defects may sometimes also have a genetic source, based on familial and twin studies (Frey and Hauser).

Environmental exposures

Since neural tube defects are rare birth defects, it is hard to definitively associate an environmental exposure to a specific NTD. However, a number of studies have identified exposures that may cause neural tube defects. A selection of these is listed in Table 2, to give an idea of the range of exposures that may give rise to neural tube defects.

Table 2. Environmental exposures associated with increased risk of neural tube defects

Exposure	Type of NTD	Exposure type	Odds ratio[1] (95% CI)	Reference
Glycol ethers	All combined	Occupational	1.94 (1.16, 3.24)	Cordier *et al.*
Nitrates	Anencephaly	Drinking water nitrates > 45 mg/L	4.0 (1.0, 15.4)	Croen *et al.*
Lead	All combined	Drinking water > 10 mcg/L	1.25[2]	Bound *et al.* (1997)
Trihalomethanes	Isolated NTDs	Highest tertile of drinking water	2.1 (1.1, 4.0)	Klotz & Pyrch
Valproic acid	Spina bifida	Anti-seizure medication	5.7 (2.9, 10.9)	Arpino *et al.*
Tea	Spina bifida	Maternal consumption	2.3 (1.2, 4.4)	Correa *et al.*
Oxytetracycline (antibiotic)	All combined	Treatment during second month of pregnancy	9.7 (2.0-47.1)	Czeizel *et al.*
Pesticides (paternal)	Spina bifida	Paternal spraying in orchards and greenhouses	2.76 (1.07, 7.13)	Kristensen *et al.*
Pesticides (maternal)	All combined	Professionally applied to home Living within ¼ mile of an agricultural plot	1.6 (1.1, 2.5) 1.5 (1.1, 2.1)	Shaw *et al.* (2003)
Landfill sites	All combined	Living within 3km of landfill site	1.86 (1.24, 2.79)	Dolk *et al.*
Heat	All combined	Hot tub use	2.8 (1.2,6.5)	Milunsky *et al.*

[1] The odds ratio is a way of comparing risk in two groups. When two groups have the same risk, the odds ratio is 1; when the odds ratio is greater than 1, the exposed group has a higher risk of a neural tube defect than the unexposed group.

[2] The odds ratio increases about 25 percent with each 10 percent increase in the number of houses with high levels of lead in the drinking water. The confidence interval is not available.

Maternal conditions

There are a number of maternal conditions that may contribute to an increased risk of an NTD-affected pregnancy. Shaw *et al.* (1998) found an odds ratio of 1.91 (95 percent confidence interval [1.35, 2.72]) for neural tube defects among infants of women who had a fever in the first trimester of their pregnancy. It is not clear whether the exposure to high temperatures or to the bacteria or virus is the cause of the maldevelopment of the neural tube.

Janssen *et al.* found that women with diabetes are four times more likely to have pregnancies involving neural tube defects (95 percent confidence interval [3.1, 5.1]). These investigators found a much smaller odds ratio of 1.3 (95 percent confidence interval [1.0, 1.6]) of neural tube defect pregnancies among women with gestational diabetes. Women who are obese prior to pregnancy (and not diabetic) also are more likely to have children with spina bifida. Watkins *et al.* found that obese women had an odds ratio of 3.5 (95 percent confidence interval [1.2, 10.3]).

Maternal psychological stress may increase the risk of neural tube defects. Carmichael *et al.* found that women who experienced death of someone close, job loss, separation or divorce – either themselves or someone close to them – in the very early stages of pregnancy had an odds ratio of 1.5 (95 percent confidence interval [1.1, 2.1]). Suarez *et al.* counted job changes, residential moves and major injuries as stressful events in the year prior to conception in Mexican Americans. Women with at least one such event had almost three times the risk of an NTD-affected pregnancy (odds ratio 2.9, 95 percent confidence interval [1.8, 4.7]). Women with low levels of emotional support also had an increased risk of an NTD-affected pregnancy (odds ratio 4.6, 95 percent confidence interval [2.2, 9.7]).

A number of medications also can give rise to neural tube defects. Several are listed in Table 2 above (oxytetracycline, valproic acid). However, sometimes the consequences of not taking such medications also may be grave for mothers and pregnancy outcomes.

Diet

Folic acid is a nutrient that is clearly needed for proper neural tube development (Watkins). In 1992, the U.S. Centers for Disease Control and Prevention recommended that all women of childbearing age consume 0.4 mg of folic acid daily. The recommendation originated in research indicating that inadequate levels of folic acid in the first weeks of pregnancy increased the risk of having a baby with a neural tube defect (MRC Vitamin Study Research Group). In 1996, the U.S. Food and Drug Administration agreed that enriched cereal grain products must be fortified with folic acid, as a means to reduce the rate of neural tube defects in the United States.

The metabolism of folic acid is very complex, and there are many reasons why an individual may not have sufficient folic acid to reduce the risk of a neural tube defect-affected pregnancy. For example, valproic acid and lead interfere with folic acid metabolism and, therefore, may lead to neural tube defects by reducing the folic acid available to the fetus in the first few weeks of pregnancy. Similarly, zinc is a micronutrient involved in folate metabolism; low zinc levels may give rise to low levels of folic acid.

RATES OF NEURAL TUBE DEFECTS IN ILLINOIS

In 1996 and 1997, the U.S. Centers for Disease Control and Prevention established seven centers of birth defect research and prevention. Four of these centers use active case ascertainment to identify birth defect cases and have published more than a single year of data. These centers are considered gold standards for the collection of birth defect information.

Neural tube defect rates among Illinois newborns from 1989 to 2002 are presented in Table 3. As the table indicates, the rates of neural tube defects reported in Illinois are about one-half to one-third of those identified by the national centers. The primary reason for the marked difference in rates is that these centers send staff to different data sources to identify cases of neural tube defects (active ascertainment). In addition, Arkansas and Texas collect birth defect information associated with elective abortions. (This issue is discussed further on page 4, in the section (Impact of miscarriage and elective termination on estimated rates of neural tube defects.))

Table 3. Rates of neural tube defects in Illinois and selected states

Program	Years	Anencephaly	Spina bifida	Encephalocele
Illinois	1989-2002	1.76	2.88	0.60
Arkansas	1993-1997	4.24	8.19	2.65
California	1989-1996	3.93	4.18	1.09
Iowa	1989-1997	3.58	5.57	1.23
Texas	1995-1996	4.20	5.35	1.64

Source: Birth Defects Surveillance Data from Selected States, 1989-1998. *Teratology* **64**:S117-173 (2001).

The analyses that follow make the assumption that the cases about which APORS is notified are similar to those not reported. For example, it may be assumed that a male child with anencephaly is no more or less likely to be terminated that a female child. This assumption allows the comparison of two observed rates, even though the absolute value of the observed rates may be an underestimation of the true underlying rates.

Table 4 shows the number and incidence rates of neural tube defects reported to APORS by year, and for years aggregated by enriched grain folic acid fortification status (pre-fortification, optional fortification and post-fortification). The active case ascertainment studies described in the introduction identified 82 additional children born with neural tube defects, an additional 6.0 percent over those identified using the standard hospital reporting and fetal death vital record data. Almost all of these (72 percent) were cases of spina bifida; only 10 new cases (an additional 2.2 percent) of anencephaly and 13 new cases (an additional 8.3 percent) of encephalocele were identified. An additional 7.8 percent of spina bifida cases were identified. These additional cases are not used in this report to allow comparability from year to year.

Table 4. Total number and incidence rates of reported neural tube defects

Neural tube defect		Anencephaly N	Anencephaly Rate[1]	Anencephaly 95% CI[2]	Spina bifida N	Spina bifida Rate[1]	Spina bifida 95% CI[2]	Encephalocele N	Encephalocele Rate[1]	Encephalocele 95% CI[2]
Total 1989-2002		460	1.76	(1.60, 1.93)	756	2.89	(2.69, 3.11)	157	0.60	(0.51, 0.70)
Pre-fortification Jan. 1989 - Dec. 1996		279	1.84	(1.62, 2.06)	479	3.15	(2.88, 3.44)	94	0.62	(0.50, 0.76)
Optional fortification Jan. 1997 - Sept. 1998		56	1.75	(1.33, 2.29)	75	2.35	(1.85, 2.95)	23	0.72	(0.46, 1.08)
Post-fortification Oct. 1998 - Dec. 2002		125	1.61	(1.34, 1.92)	202	2.60	(2.25, 2.99)	40	0.51	(0.37, 0.70)
Pre-fortification	**1989**	36	1.89	(1.33, 2.62)	67	3.52	(2.73, 4.47)	16	0.84	(0.48, 1.37)
	1990	31	1.59	(1.07, 2.25)	66	3.38	(2.61, 4.30)	8	0.41	(0.18, 0.80)
	1991	23	1.19	(0.75, 1.78)	51	2.63	(1.96, 3.45)	10	0.52	(0.25, 0.95)
	1992	35	1.83	(1.28, 2.55)	64	3.35	(2.58, 4.28)	12	0.63	(0.33, 1.10)
	1993	41	2.15	(1.54, 2.92)	61	3.20	(2.45, 4.11)	12	0.63	(0.33, 1.10)
	1994	37	1.96	(1.38, 2.69)	60	3.17	(2.42, 4.08)	6	0.32	(0.11, 0.69)
	1995	33	1.78	(1.22, 2.50)	55	2.96	(2.23, 3.85)	14	0.75	(0.41, 0.26)
	1996	43	2.35	(1.70, 3.16)	55	3.00	(2.26, 3.91)	16	0.87	(0.50, 1.42)
Optional fortification	***1997***	*31*	*1.72*	*(1.16, 2.44)*	*35*	*1.94*	*(1.35, 2.70)*	*12*	*0.66*	*(0.35, 1.16)*
	1998	*32*	*1.75*	*(1.20, 2.47)*	*48*	*2.63*	*(1.94, 3.48)*	*12*	*0.66*	*(0.34, 1.15)*
Mandatory fortification	**1999**	32	1.76	(1.21, 2.48)	59	3.24	(2.47, 4.18)	11	0.60	(0.30, 1.09)
	2000	29	1.57	(1.05, 2.25)	44	2.38	(1.73, 3.19)	11	0.59	(0.29, 1.07)
	2001	30	1.63	(1.10, 2.33)	52	2.83	(2.11, 3.71)	8	0.43	(0.19, 0.86)
	2002	27	1.50	(0.98, 2.18)	39	2.16	(1.54, 2.96)	9	0.50	(0.23, 0.94)

