Published in final edited form as:
Birth Defects Res A Clin Mol Teratol. 2006 October ; 76(10): 718–722. doi:10.1002/bdra.20313.

A Potential Association Between Infertility and Spinal Neural Tube Defects in Offspring

Yvonne W. Wu[a], **Lisa A. Croen**[b], **Louis Henning**[c], **Daniel V. Najjar**[d], **Michael Schembri**[e], and **Mary S. Croughan**[f]

[a]Department of Neurology, Pediatrics, University of California, San Francisco, CA

[b]Department of Kaiser Permanente Division of Research, Oakland, CA

[c]Department of Neurology, Obstetrics, University of California, San Francisco, CA

[d]Department of Kaiser Permanente Division of Research, Oakland, CA

[e]Department of Gynecology and Reproductive Sciences, University of California, San Francisco, CA

[f]Department of Gynecology and Reproductive Sciences and Epidemiology and Biostatistics, University of California, San Francisco, CA

Abstract

Background—To examine the possible association between infertility and spinal neural tube defects.

Methods—This is a nested case-control study within the Kaiser Permanente Medical Care Program (KPMCP) in northern California. Among a birth cohort of 110,624 singleton infants ≥36 weeks gestation, 1994–1997, we electronically identified cases of spinal neural tube defects and confirmed the diagnosis by chart review. Controls (n = 1608) were randomly selected from the birth population. History of infertility was defined as: 1) physician diagnosis of infertility; 2) prescription for an infertility medication noted in the KPMCP pharmacy; and/or 3) evaluation at one of 15 infertility clinics in northern California.

Results—Eighteen infants diagnosed with spinal neural tube defects (prevalence 1.6/10,000) included 13 with spina bifida cystica and 5 with spina bifida occulta. Case mothers were more likely to have a history of infertility (4/18 vs. 96/1608, OR 4.3, 95% CI 1.01–14.0), and to have been prescribed clomiphene citrate within the window spanning 60 days before to 15 days after conception (3/18 vs. 32/1608, OR 11.7, 95% CI 2.0–44.8).

Conclusions—This exploratory study suggests that infertility may be associated with an increased risk of spinal neural tube defects among liveborn, term infants.

Introduction

Since the 1960s, clomiphene citrate has been used for ovulation induction in the treatment of infertility. The possibility that infertility and clomiphene citrate might increase the risk of neural tube defects (NTD) was raised in the 1970s when several case reports suggested a

Corresponding Author: Yvonne Wu, MD, MPH UCSF Dept. of Child Neurology, Box 0137 350 Parnassus Ave, Suite 609 San Francisco, CA 94143-0137 wuy@neuropeds.ucsf.edu.

The authors have no conflicts of interest to report, financial or otherwise.

Presented at the 17th annual Society for Pediatric Research, May 2005, Wash DC, and at the 34th annual Child Neurology Society meeting, September 2005, Los Angeles.

possible association (Ahlgren and others, 1976; Dyson and Kohler, 1973; Field and Kerr, 1974; Singh and Singhi, 1978; Ylikorkala, 1975). Subsequently, studies in Europe, Australia and the United States provided conflicting results (Cornel and others, 1989; Cuckle and Wald, 1989; Lancaster, 1987; Mills and others, 1990; Robert and others, 1991; Whiteman and others, 2000), and a pooled analysis of all studies performed prior to 1995 concluded that the existing data were "insufficient to either confirm or refute an effect of clomiphene citrate on neural tube defect risk." (Greenland and Ackerman, 1995) Recently, in the largest case-control study reported to date, investigators found an odds ratio (OR) of 2.1 (95% CI 1.0–4.5) for clomiphene citrate and NTDs.(Medveczky and others, 2004) Thus, whether or not infertility or clomiphene citrate increase the risk of NTDs remains unclear.

Given the possible association between infertility, clomiphene citrate and NTDs, we combined data from two existing studies of cerebral palsy (Wu and others, 2003) and infertility outcomes (Croughan and others, 2004) being conducted in the same patient population. Among a live-birth cohort of singleton term and near-term infants, we explored whether infertility and infertility treatment are associated with an increased risk of NTDs involving the spine.