[1] Rate per 10,000 live births [2] 95% confidence interval for rate

Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 1. Incidence rates of reported neural tube defects, by fortification period

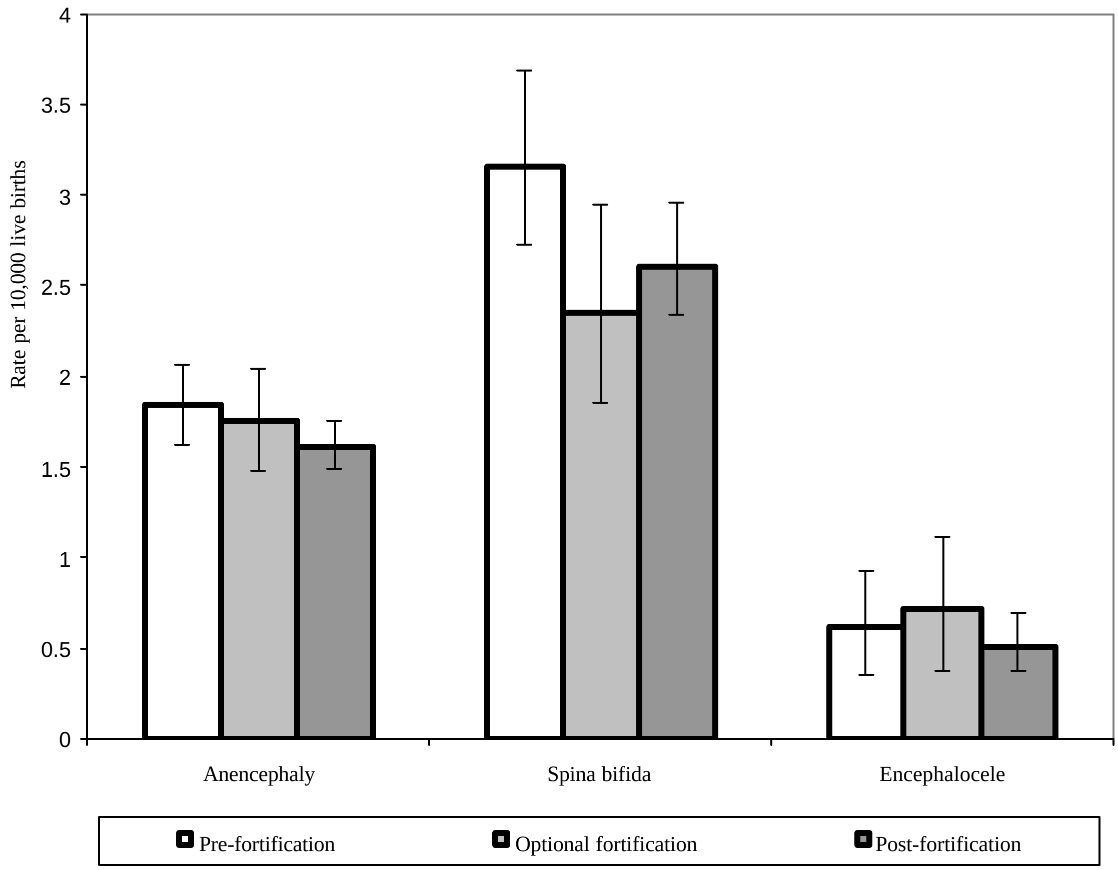
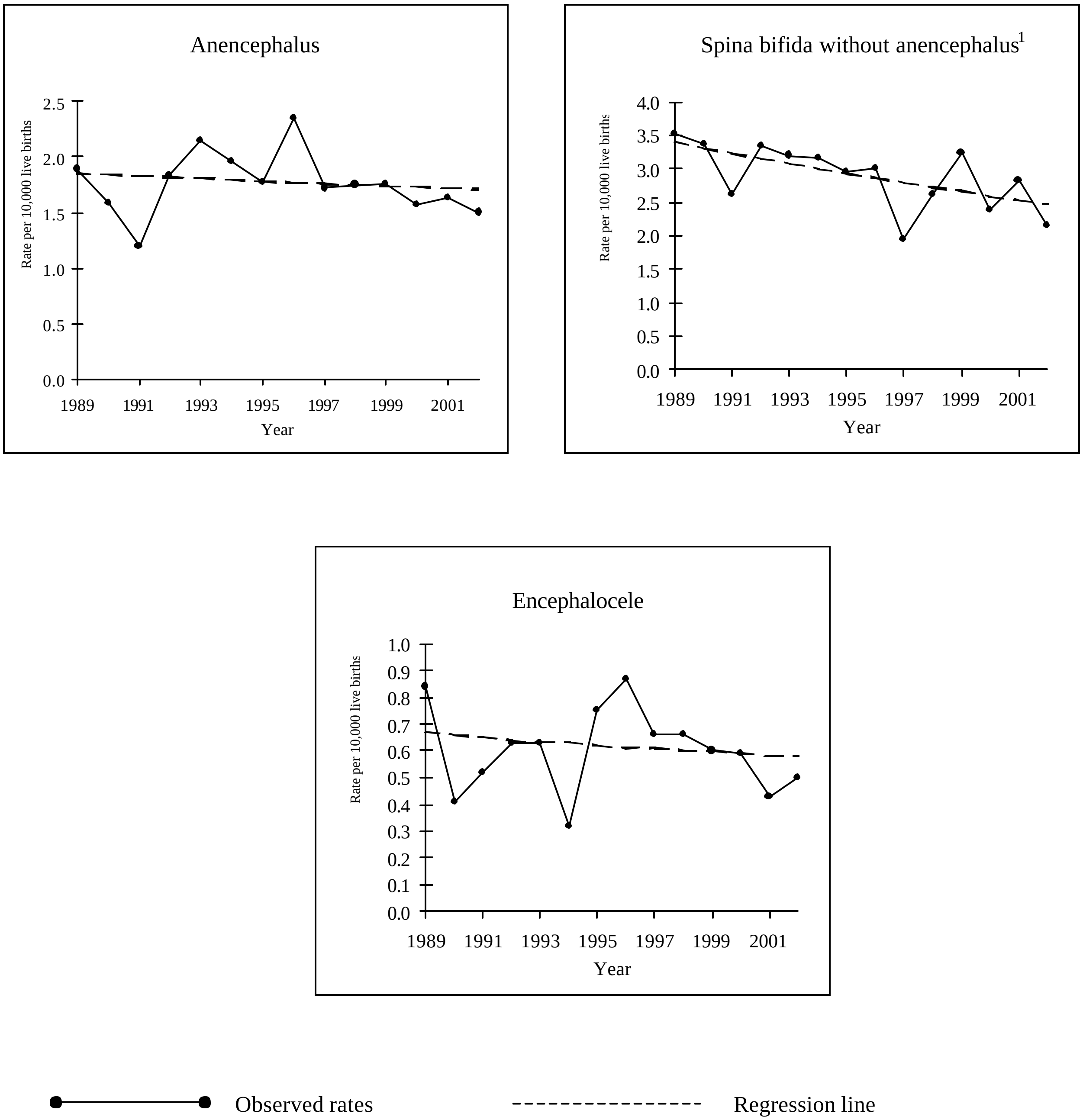


Table 4 (illustrated in Figure 1) shows some evidence of a decline in anencephaly and spina bifida since the introduction of folic acid fortification. Figure 2 shows the results of a trend analysis for anencephaly, spina bifida and encephalocele. The rate of spina bifida without anencephalus is significantly decreasing by an average of 2.5 percent each year.

Figure 2. Trends in the reported incidence rates of neural tube defects per 10,000 live births, 1989-2002



[1]Trend is significant; rate is declining by an average of 2.5 percent annually.
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

RATES OF NEURAL TUBE DEFECTS BY DEMOGRAPHIC FACTORS

Gender

Females are more likely than males to have anencephaly and spina bifida. Whiteman *et al.* found that in a case-control study, about 70 percent of the children with anencephaly were female and 60 percent of the children with spina bifida were female. Hendricks *et al.* reported that 75 percent of the spina bifida defects at the thoracic level or higher were in females, while there was a 1:1 male:female ratio for lumbar or lower cases of spina bifida. Table 5 shows the rates of neural tube defects by gender for Illinois. Fifty-five percent of the anencephaly cases reported to APORS were female, 46 percent of the spina bifida cases were female and 60 percent of the encephalocele cases were female.

Table 5. Total number[1] and incidence rates of reported neural tube defects, by gender, 1998-2002

	Anencephaly			Spina bifida			Encephalocele		
	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]
Male	67	1.43	(1.11, 1.82)	130	2.78	(2.32, 3.30)	20	0.43	(0.26, 0.66)
Female	83	1.86	(1.48, 2.30)	111	2.48	(2.04, 2.99)	30	0.67	(0.45, 0.96)

[1] One case of spina bifida and one of encephalocele had unknown gender.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