Materials and Methods

This case-control study is nested within the cohort of all singleton term and near-term (≥ 36 weeks gestation) infants born between January 1, 1994 and December 31, 1997 at the Kaiser Permanente Medical Care Program (KPMCP), a large managed care organization that provides care for over 30% of the population in Northern California. The members of KPMCP are demographically similar to the California population, except that the very poor and very wealthy are under-represented (Krieger, 1992). During the years of study, Kaiser covered all costs related to evaluation, diagnoses, monitoring, and pharmacologic treatment of infertility, excluding in vitro fertilization. All study procedures were approved by the Institutional Review Boards at KPMCP and at the University of California, San Francisco.

Case Ascertainment

This study is an extension of an on-going case-control study of cerebral palsy performed within the same study population (Wu et al., 2003). We had previously identified infants with spinal NTDs by searching KPMCP electronic clinical databases for infants who were given an inpatient or outpatient physician diagnosis of spina bifida (ICD9-CM 741)(1999), other spinal cord anomalies (ICD9-CM 742.5), or spinocerebellar disease (ICD9-CM 334) prior to June 30, 2004. Exclusion criteria included a physician diagnosis of cerebral palsy (ICD9-CM(1999) 343.0–343.9, 342.1, 342.8, 342.9, 344.0, 344.1, 344.30–344.32, and 344.5), genetic disease (ICD9-CM 237.7x, 277.2, 277.5, 333.6, 755.55, 759.5, 759.81), chromosomal abnormalities (ICD9-CM 758.x), arthrogryposis (ICD9-CM 754.59) or muscle disease (ICD9-CM 335.x, 358.x, 359.x).

For the current study, a child neurologist (YW) who was blinded to information regarding infertility reviewed the medical records of all children with a spinal diagnosis to confirm the presence of a spinal NTD. A spinal NTD was defined as a spinal anomaly resulting from a defect in neurulation including spina bifida cystica (myelomeningocele or meningocele) and spina bifida occulta (intraspinal lipoma with tethered cord or dermal sinus tract) (Barkovich, 2000). We excluded infants with the following diagnoses who had no evidence of a NTD on chart review: cerebellar anomaly or ataxia (N = 17), vertebral bony abnormality (N = 4), syringomyelia (N = 2), dermoid cyst or cystic hygroma that physically resembled a myelomeningocele (N = 2), sacral dimple (N = 1), or no spinal abnormality (N = 5).

Control Ascertainment

As part of our ongoing study of cerebral palsy(Wu et al., 2003), we had selected a random sample of 1,608 (4:1 controls to cases) singleton, ≥ 36 weeks gestation infants born in the years 1994–97 who did not have a diagnosis of spinal cord abnormalities, cerebral palsy (ICD9-CM(1999) 343.0–343.9, 342.1, 342.8, 342.9, 344.0, 344.1, 344.30-344.32, and 344.5), genetic disease (ICD9-CM 237.7x, 277.2, 277.5, 333.6, 755.55, 759.5, 759.81), chromosomal abnormalities (ICD9-CM 758.x), arthrogryposis (ICD9-CM 754.59) or muscle disease (ICD9-CM 335.x, 358.x, 359.x). These infants constituted the control group in the current study.

Exposure data. For all case and control study subjects, the following demographic data were retrieved from KPMCP electronic data sources: date of birth, maternal age at delivery, maternal ethnicity, gender of infant, gestational age and birth weight. The date of conception was estimated as the birth date – (gestational age × 7). Due to the relative imprecision in determinations of gestational age and date of conception, we defined the periconception window as spanning from 60 days before to 15 days after conception. Infertility data were derived from: 1) infertility diagnoses within KPMCP; 2) infertility drug prescriptions identified in the KPMCP pharmacy database; and 3) 15 infertility clinics located throughout California. Details of each of these data sources are provided below.

We identified infertility diagnoses given to case and control women by electronically searching all inpatient and outpatient diagnoses during the years 1993–1998 within KPMCP. A previous diagnosis of female infertility was considered to be present if any of the following diagnoses (ICD-9 CM code)(1999) were present prior to delivery: congenital adrenal hyperplasia (255.2); diminished or decreased ovarian reserve (256.39); ovulatory dysfunction (256.9); pelvic adhesions (614.6); intrauterine adhesions (621.5); female infertility (628); anovulation (628.0); tubal disease (628.2); congenital uterine anomaly (628.3); hostile cervical mucus (628.4); female infertility NEC (328.8); female infertility NOS (628.9); habitual aborter (646.31 and 646.33); or pregnancy with history of infertility (V23.0).