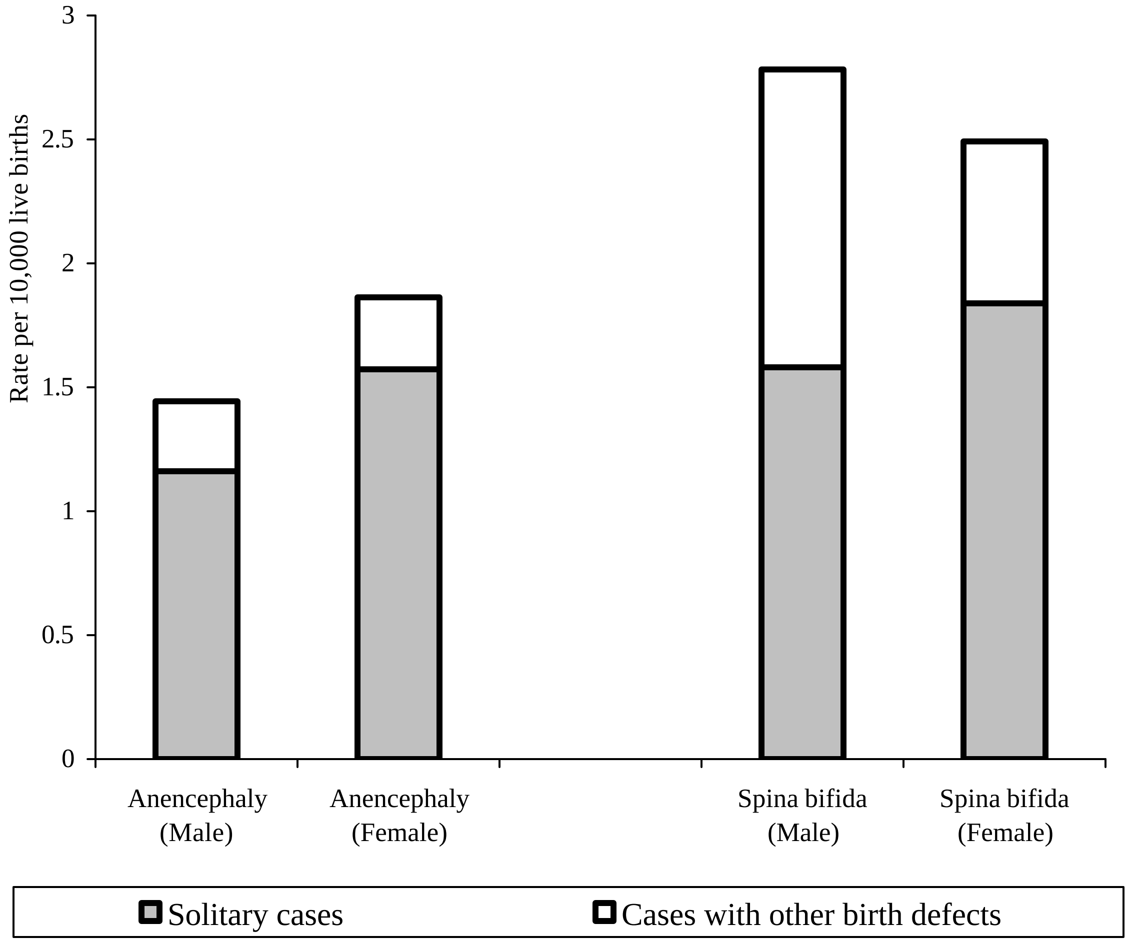
Little and Elwood suggest that the observed gender differences may be explained by differences between the sexes in embryonic development, susceptibility to teratogens and spontaneous abortion rates. Davies and Duran conclude that localized lesions are formed by a mechanism that favors females, while upper lesions, usually also involving the head, are a result of a different mechanism, and are often associated with other malformations. APORS does not usually receive information about the location of spina bifida lesions, but some information is available about the occurrence of neural tube defects with other birth defects (Table 6).

Table 6. Total numbers[1] and incidence rates of solitary neural tube defects and neural tube defects associated with other birth defects, by gender, 1998-2002

	Anencephaly						Spina bifida					
	Solitary			Plus other BDs			Solitary			Plus other BDs		
	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]
Male	54	1.16	(0.87, 1.50)	13	0.28	(0.15, 0.47)	74	1.58	(1.25, 1.99)	56	1.20	(0.90, 1.56)
Female	70	1.57	(1.22, 1.98)	13	0.29	(0.16, 0.50)	82	1.84	(1.46, 2.28)	29	0.65	(0.43, 0.93)

[1] One case of spina bifida had unknown gender.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 3. Incidence rates of reported cases of anencephaly and spina bifida, by gender and type of neural tube defect, 1998-2002



The Illinois data are in accordance with the literature; when solitary neural tube defects only are considered, there is an excess of cases among Illinois females (56 percent for anencephaly and 53 percent for spina bifida). The high number of spina bifida cases among males from 1998-2002 reflects a 65 percent male excess among spina bifida associated with other birth defects (Table 6). Generally, males have an excess of non-neural tube defects (Lary and Paulozzi).

Maternal Race and Ethnicity

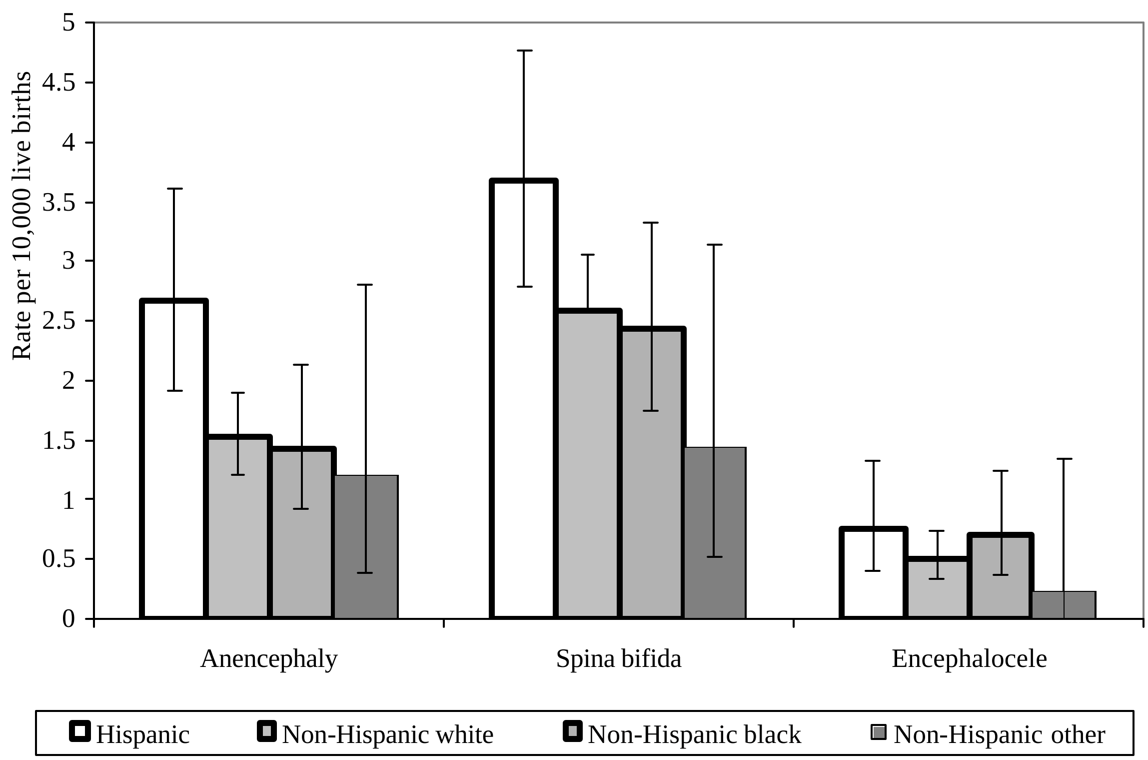
It has been well documented by Fray and Hauser and others that, in the United States, Hispanics have a high risk of having an NTD-affected pregnancy, and that black mothers have a lower risk of having such a pregnancy. APORS data (Table 7) clearly show that Hispanic mothers living in Illinois have a 50 percent higher rate of neural tube defect-affected pregnancies than white non-Hispanic mothers. The rates among non-Hispanics are very similar.

Table 7. Total numbers[1] and incidence rates of reported neural tube defects, by maternal race and ethnicity, 1998-2002

	Anencephaly			Spina bifida			Encephalocele		
	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]
Hispanic	42	2.67	(1.92, 3.61)	58	3.68	(2.79, 4.76)	12	0.76	(0.40, 1.33)
White non-Hispanic	78	1.52	(1.21, 1.90)	132	2.58	(2.16, 3.06)	26	0.51	(0.33, 0.74)
Black non-Hispanic	24	1.43	(0.92, 2.13)	41	2.44	(1.75, 3.32)	12	0.71	(0.37, 1.24)
Other non-Hispanic	5	1.20	(0.39, 2.81)	6	1.44	(0.53, 3.13)	1	0.24	(0.00, 1.34)

[1] One case of anencephaly and five cases of spina bifida had unknown maternal race and ethnicity.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 4. Incidence rates of reported neural tube defects, by maternal race and ethnicity, 1998-2002



Areas of Illinois

The rate of neural tube defects is known to vary geographically (Frey and Hauser). Part of this difference may be attributable to race or ethnicity, but there are unexplained pockets of excess cases around the world. In order to examine the ways in which rates of neural tube defects vary geographically, Illinois first had to be divided into regions. These regions had to have a sizeable population in order to obtain stable estimates of the rates of neural tube defects. Table 8 shows the rates in Chicago, in suburban Cook County and in the remainder of Illinois. There is no evidence of significant differences in rates of neural tube defects between the different areas of Illinois.

Table 8. Total numbers and incidence rates of reported neural tube defects, by area of Illinois, 1998-2002

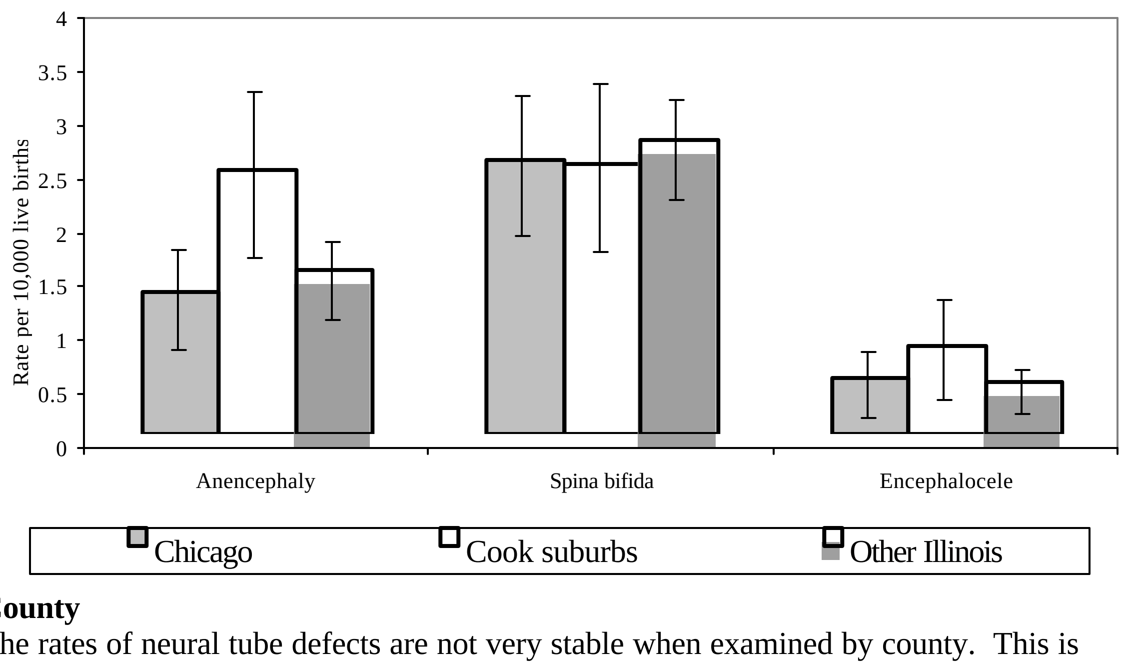
	Anencephaly			Spina bifida			Encephalocele		
	N	Rate	95% CI	N	Rate	95% CI	N	Rate	95% CI
City of Chicago	33	1.32	(0.91, 1.85)	64	2.55	(1.97, 3.27)	13	0.52	(0.28, 0.89)
Suburban Cook County	42	2.45	(1.77, 3.31)	43	2.51	(1.82, 3.38)	14	0.82	(0.44, 1.37)
Other areas of Illinois	75	1.52	(1.20, 1.91)	135	2.74	(2.30, 3.24)	24	0.49	(0.32, 0.72)

[1] Rate per 10,000 live births

[2] 95% confidence interval for rate

Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 5. Incidence rates of reported neural tube defects, by areas of Illinois, 1998-2002



County

The rates of neural tube defects are not very stable when examined by county. This is reflected in the very wide confidence intervals found for counties with small populations. However, because of general interest in knowing the observed county rates, tables 9, 10 and 11 report the county-specific incidence rates of anencephaly, spina bifida and encephalocele, respectively.

Table 9. Total number and incidence rates of reported cases of anencephaly, by maternal county of residence, 1998 – 2002

County	Cases	Rate[1]	95% CI[2] Lower	Upper	County	Cases	Rate[1]	95% CI[2] Lower	Upper
ILLINOIS	150	1.64	1.39	1.92	Lee	0	0.00	0.00	19.86
Adams	0	0.00	0.00	8.87	Livingston	0	0.00	0.00	14.97
Alexander	0	0.00	0.00	56.07	Logan	0	0.00	0.00	21.85
Bond	0	0.00	0.00	39.12	McDonough	0	0.00	0.00	24.83
Boone	2	6.70	0.81	24.18	McHenry	4	1.98	0.54	5.06
Brown	0	0.00	0.00	137.72	McLean	2	2.00	0.25	7.22
Bureau	0	0.00	0.00	17.54	Macon	2	2.69	0.33	9.72
Calhoun	0	0.00	0.00	145.32	Macoupin	0	0.00	0.00	13.35
Carroll	0	0.00	0.00	41.55	Madison	1	0.60	0.01	3.34
Cass	0	0.00	0.00	38.35	Marion	0	0.00	0.00	14.00
Champaign	1	0.89	0.02	5.01	Marshall	0	0.00	0.00	53.94
Christian	0	0.00	0.00	18.40	Mason	1	10.96	0.28	60.94
Clark	0	0.00	0.00	38.59	Massac	0	0.00	0.00	38.75
Clay	0	0.00	0.00	40.23	Menard	0	0.00	0.00	54.91
Clinton	0	0.00	0.00	18.94	Mercer	0	0.00	0.00	38.75
Coles	0	0.00	0.00	12.44	Monroe	0	0.00	0.00	21.78
Cook	75	1.78	1.40	2.23	Montgomery	0	0.00	0.00	21.54
Crawford	0	0.00	0.00	34.38	Morgan	0	0.00	0.00	17.54
Cumberland	0	0.00	0.00	58.38	Moultrie	0	0.00	0.00	38.84
DeKalb	4	7.11	1.94	18.20	Ogle	0	0.00	0.00	12.18
DeWitt	0	0.00	0.00	35.41	Peoria	1	0.76	0.02	4.23
Douglas	0	0.00	0.00	24.94	Perry	0	0.00	0.00	30.19
DuPage	14	2.11	1.15	3.53	Piatt	0	0.00	0.00	42.75
Edgar	0	0.00	0.00	33.97	Pike	0	0.00	0.00	38.71
Edwards	0	0.00	0.00	95.85	Pope	0	0.00	0.00	227.91
Effingham	0	0.00	0.00	15.99	Pulaski	0	0.00	0.00	73.22
Fayette	0	0.00	0.00	29.35	Putnam	0	0.00	0.00	111.50
Ford	0	0.00	0.00	42.36	Randolph	0	0.00	0.00	18.98
Franklin	1	4.33	0.11	24.09	Richland	0	0.00	0.00	37.15
Fulton	0	0.00	0.00	18.25	Rock Island	1	1.02	0.03	5.69
Gallatin	0	0.00	0.00	111.50	St. Clair	2	1.08	0.13	3.91
Greene	0	0.00	0.00	43.92	Saline	0	0.00	0.00	24.04
Grundy	0	0.00	0.00	15.25	Sangamon	3	2.37	0.49	6.94
Hamilton	0	0.00	0.00	81.82	Schuyler	1	26.74	0.68	148.07
Hancock	0	0.00	0.00	33.24	Scott	0	0.00	0.00	118.67
Hardin	0	0.00	0.00	169.33	Shelby	0	0.00	0.00	30.31
Henderson	0	0.00	0.00	99.21	Stark	0	0.00	0.00	98.94
Henry	0	0.00	0.00	12.93	Stephenson	0	0.00	0.00	12.26
Iroquois	0	0.00	0.00	20.47	Tazewell	2	2.53	0.31	9.14
Jackson	2	6.02	0.73	21.72	Union	1	9.63	0.24	53.56
Jasper	0	0.00	0.00	66.12	Vermilion	1	1.73	0.04	9.64
Jefferson	0	0.00	0.00	15.61	Wabash	0	0.00	0.00	52.11
Jersey	0	0.00	0.00	31.09	Warren	0	0.00	0.00	35.38
JoDaviess	0	0.00	0.00	31.16	Washington	0	0.00	0.00	43.71
Johnson	0	0.00	0.00	54.98	Wayne	0	0.00	0.00	35.92
Kane	9	2.32	1.07	4.41	White	0	0.00	0.00	44.72
Kankakee	0	0.00	0.00	4.80	Whiteside	0	0.00	0.00	9.60
Kendall	2	4.48	0.55	16.18	Will	8	1.95	0.84	3.84
Knox	0	0.00	0.00	11.52	Williamson	0	0.00	0.00	10.32
Lake	5	0.95	0.31	2.21	Winnebago	4	2.02	0.55	5.16
LaSalle	0	0.00	0.00	5.21	Woodford	1	4.64	0.11	25.83
Lawrence	0	0.00	0.00	44.24					

[1] Per 10,000 live births
[2] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Table 10. Total number and incidence rates of reported cases of spina bifida, by maternal county of residence, 1998 – 2002

			95% CI[2]					95% CI[2]	
County	Cases	Rate[1]	Lower	Upper	County	Cases	Rate[1]	Lower	Upper
ILLINOIS	242	2.65	2.32	3.00	Lee	0	0.00	0.00	19.86
Adams	3	7.22	1.499	21.08	Livingston	0	0.00	0.00	14.97
Alexander	0	0.00	0.00	56.07	Logan	2	11.86	1.44	42.79
Bond	0	0.00	0.00	39.12	McDonough	1	6.74	0.17	37.49
Boone	1	3.35	0.08	18.65	McHenry	5	2.47	0.81	5.77
Brown	0	0.00	0.00	137.72	McLean	4	4.00	1.09	10.24
Bureau	1	4.76	0.12	26.49	Macon	2	2.69	0.33	9.72
Calhoun	0	0.00	0.00	145.32	Macoupin	0	0.00	0.00	13.35
Carroll	0	0.00	0.00	41.55	Madison	6	3.60	1.32	7.84
Cass	0	0.00	0.00	38.35	Marion	1	3.80	0.09	21.14
Champaign	1	0.90	0.02	5.01	Marshall	1	14.66	0.37	81.42
Christian	0	0.00	0.00	18.40	Mason	0	0.00	0.00	40.36
Clark	0	0.00	0.00	38.59	Massac	0	0.00	0.00	38.75
Clay	1	10.93	0.27	60.74	Menard	0	0.00	0.00	54.91
Clinton	2	10.28	1.25	37.10	Mercer	1	10.53	0.26	58.51
Coles	0	0.00	0.00	12.44	Monroe	1	5.91	0.15	32.89
Cook	107	2.54	2.08	3.07	Montgomery	0	0.00	0.00	21.54
Crawford	1	9.34	0.23	51.91	Morgan	1	4.76	0.12	26.49
Cumberland	0	0.00	0.00	58.37	Moultrie	0	0.00	0.00	38.84
DeKalb	0	0.00	0.00	6.56	Ogle	2	6.61	0.80	23.85
DeWitt	0	0.00	0.00	35.41	Peoria	9	6.83	3.13	12.96
Douglas	2	13.54	1.64	48.83	Perry	1	8.20	0.20	45.58
DuPage	17	2.56	1.49	4.10	Piatt	0	0.00	0.00	42.75
Edgar	0	0.00	0.00	33.97	Pike	0	0.00	0.00	38.71
Edwards	0	0.00	0.00	95.85	Pope	0	0.00	0.00	227.91
Effingham	1	4.34	0.11	24.15	Pulaski	0	6.78	0.17	73.22
Fayette	0	0.00	0.00	29.35	Putnam	0	0.00	0.00	111.50
Ford	0	0.00	0.00	42.36	Randolph	0	0.00	0.00	18.98
Franklin	1	4.33	0.11	24.09	Richland	0	0.00	0.00	37.15
Fulton	1	4.95	0.12	27.56	Rock Island	2	2.04	0.25	7.37
Gallatin	0	0.00	0.00	111.50	St. Clair	4	2.16	0.59	5.53
Greene	0	0.00	0.00	43.92	Saline	3	19.57	4.04	57.08
Grundy	0	0.00	0.00	15.25	Sangamon	4	3.16	0.86	8.10
Hamilton	0	0.00	0.00	81.82	Schuyler	0	0.00	0.00	98.15
Hancock	0	0.00	0.00	33.24	Scott	0	0.00	0.00	118.67
Hardin	0	0.00	0.00	169.33	Shelby	1	8.23	0.20	45.77
Henderson	0	0.00	0.00	99.21	Stark	1	26.95	0.68	149.26
Henry	0	0.00	0.00	12.93	Stephenson	0	0.00	0.00	12.26
Iroquois	0	0.00	0.00	20.47	Tazewell	2	2.53	0.31	9.14
Jackson	0	0.00	0.00	11.10	Union	0	0.00	0.00	35.47
Jasper	0	0.00	0.00	66.12	Vermilion	2	3.46	0.42	12.51
Jefferson	0	0.00	0.00	51.61	Wabash	0	0.00	0.00	52.11
Jersey	0	0.00	0.00	31.09	Warren	0	0.00	0.00	35.38
JoDaviess	0	0.00	0.00	31.16	Washington	1	11.88	0.30	66.00
Johnson	1	14.95	0.38	83.00	Wayne	1	9.76	0.24	54.23
Kane	11	2.84	1.42	5.08	White	0	0.00	0.00	44.72
Kankakee	2	2.60	0.32	9.41	Whiteside	1	2.60	0.06	14.50
Kendall	1	2.24	0.06	12.48	Will	6	1.46	0.53	3.18
Knox	2	6.25	0.76	22.55	Williamson	1	2.80	0.07	15.60
Lake	10	1.90	0.91	3.48	Winnebago	5	2.52	0.82	5.88
LaSalle	3	4.24	0.87	12.37	Woodford	1	4.64	0.11	25.83
Lawrence	1	12.02	0.30	66.78					