Prescribed drugs are recorded in an electronic database within KPMCP, along with the date that the prescription was picked up by the patient, and the total number of days' supply that was provided. We electronically searched for the following text strings to indicate an infertility drug prescription prior to delivery: clomiphene, clomid, serophene, humegon, pergonal, repronex, metrodin, fertinex, follistim, gonal-f, chorionic, gonadotropin, hCG, humanchorionic, novarel, pregnyl, profasi, progesterone, crinone, prometrium, factrel, GNRH pump, and lutrepulse. Medroxyprogesterone was not included as an infertility drug, and progesterone was considered an infertility drug only if taken within 60 days after conception for pregnancy support.

In order to identify case and control mothers who might have received infertility evaluations outside of Kaiser, we determined whether our study subjects had been identified in a separate study of infertility and neurodevelopmental outcomes (Croughan et al., 2004). By linking our study subjects to this larger infertility dataset that included information from 11 non-Kaiser infertility clinics throughout the northern California region, we were able to identify women in our study who received infertility evaluations and treatment outside of the Kaiser facilities during the study years. The 11 non-Kaiser infertility clinics represent 92% (11/12) of the clinics providing IVF services in the study catchment area at that time

If a mother was identified as having prior infertility from any of the three sources outlined above (KPMCP diagnoses, infertility drug prescription, or non-Kaiser infertility clinic visit), the woman was considered to have had a history of infertility. Although we do not have data

regarding duration of prenatal coverage for the women in the current study, women who were not covered in Kaiser during pregnancy, but who were in the Northern California region, would have been very likely to receive infertility care in one of the area's 11 other infertility clinics.

We considered a woman to have conceived during infertility treatment if an infertility drug prescribed for the mother was picked up from the pharmacy within the periconception window. If the pick-up date fell outside of the periconception window, but the woman was given enough medication to allow her to utilize this prescription into the periconception window, we also considered the woman to have conceived during infertility treatment. Although we lacked data regarding the actual dates that infertility medications were taken, we considered the fifth day after clomiphene citrate was picked up from the pharmacy to be the final day of clomiphene citrate use, as a conservative estimate of the proximity of clomiphene use to date of conception.

Data analysis

We estimated relative risks with univariate odds ratios (OR) and 95% confidence intervals (95% CI) using the exact method (2000), and used a t-test to compare means of continuous variables. We calculated multivariable odds ratios by performing a logistic regression that included potentially confounding demographic variables. Given the small number of cases, only one potential confounder could be included in each model. Our study had 80% power to detect an OR of 6.7 for infertility and spinal neural tube defects, and 80% power to detect an OR of 12.9 for clomiphene citrate use, given a two-tailed alpha of 0.05.

Results

Of 110,624 infants in the study population, we electronically identified 49 infants who were given one of three spine abnormality diagnoses suggesting a possible NTD. Chart review confirmed the presence of a spinal NTD in 18 children, resulting in a prevalence of 1.6 per 10,000 live births. Specific abnormalities included myelomeningocele (N = 11), meningocele (N = 2), and spina bifida occulta (N = 5). All infants with spina bifida occulta demonstrated cutaneous abnormalities in the sacral region, as well as at least one of the following: intraspinal lipoma with tethered cord (N = 4), dermal sinus tract (N = 2), or diastematomyelia (N = 1). Of the 13 myelomeningoceles and meningoceles, 10 were located in the lumbosacral region and three lesions were in the cervical region. All cases involved a lumbosacral cutaenous abnormality that was noted at birth, with the exception of one infant with a sacral dimple and capillary hemangioma who did not come to medical attention until 10 months of age when the cutateous lesion began to grow.

Six percent of the control population had a history of infertility prior to the index delivery. Of those with a history of infertility, 88% received an infertility diagnosis within KPMCP and 41% received an infertility medication prior to delivery. Only 28% had been evaluated at an infertility clinic either within or outside of KPMCP, suggesting that the majority of mothers with infertility were treated by their KPMCP primary physicians and not at a designated infertility clinic.