[1] Per 10,000 live births
[2] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Table 11. Total number and incidence rates of reported cases of encephalocele, by maternal county of residence, 1998 – 2002

County	Cases	Rate[1]	95% CI[2] Lower	Upper	County	Cases	Rate[1]	95% CI[2] Lower	Upper
ILLINOIS	51	0.56	0.41	0.73	Lee	0	0.00	0.00	19.86
Adams	0	0.00	0.00	8.87	Livingston	0	0.00	0.00	14.97
Alexander	0	0.00	0.00	56.07	Logan	0	0.00	0.00	21.85
Bond	0	0.00	0.00	39.12	McDonough	0	0.00	0.00	24.83
Boone	0	0.00	0.00	12.35	McHenry	2	0.99	0.12	3.57
Brown	0	0.00	0.00	137.72	McLean	0	0.00	0.00	3.69
Bureau	2	9.52	1.16	34.34	Macon	2	2.69	0.33	9.72
Calhoun	0	0.00	0.00	145.32	Macoupin	0	0.00	0.00	13.35
Carroll	0	0.00	0.00	41.55	Madison	2	1.20	0.15	4.33
Cass	0	0.00	0.00	38.35	Marion	0	0.00	0.00	14.00
Champaign	0	0.00	0.00	3.31	Marshall	0	0.00	0.00	53.94
Christian	0	0.00	0.00	18.40	Mason	0	0.00	0.00	40.36
Clark	0	0.00	0.00	.38.59	Massac	0	0.00	0.00	38.75
Clay	0	0.00	0.00	40.23	Menard	0	0.00	0.00	54.91
Clinton	0	0.00	0.00	18.94	Mercer	0	0.00	0.00	38.75
Coles	0	0.00	0.00	12.44	Monroe	0	0.00	0.00	21.78
Cook	27	0.64	0.42	0.93	Montgomery	0	0.00	0.00	21.54
Crawford	0	0.00	0.00	34.38	Morgan	0	1.66	0.04	17.54
Cumberland	0	0.00	0.00	58.38	Moultrie	0	0.00	0.00	38.84
DeKalb	0	0.00	0.00	6.56	Ogle	0	0.00	0.00	12.18
DeWitt	0	0.00	0.00	35.41	Peoria	0	0.00	0.00	2.80
Douglas	0	0.00	0.00	24.94	Perry	0	0.00	0.00	30.19
DuPage	4	0.60	0.16	1.54	Piatt	0	0.00	0.00	42.75
Edgar	0	0.00	0.00	33.97	Pike	0	0.00	0.00	38.71
Edwards	0	0.00	0.00	95.85	Pope	0	0.00	0.00	227.91
Effingham	0	0.00	0.00	15.99	Pulaski	0	0.00	0.00	73.22
Fayette	0	0.00	0.00	29.35	Putnam	0	0.00	0.00	111.50
Ford	0	0.00	0.00	42.36	Randolph	0	0.00	0.00	18.98
Franklin	0	0.00	0.00	15.96	Richland	0	0.00	0.00	37.15
Fulton	0	0.00	0.00	18.25	Rock Island	0	0.00	0.00	3.76
Gallatin	0	0.00	0.00	111.50	St. Clair	0	0.00	0.00	2.00
Greene	0	0.00	0.00	43.92	Saline	0	0.00	0.00	24.04
Grundy	0	0.00	0.00	15.25	Sangamon	1	0.79	0.02	4.41
Hamilton	0	0.00	0.00	81.82	Schuyler	0	0.00	0.00	98.15
Hancock	0	0.00	0.00	33.24	Scott	0	0.00	0.00	118.67
Hardin	0	0.00	0.00	169.33	Shelby	0	0.00	0.00	30.31
Henderson	0	0.00	0.00	99.21	Stark	0	0.00	0.00	98.94
Henry	1	3.51	0.09	19.53	Stephenson	0	0.00	0.00	12.26
Iroquois	0	0.00	0.00	20.47	Tazewell	1	1.27	0.03	7.05
Jackson	0	0.00	0.00	11.10	Union	0	0.00	0.00	35.47
Jasper	0	0.00	0.00	66.12	Vermilion	0	0.00	0.00	6.38
Jefferson	0	0.00	0.00	15.61	Wabash	0	0.00	0.00	52.11
Jersey	0	0.00	0.00	31.09	Warren	0	0.00	0.00	35.38
JoDaviess	0	0.00	0.00	31.16	Washington	0	0.00	0.00	43.71
Johnson	0	0.00	0.00	54.98	Wayne	0	0.00	0.00	35.92
Kane	2	0.52	0.06	1.87	White	0	0.00	0.00	44.72
Kankakee	1	1.30	0.03	7.26	Whiteside	0	0.00	0.00	9.60
Kendall	1	2.24	0.06	12.48	Will	1	0.24	0.00	1.35
Knox	0	0.00	0.00	11.52	Williamson	0	0.00	0.00	10.32
Lake	2	0.38	0.04	1.37	Winnebago	2	1.01	0.12	3.64
LaSalle	0	0.00	0.00	5.21	Woodford	0	0.00	0.00	17.10
Lawrence	0	0.00	0.00	44.24					

[1] Per 10,000 live births
[2] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

RATES OF NEURAL TUBE DEFECTS BY DELIVERY FACTORS

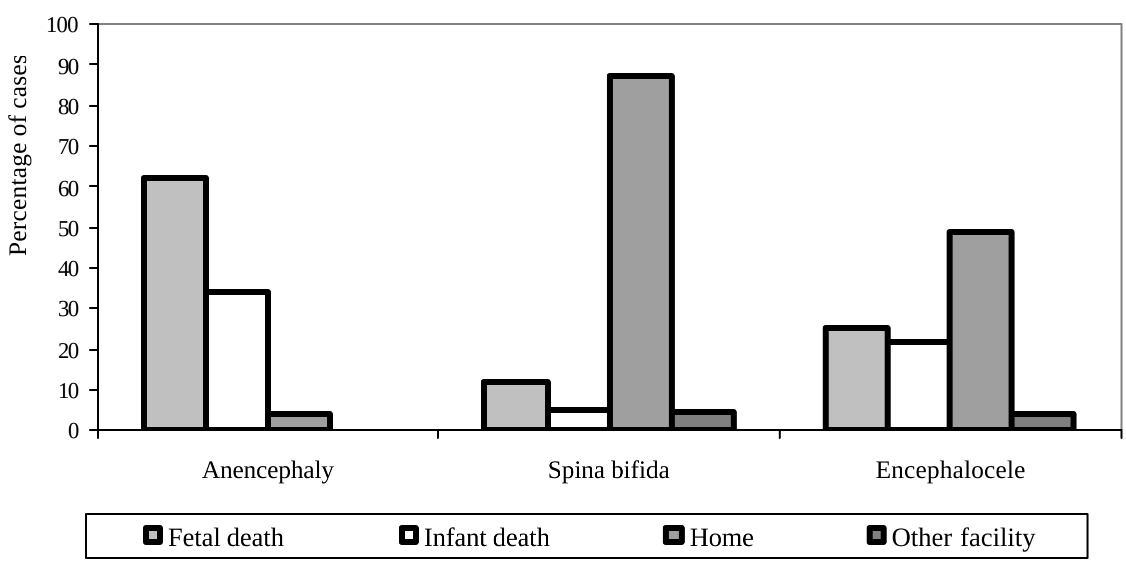
Birth Outcome
Many children with severe neural tube defects die before birth. Table 12 shows the birth outcomes for the NTD-affected children reported to the APORS program. Almost all children with anencephaly (96 percent) die before delivery (fetal deaths) or during the newborn stay (infant deaths). Those who survive to go home will die shortly thereafter. However, half the children with encephalocele and almost 80 percent of children with spina bifida survive to go home.