Infants with spinal NTDs did not differ from control infants in gender, maternal age at delivery, maternal race, gestational age or birth weight (Table 1). There was also no significant difference between the groups as to whether infertility treatment was received within or outside of Kaiser (P = 0.79). However, mothers of case infants were more likely to have had a history of infertility prior to delivery (22% vs. 6%, P = 0.02), and to have received infertility medications prior to delivery (22% vs. 3%, P = 0.001) (Table 1). A periconceptional prescription of clomiphene citrate also was more common in case mothers

than in control mothers (17% vs. 2%, P = 0.004). Of the three infants with spinal NTDs whose mothers had received clomiphene citrate during the periconceptional window, two had a myelomeningocele and one had a dermal sinus tract with cutaneous sacral abnormalities. None of the cases, and only one mother in the control group, received in vitro fertilization.

The small number of cases could not support complex multivariable modeling. However, using logistic regression analysis, we found that the association between history of infertility and spinal NTDs persisted after single-variable adjustment for maternal race (OR 4.3, 95% CI 1.4–13.6), maternal age (OR 5.2, 95% CI 1.6–17.0), and infant gender (OR 4.3, CI 1.4–13.3). Having received a periconceptional prescription for clomiphene citrate also was significantly associated with an increased risk for spinal NTDs after adjusting for maternal race (OR 12.4, 95% CI 3.3–46.6).

Six mothers did not have any record of infertility medications or diagnoses within Kaiser, and received infertility care outside of Kaiser only. All these mothers are in the control group. We do not have detailed information regarding the infertility medications given to these 6 women. However, even if all 6 women conceived while taking clomiphene citrate, the OR of periconceptional clomiphene citrate exposure for NTD would still be very significant (OR 9.5, 95% CI 2.6–34.5).

Among women who did not take periconceptional clomiphene citrate, a history of infertility was not associated with spinal NTDs (OR 1.5, 95% CI 0.03–10.0), although this analysis was limited by the small sample size and inadequate power. We were unable to analyze the effects of infertility medications other than clomiphene citrate given that only three women received other treatments. None of the women who conceived an infant with a spinal NTD during treatment with clomiphene took other infertility medications.

Most (80%) women who received clomiphene citrate in the periconception window received more than one course of the medication over the previous year (mean 2.9, range 1–8 courses of medication). The number of clomiphene citrate courses prescribed in the 12 months prior to conception was higher among mothers of infants with NTDs than control mothers (mean 5.7 vs. 2.6 courses, P = 0.01).

We do not have information on women who had a prenatal diagnosis and then terminated their pregnancy. Each of the four infertile mothers with affected infants received a prenatal ultrasound, and only one resulted in a prenatal diagnosis of a neural tube defect. Two infants who were born to mothers with infertility had a dermal sinus tract which is difficult to diagnose on prenatal ultrasound.

Discussion

Neural tube defects affect approximately 400,000 infants worldwide each year (Rieder, 1994), and as a group represent the second most common congenital anomaly in the United States. The pathogenesis of NTDs is multifactorial, involving both environmental risk factors such as folate deficiency (Czeizel and Dudas, 1992) and in-utero exposure to valproate (Medveczky et al., 2004; Nau, 1994), as well as genetic risk factors (Kirke et al., 2004; van der Put et al., 1997). Our findings suggest that among singleton infants born alive at term, both a history of infertility and prescription of clomiphene citrate in the periconceptional period may be associated with an increased risk of spinal NTDs.

This exploratory study has a number of limitations. Most importantly, neural tube defects are a rare entity, and the small number of cases (N = 3) associated with clomiphene citrate raises the possibility that our findings may be particularly susceptible to confounding or

other factors that could lead to bias. Thus, our results will require confirmation in larger studies. For example, we did not include cases of NTDs that were aborted or that led to a stillbirth. If mothers with a history of infertility were less likely to terminate a pregnancy complicated by a prenatal diagnosis of NTD, then there would be preferential ascertainment of NTDs among mothers with infertility which could explain the association we found. Furthermore, owing to the small number of cases, we could not determine whether clomiphene citrate or the underlying infertility was responsible for the observed increased risk of spinal NTDs. Furthermore, we could not determine actual dates of clomiphene citrate use, only the date when medication was picked up from the pharmacy. Whether the observed associations could be attributed to unmeasured confounders or other risk factors, such as folate deficiency, obesity, (Shaw et al., 2000) anticonvulsant use, diabetes, or genetic risk factors such as the thermolabile variant of methylenetetrahydrofolate (MTHFR) (Kirke et al., 2004; van der Put et al., 1997), was not addressed in this study.