Table 12. Total numbe r and percentage of reported neural tube defects, by birth outcome, 1998-2002

	Anencephaly		Spina bifida		Encephalocele	
	N	%	N	%	N	%
Fetal death	93	62.0	29	12.0	13	25.5
Infant death	51	34.0	12	5.0	11	21.6
Home	6	4.0	190	78.5	25	49.0
Other facility	0	0.0	11	4.5	2	3.9
TOTAL	150	100.0	242	100.0	51	100.0

Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 6. Percentage of reported neural tube defect cases, by birth outcome, 1998-2002



Gestational Age
A woman pregnant with a child with severe birth defects is likely to deliver early. At the extreme, such a child may be miscarried before the mother realizes she is pregnant. The data available from APORS support this observation (Table 13). Almost 40 percent of children reported to APORS with anencephaly were delivered before the 25th week of

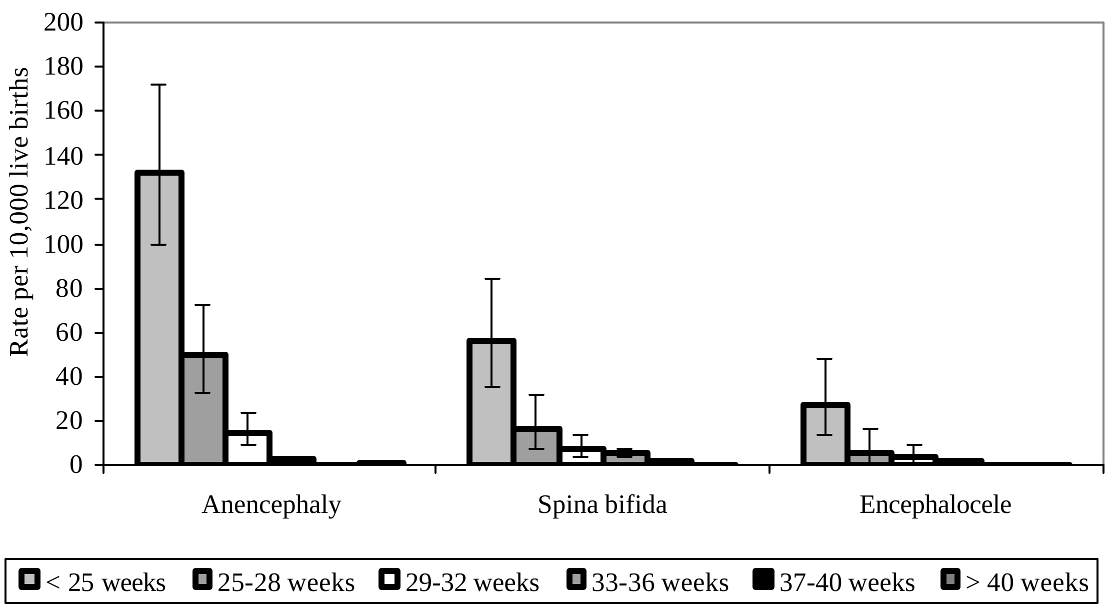
pregnancy, while almost 70 percent of children were delivered before the 33rd week of pregnancy. With encephalocele, 36.5 percent of these cases were delivered before the 33rd week of pregnancy. Spina bifida is the least severe of these neural tube defects; only 16.9 percent of these cases were delivered before the 33rd week of pregnancy.

Table 13. Total number[1] and incidence rates of reported neural tubes defects, by gestational age, 1998-2002

	Anencephaly			Spina bifida			Encephalocele		
	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]
<=24 weeks	54	131.93	(99.26, 171.79)	23	56.19	(35.65, 84.20)	11	26.88	(13.42, 48.03)
25-28	27	49.99	(32.97, 72.66)	9	16.66	(7.62, 31.61)	3	5.55	(1.15, 16.22)
29-32	18	14.86	(8.81, 23.47)	9	7.43	(3.40, 14.10)	5	4.13	(1.34, 9.63)
33-36	18	2.67	(1.58, 4.22)	38	5.63	(3.98, 7.72)	11	1.63	(0.81, 2.91)
37-40	17	0.23	(0.14, 0.37)	157	2.17	(1.84, 2.53)	17	0.23	(0.14, 0.37)
40+	12	1.27	(0.66, 2.22)	6	0.64	(0.23, 1.38)	4	0.42	(0.12, 1.08)

[1] Four cases of anencephaly had unknown gestational age.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 7. Incidence rates of reported neural tube defects, by gestational age, 1998-2002



Of the pregnancies delivered at less than 25 weeks, 22.5/10,000 live births were affected by a neural tube defect. Since APORS does not receive reports of birth defects prior to 20 weeks nor of elective abortions, this rate should really be higher. This table emphasizes the impact of missing case reports on the reported rates of neural tube defects.

Birth weight

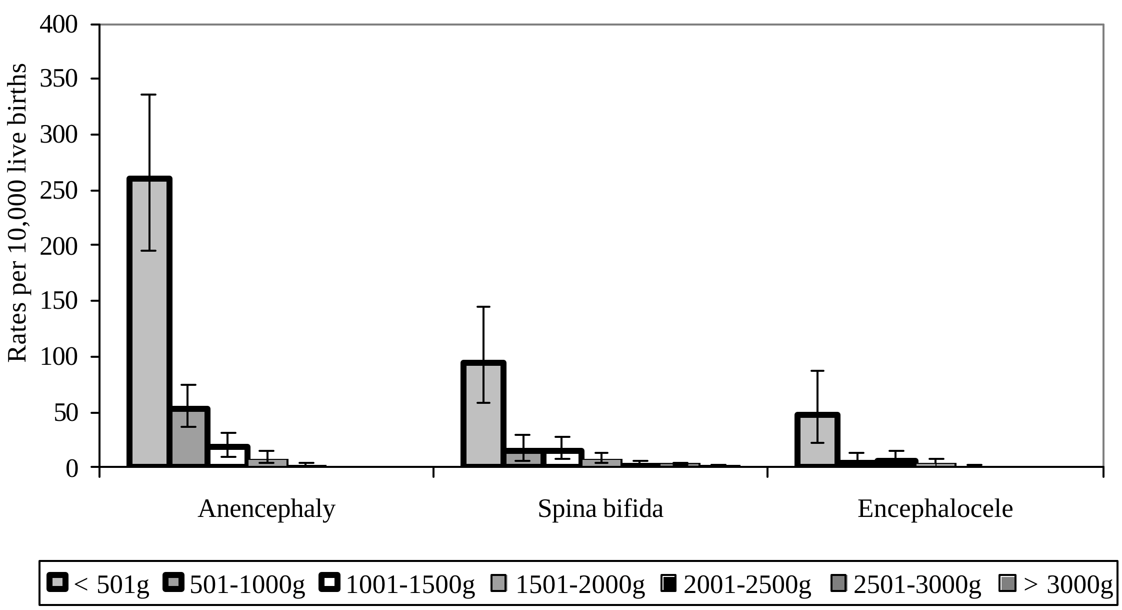
Birth weight is, of course, closely associated with gestational age. Table 14 demonstrates that there is a higher rate of neural tube defects among children delivered with low birth weights (40 percent of the children with birth weights less than 500g). This suggests that lethal neural tube defects are a likely cause of early miscarriage.

Table 14. Total number[1] and incidence rates of reported neural tubes defects by birth weight, 1998-2002

	Anencephaly			Spina bifida			Encephalocele		
Birth weight (g)	**N**	**Rate[2]**	**95% CI[3]**	**N**	**Rate[2]**	**95% CI[3]**	**N**	**Rate[2]**	**95% CI[3]**
< 500	55	259.68	(196.21, 336.68)	20	94.43	(57.77, 145.46)	10	47.21	(22.66, 86.66)
501-1000	31	53.19	(36.17, 75.41)	9	15.44	(7.06, 29.29)	2	3.43	(0.42, 12.39)
1001-1500	13	18.52	(9.86, 31.63)	11	15.66	(7.82, 28.01)	4	5.70	(1.56, 14.59)
1501-2000	12	8.26	(4.27, 14.42)	11	7.57	(3.78, 13.54)	5	3.44	(1.12, 8.03)
2001-2500	12	2.72	(1.41, 4.76)	16	3.63	(2.08, 5.90)	6	1.36	(0.50, 2.97)
2501-3000	11	0.72	(0.36, 1.29)	55	3.62	(2.73, 4.71)	13	0.86	(0.46, 1.46)
3001-3500	7	0.21	(0.08, 0.43)	69	2.04	(1.59, 2.58)	6	0.18	(0.06, 0.38)
3501-4000	2	0.08	(0.00, 0.27)	39	1.49	(1.06, 2.04)	3	0.11	(0.03, 0.34)
> 4000	0	0.00	(0.00, 0.41)	8	0.89	(0.39, 1.77)	0	0.00	(0.00, 0.41)

[1] Seven case of anencephaly, four of spina bifida and two of encephalocele had unknown gestational age.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 8. Incidence rates of reported neural tube defects, by birth weight (g), 1998-2002



Maternal age

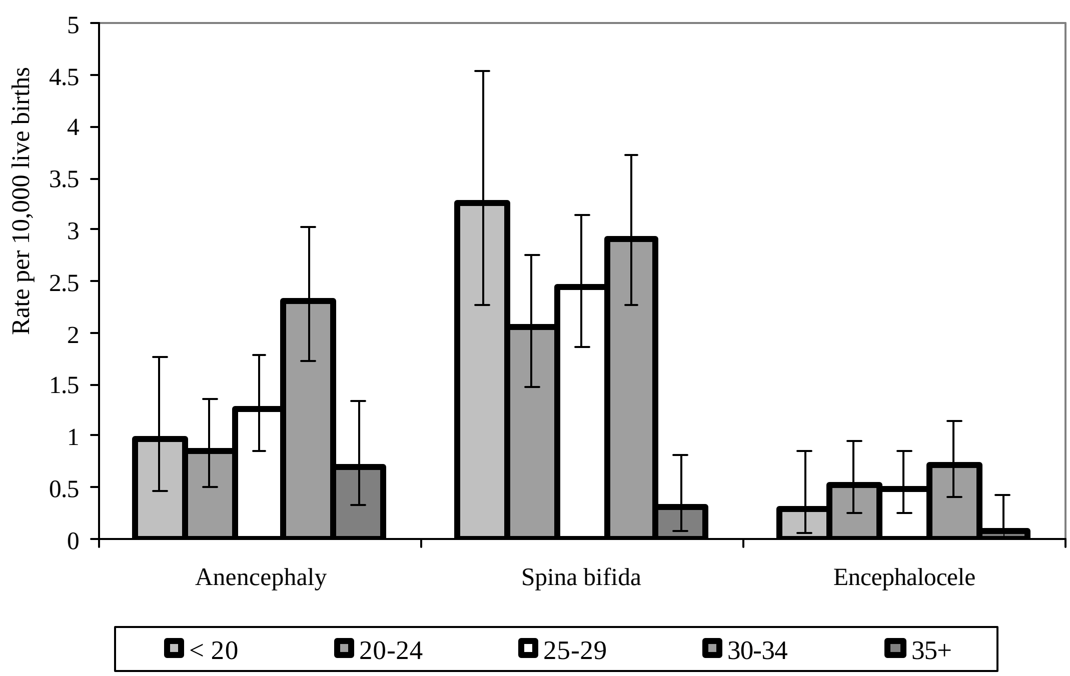
The literature reports associations between maternal age and the incidence of neural tube defects. Owens *et al.* and McDonnell *et al.* found that the incidence of NTD-affected pregnancies decreased with increasing maternal age. Hendricks *et al.*, and Whiteman *et al.* found a U-shaped distribution of neural tube defects. As presented in Table 15 and Figure 9, data in Illinois indicate the distribution depends on the type of neural tube defect. Anencephaly and encephalocele have a tendency towards an increasing incidence with maternal age while spina bifida appears to have the U-shaped distribution found by other authors.

Table 15. Total number[1] and incidence rates of reported neural tubes defects, by maternal age, 1998-2002

Maternal Age	Anencephaly N	Anencephaly Rate[2]	Anencephaly 95% CI[3]	Spina bifida N	Spina bifida Rate[2]	Spina bifida 95% CI[3]	Encephalocele N	Encephalocele Rate[2]	Encephalocele 95% CI[3]
< 20	10	0.96	(0.46, 1.76)	34	3.26	(2.26, 4.55)	3	0.29	(0.06, 0.85)
20-24	18	0.86	(0.51, 1.36)	43	2.05	(1.48, 2.76)	11	0.52	(0.26, 0.94)
25-29	31	1.26	(0.85, 1.79)	60	2.44	(1.87, 3.14)	12	0.49	(0.26, 0.86)
30-34	52	2.30	(1.72, 3.02)	66	2.92	(2.26, 3.72)	16	0.71	(0.41, 1.15)
35+	9	3.04	(2.17, 4.16)	4	3.04	(2.17, 4.16)	1	0.70	(0.32, 1.34)

[1] Thirty cases of anencephaly, 35 of spina bifida and eight of encephalocele had unknown maternal age.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 9. Incidence rates of reported neural tube defects, by maternal age, 1998 - 2002



Parity

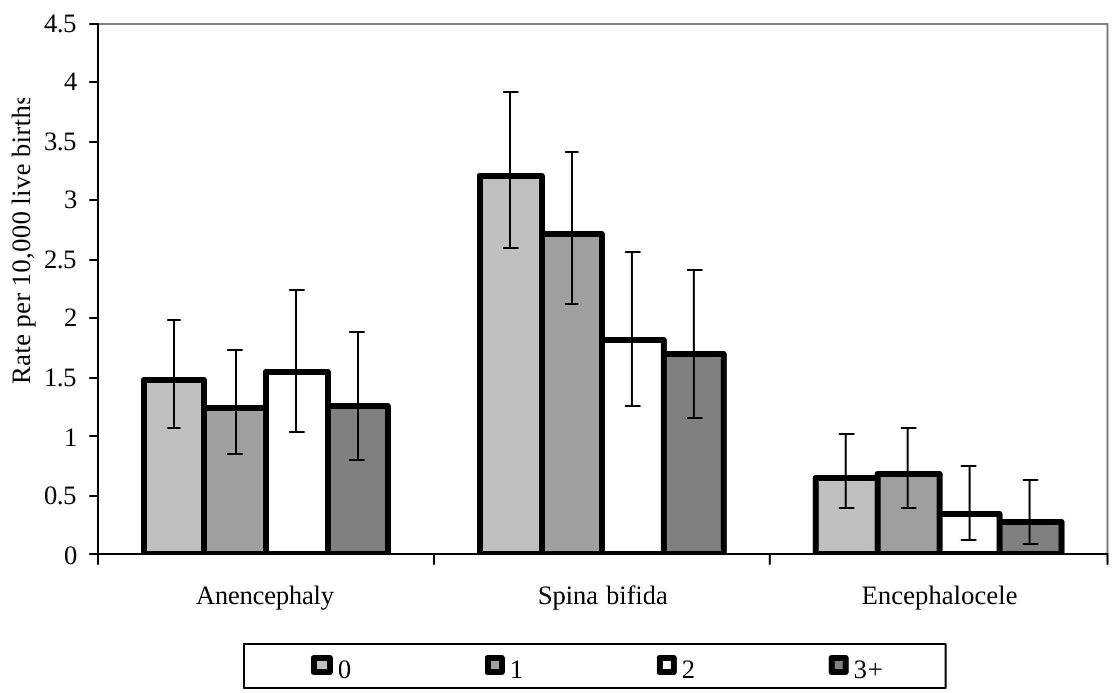
Parity is the number of pregnancies a woman has experienced prior to the one under consideration (in this report, a pregnancy producing a child with a neural tube defect). Vieira performed a meta-analysis looking at previous studies of the risk of neural tube defects with parity. This analysis found that pregnancies with higher parity were more likely to have a spina bifida defect than those with lower parity. This was not observed for anencephaly. This is in striking contrast to the Illinois data. APORS data indicate that the risk of spina bifida (and perhaps encephalocele) decreased with parity. No pattern was observed for anencephaly.

Table 16. Total number[1] and incidence rates of reported neural tube defects, by parity, 1998-2002

Parity	Anencephaly			Spina bifida			Encephalocele		
	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]
0	43	1.48	(1.07, 1.99)	93	3.20	(2.59, 3.92)	19	0.65	(0.39, 1.02)
1	33	1.24	(0.86, 1.74)	72	2.71	(2.12, 3.41)	18	0.68	(0.40, 1.07)
2	27	1.54	(1.01, 2.24)	32	1.82	(1.25, 2.57)	6	0.34	(0.13, 0.75)
3+	23	1.26	(0.80, 1.89)	31	1.70	(1.15, 2.41)	5	0.27	(0.09, 0.64)

[1] Twenty-four cases of anencephaly, 14 of spina bifida and three of encephalocele had unknown parity information.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 10. Incidence rates of reported neural tube defects, by parity, 1998-2002



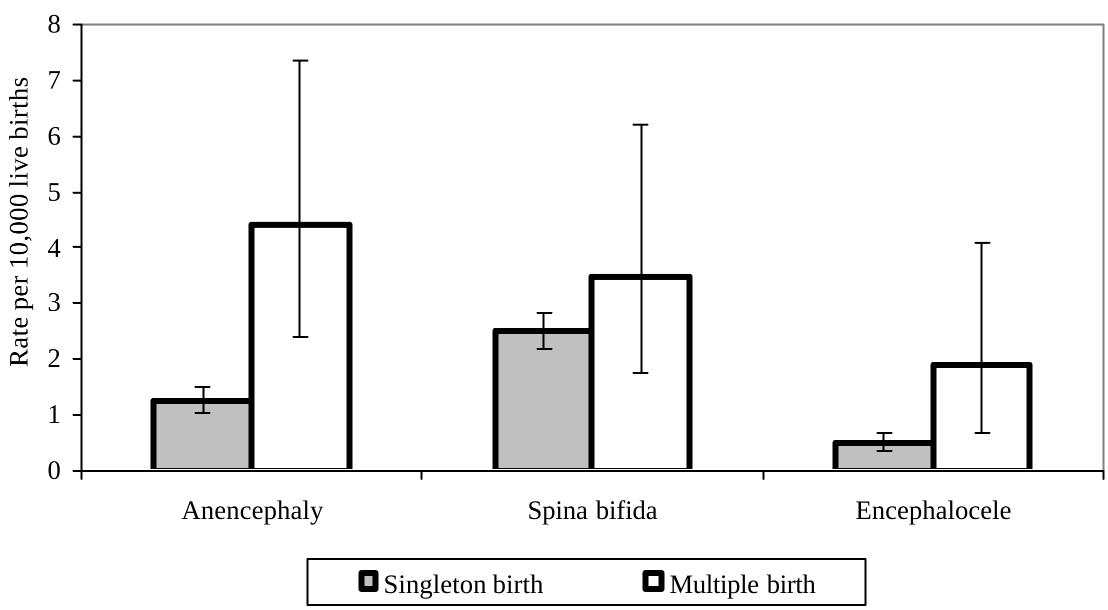
Multiple births (plurality)
Plurality is the number of children delivered from an NTD-affected pregnancy. Owens *et al.*, Whiteman *et al.* and others have reported that members of multiple births are more likely to be affected by a neural tube defect. Illinois data reflect the same pattern with twins or higher plurality pregnancies having higher incidence rates of neural tube defects.

Table 17. Total number[1] and incidence rates of reported neural tube defects, by plurality, 1998-2002

Plurality	Anencephaly			Spina bifida			Encephalocele		
	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]	N	Rate[2]	95% CI[3]
Singleton birth	109	1.24	(1.02, 1.49)	220	2.49	(2.18, 2.84)	43	0.49	(0.35, 0.65)
Multiple birth	14	4.40	(2.40, 7.38)	11	3.46	(1.73, 6.19)	6	1.89	(0.68, 4.10)

[1] Twenty-seven cases of anencephaly, 11 of spina bifida and two of encephalocele had unknown plurality information.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 12. Incidence rates of reported neural tube defects, by plurality, 1998-2002



Seasonality
Castilla *et al*. examined three sets of data from different parts of the world to determine whether there was any seasonality effect on the number of birth defects, including anencephaly and spina bifida. The only borderline significant seasonal variation in neural tube defects was found for anencephaly in Italy. Bound *et al.* (1989) looked at seasonal variation in a single area and found an increase in cases of neural tube defects conceived from May to November. In order to examine this in Illinois data, for NTD pregnancies the conception date was estimated by the delivery date minus the gestational age. It is important to use the conception date since neural tube defects develop in the few weeks

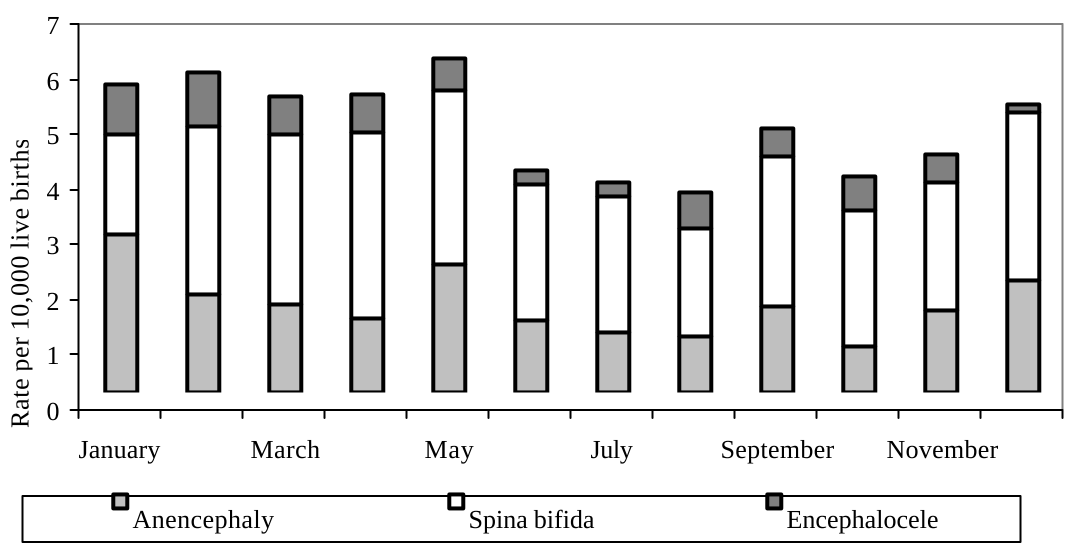
after conception. The population conception dates were estimated by the delivery date minus 9 months (the expected gestational age was used since individual information was not available). Illinois data showed a contrasting decrease in neural tube defect cases conceived between May and November.