Despite these limitations, our study has several strengths including the large representative population from counties served by KPMCP, the comprehensive data available regarding infertility, and the minimization of recall bias through the use of medical record review. We report the largest effect size to date for clomiphene citrate and NTDs, suggesting that this potential association deserves further study.

Despite early reports linking clomiphene citrate and NTDs (Cornel et al., 1989; Lancaster, 1987; Robert et al., 1991), the majority of research has not supported this association (Cuckle and Wald, 1989; Czeizel, 1989; Dhont et al., 1999; Greenland and Ackerman, 1995; Kurachi et al., 1983; Lammer, 1995; Mills et al., 1990; Stromberg et al., 2002; Werler et al., 1994; Whiteman et al., 2000). A meta-analysis performed in 1995 found that studies performed in Europe, which together supported the association between clomiphene citrate and NTDs, uniformly analyzed the *periconceptional* use of clomiphene citrate (Greenland and Ackerman, 1995). In contrast, other studies either included clomiphene citrate use in the 6–12 months prior to conception (Lammer, 1995; Mills et al., 1990; Werler et al., 1994), or did not specify the timing of the medication (Kurachi et al., 1983; Medveczky et al., 2004; Whiteman et al., 2000). Our preliminary finding of an association between periconceptional clomiphene citrate use and spinal NTDs supports the results from studies using a similar definition of exposure, although it can not be determined from our study whether the observed association is due to the underlying infertility or to infertility treatment effects.

Neural tube defects have become increasingly rare over the past two decades, due in part to the implementation of prenatal folate supplementation (Czeizel and Dudas, 1992). In England, the birth prevalence of spinal NTDs fell 96% between the years 1970 and 1997, from 17 to 0.7 per 10,000 births (Morris and Wald, 1999). In the United States, the prevalence of spinal NTDs ranged from 1.5 to 4.7 per 10,000 births in the 1990s (Rosano et al., 1999; Williams et al., 2005). Our rate of spinal NTDs (1.6 per 10,000) and myelomeningocele (1.0 per 10,000) falls within the lower end of the expected range based on these other studies. This may be because previous studies often include NTDs resulting in still births and pregnancy terminations (Morris and Wald, 1999; Rosano et al., 1999).

How infertility or clomiphene citrate therapy could affect neural tube closure in the fetus is unknown. Small amounts of clomiphene citrate are still detectable in the bloodstream 6 weeks after a single dose (Schreiber et al., 1966), and the active isoform of clomiphene citrate has been shown to accumulate in the bloodstream when a single 50 mg dose of clomiphene citrate is given on a monthly basis (Mikkelson et al., 1986). Since the 50 mg tablet of clomiphene citrate is typically prescribed once a day over 5 consecutive days, it is expected that the active isomer will accumulate in patients who receive chronic clomiphene citrate therapy over several months, such that a significant level of this medication will

remain in the bloodstream at 3–4 weeks after conception, the time that the neural tube is expected to close.

Mothers of infants with spinal NTDs who received clomiphene citrate around the time of conception were prescribed, on average, more courses of clomiphene citrate prior to delivery than mothers who conceived a healthy infant on clomiphene citrate. It is possible that large doses of clomiphene citrate merely reflect a more severe degree of infertility, and that the drug itself plays no role in the pathogenesis of NTDs. As in previous studies (Greenland and Ackerman, 1995), we could not separate the effect of clomiphene citrate from the effect of the underlying severity of infertility. Further studies with larger numbers of cases are needed to determine whether clomiphene citrate exhibits an independent effect on risk of NTDs.

Although we found a significant association between clomiphene citrate and spinal NTDs, it is important to stress that the absolute risk difference is small (14.8/10,000 live births). If one assumes a causal relationship between periconceptional clomiphene citrate and spinal NTDs, the calculated population attributable risk percent would be 18%. The finding that spinal NTDs may be related to infertility or clomiphene citrate exposure among children born alive at or near term needs to be confirmed in larger and more comprehensive studies. Given the low baseline prevalence of NTDs, even relatively large cohort studies are underpowered to observe a significant association between clomiphene citrate and spinal NTDs (Dhont et al., 1999; Stromberg et al., 2002). Therefore, future case-control studies that include all identified cases of NTDs from within a population, as well as detailed information regarding infertility diagnoses, infertility treatments, and other environmental and genetic risk factors, are needed to increase our understanding of the association between infertility history, infertility treatment, and spinal neural tube defects.