Table 17. Total number[1] and incidence rates of reported neural tubes defects, by month of conception, 1998-2002

Month of conception	Anencephaly			Spina bifida			Encephalocele		
	N	Rate[1]	95% CI[2]	N	Rate[1]	95% CI[2]	N	Rate[1]	95% CI[2]
January	22	2.86	(1.79, 4.34)	14	1.82	(0.99, 3.06)	7	0.91	(0.37, 1.88)
February	13	1.79	(0.96, 3.07)	22	3.03	(1.90, 4.60)	7	0.97	(0.39, 1.99)
March	12	1.61	(0.83, 2.81)	23	3.08	(1.95, 4.62)	5	0.67	(0.22, 1.56)
April	10	1.35	(0.64, 2.48)	25	3.37	(2.18, 4.97)	5	0.67	(0.22, 1.57)
May	16	2.31	(1.32, 3.74)	22	3.17	(1.98, 4.80)	4	0.58	(0.16, 1.48)
June	10	1.30	(0.62, 2.40)	19	2.48	(1.50, 3.87)	2	0.26	(0.03, 0.94)
July	8	1.09	(0.47, 2.16)	18	2.46	(1.45, 3.88)	2	0.27	(0.03, 0.98)
August	8	1.03	(0.45, 2.04)	15	1.94	(1.09, 3.88)	5	0.65	(0.21, 1.51)
September	12	1.56	(0.81, 2.72)	21	2.72	(1.68, 4.17)	4	0.52	(0.14, 1.32)
October	7	0.85	(0.34, 1.77)	20	2.44	(1.49, 3.77)	5	0.61	(0.20, 1.43)
November	12	1.48	(0.77, 2.58)	19	2.34	(1.41, 3.65)	4	0.49	(0.13, 1.26)
December	16	2.03	(1.16, 3.30)	24	3.05	(1.96, 4.54)	1	0.13	(0.00, 0.70)

[1] Four cases of anencephaly had unknown gestational age, and so unknown month of conception.
[2] Rate per 10,000 live births
[3] 95% confidence interval for rate
Source: Illinois Department of Public Health, Adverse Pregnancy Outcomes Reporting System, March 2004

Figure 12. Incidence rates of reported neural tubes defects, by month of conception, 1998-2002



REFERENCES

Armitage P. and Berry G. *Statistical Methods in Medical Research*, Second Edition. 1987. Blackwell Scientific Publications.

Arpino C., Brescianini S., Robert E., Castilla E.E., Cocchi G., Cornel M.C., de Vigan C., Lancaster P.A.L., Merlob P., Sumiyoshi Y., Zampino G., Renzi C., Rosano A., Mastroiacovo P. Teratogenic effects of antiepileptic drugs: use of an international database on malformations and drug exposure (MADRE). *Epilepsia* 2000; **41(11)**:1436-1443.

Bound J.P., Harvey P.W., Francis B.J. Seasonal Prevalence of Major Congenital Malformations in the Fylde of Lancashire 1957-1981. *Journal of Epidemiology and Community Health*. 1989; **43(4):** 330-342.

Bound J.P., Harvey P.W., Francis B.J., Awwad F., Gatrell A.C. *Archives of Disease in Childhood* 1997; **76**: 107-112.

Carmichael S.L., Shaw G.M. Maternal Life Event Stress and Congenital Anomalies. *Epidemiology* 2000; **11(1):** 30-35.

Castilla E.E., Orioli I.M., Lugarinho R., Dutra G.P., Lopez-Camelo J.S., Campana H.E., Spagnolo A., Mastroiacovo P. Monthly and seasonal variations in the frequency of congenital anomalies. *International Journal of Epidemiology*. 1990; **19(2):** 399-404.

Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *Morbidity and Mortality Weekly Review* 1992; **41(No. RR-14)**:1-7.

Cordier S., Bergeret A., Goujard J., Ha M.C., Aymé S., Bianchi F., Calzolari E., De Walle H.E., Knill-Jones R., Candela S., Dale I., Dananché B., de Vigan C., Fevotte J., Kiel G., Mandereau L. Congenital malformation and maternal occupational exposure to glycol ethers. Occupational Exposure and Congenital Malformations Working Group. *Epidemiology* 1997; **8(4)**: 355-363.

Correa A., Stolley A., Liu Y. Prenatal tea consumption and risks of anencephaly and spina bifida. *Annals of Epidemiology* 2000; **10(7)**: 476-477.

Cragan J.D., Robert H.E., Edmonds L.D., Khoury MJ, Kirby RS, Shaw GM, Velie EM, Merz RD, Forrester MB, Williamson RA, Krishnamurti DS, Stevenson RE, Dean JH. Surveillance for Anencephaly and Spina Bifida and the Impact of prenatal diagnosis – United States, 1985-1994. *Morbidity and Mortality Weekly Review* 1995; **44/No SS04;001**.

Czeizel A.E., Rockenbauer M.. A population-based case-control teratologic study or ora;l oxytetracycline treatement during pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2000; **88(1)**: 27-33.

Davies B.R., Duran M. Malformations of the cranium, vertebral colum, and related central nervous system: morphologic heterogeneity may indicate biological diversity. *Birth Defects Research. Part A, Clinical and molecular teratology.* 2003; **67(8)**: 563-571.

Dolk H., Vrijheid M., Armstrong B., Abramsky L., Bianchi F., Garne E., Nelen V., Robert E., Scott J.E., Stone D., Tenconi R. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. *Lancet* 1998; **352(9126)**: 423-427.

Forrester M.B., Merz, R.D. Inclusion of Early Fetal Deaths in a Birth Defects Surveillance System. *Teratology* 2001. 64 (Supplement 1): S20-S25.

Forrester M.B., Merz R.D., Yoon P.W. Impact of Prenatal Diagnosis and Elective Termination on the Prevalence of Selected Birth Defects in Hawaii. *American Journal of Epidemiology* 1998; **148(12):** 1206-1211.

Frey L., Hauser W.A. Epidemiology of Neural Tube Defects. *Epilepsia* 2003; **44(Suppl. 3)**: 4-13.

Hendricks K.A., Simpson J.S., Larsen R.D. Neural Tube Defects along the Texas-Mexico Border, 1993-1995. *American Journal of Epidemiology* 1999; **149(12)**: 1119-1127.

Illinois Department of Public Health http://www.idph.state.il.us//health/abortion/Abortion73-01.htm

Janssen P.A., Rothman I., Schwartz S.M. Congential malformations in newborns of women with established and gestational diabetes in Washington State, 1984-91. *Paediatric and Perinatal Epidemiology* 1996; **10(1)**: 52-63.

Klotz J.B., Pyrch L.A. Neural tube defects and drinking water disinfection by-products. *Epidemiology* 1999; **10(4)**: 383-390.

Kristensen P., Irgens L.M., Andersen A., Bye A.S., Sundheim L. Birth defects among offspring of Norwegian farmers, 1967-1991. *Epidemiology* 1997; **8(5)**: 537-44.

Lary J.M., Paulozzi L.J. Sex differences in the prevalence of human birth defects: a population-based study. *Teratology* 2001; **64(5)**: 237-51.

Little L., Elwood J.M. *Epidemiology of Neural Tube Defects. Reproductive and Perinatal Epidemiology.* Kiley M., Ed. 1991. CRC Press, Boston.

McDonnell R.J., Johnson Z., Delaney V., Dack P. East Ireland 1980-1994: Epidemiology of Neural Tube Defects. *Journal of Epidemiology and Community Health.* 1999; **53(12)**: 782-788.

Milunsky A., Ulcickas M., Rothman K.J., Willett W., Jick S.S., Jick H. Maternal heat exposure and neural tube defects. *Journal of the American Medical Association*1992; **268(7)**: 882-885.

MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991; **338**:131-7.

Owen T.J., Halliday J.L., Stone C.A. Neural Tube Defects in Victoria, Australia: Potential Contributing Factors and Public Health Implications. *Australian & New Zealand Journal of Public Health* 2001; **24(6)**: 584-589.

Shaw G.M., Nelson V., Iovannisci D.M., Finnell R.H., Lammer E.J. Maternal occupational chemical exposures and biotransformation genotypes as risk factors for selected congenital anomalies. *American Journal of Epidemiology* 2003; **157(6)**: 475-484.

Shaw G.M., Todoroff K., Velie E.M., Lammer E.J. Maternal illness, including fever and medication use as risk factors for neural tube defects. *Teratology* 1998; **57(1)**: 1-7.

Suarez L., Cardarelli K., Hendricks K. Maternal stress, social support, and risk of neural tube defects among Mexican Americans. *Epidemiology* 2003; **14(5)**: 612-616.

Trust for America's Health. *Birth defects tracking and prevention: too many states are not making the grade.* February 2002. http://healthyamericans.org/state/birthdefects/

Vieira A.R. Birth Order and Neural Tube Defects: A Reappraisal. *Journal of the Neurological Sciences* 2004; **217(1)**: 65-72.

Watkins M.L. Efficacy of folic acid prophylaxis for the prevention of neural tube defects. *Mental Retardation and Developmental Disabilities Research Reviews* 1998; **4**: 282-290.

Watkins M.L., Rasmussen S.A., Honein M.A., Botto L.D., Moore C.A. Maternal obesity and risk for birth defects. *Pediatrics* 2003; **111(5) Part 2**: 1152-8.

Whiteman D., Murphy M., Hey K., O'Donnell M., Goldacre M. Reproductive factors, subfertility and risk of neural tube defects: a case-control study based on the Oxford Record Linkage Study Register. *American Journal of Epidemiology* 2000; **152(9)**: 823-828.