Acknowledgments

The authors would like to thank Carla Stelling and John Green for their research assistance, Thomas B. Newman, MD for his careful review of the manuscript, and S. Claiborne Johnston and the Stroke Sciences Group at UCSF for their intellectual support.

Research support:

This study was funded in part by the United Cerebral Palsy Foundation (HD007446), the APS-SPR Student Research Program, the National Institute of Child Health and Human Development (1P01 HD37074-05), and Yvonne Wu was supported in part by NS35902.

REFERENCES

International Classication of Diseases, 9th Revision. 1999.

STATA 7 reference manual. Vol. 220. Stata Press; College Station: 2000. p. 358

Ahlgren M, Kallen B, Rannevik G. Outcome of pregnancy after clomiphene therapy. Acta Obstet Gynecol Scand. 1976; 55(4):371–375. [PubMed: 973567]

Barkovich, AJ. Pediatric Neuroimaging. 3rd ed. Lippincott Williams & Wilkins; 2000. p. 621-363.p. 621-636.

Cornel MC, ten Kate LP, Dukes MN, de Jong-v DBLT, Meyboom RH, Garbis H, Peters PW. Ovulation induction and neural tube defects. Lancet. 1989; 1(8651):1386. [PubMed: 2567395]

Croughan MS, Camarano L, Bernstein D. Childhood outcomes following infertility and infertility treatment. Fertil Steril. 2004; 82:S79–S80. al. e.

Cuckle H, Wald N. Ovulation induction and neural tube defects. Lancet. 1989; 2(8674):1281. [PubMed: 2573796]

Czeizel A. Ovulation induction and neural tube defects. Lancet. 1989; 2(8655):167. [PubMed: 2567941]

Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992; 327(26):1832–1835. [PubMed: 1307234]

Dhont M, De Sutter P, Ruyssinck G, Martens G, Bekaert A. Perinatal outcome of pregnancies after assisted reproduction: a case-control study. Am J Obstet Gynecol. 1999; 181(3):688–695. [PubMed: 10486485]

Dyson JL, Kohler HG. Anencephaly and ovulation stimulation. Lancet. 1973; 1(7814):1256–1257. [PubMed: 4122609]

Field B, Kerr C. Letter: Ovulation stimulation and defects of neural-tube closure. Lancet. 1974; 2(7895):1511. [PubMed: 4140417]

Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. Fertil Steril. 1995; 64(5):936–941. [PubMed: 7589637]

Kirke PN, Mills JL, Molloy AM, Brody LC, O'Leary VB, Daly L, Murray S, Conley M, Mayne PD, Smith O, Scott JM. Impact of the MTHFR C677T polymorphism on risk of neural tube defects: case-control study. BMJ. 2004; 328(7455):1535–1536. [PubMed: 15155469]

Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. American Journal of Public Health. 1992; 82(5):703–710. [PubMed: 1566949]

Kurachi K, Aono T, Minagawa J, Miyake A. Congenital malformations of newborn infants after clomiphene-induced ovulation. Fertil Steril. 1983; 40(2):187–189. [PubMed: 6873315]

Lammer EJ. Clomiphene-induced ovulation and the risk of neural tube defects. Reprod Toxicol. 1995; 9(5):491–493. [PubMed: 8563192]

Lancaster PA. Congenital malformations after in-vitro fertilisation. Lancet. 1987; 2(8572):1392–1393. [PubMed: 2890969]

Medveczky E, Puho E, Czeizel EA, Whiteman D, Murphy M, Hey K, O'Donnell M, Goldacre M. The use of drugs in mothers of offspring with neural-tube defects. Pharmacoepidemiol Drug Saf. 2004; 13(7):443–455. [PubMed: 15269928]

Mikkelson TJ, Kroboth PD, Cameron WJ, Dittert LW, Chungi V, Manberg PJ. Single-dose pharmacokinetics of clomiphene citrate in normal volunteers. Fertil Steril. 1986; 46(3):392–396. [PubMed: 3091405]

Mills JL, Simpson JL, Rhoads GG, Graubard BI, Hoffman H, Conley MR, Lassman M, Cunningham G. Risk of neural tube defects in relation to maternal fertility and fertility drug use. Lancet. 1990; 336(8707):103–104. [PubMed: 1975286]

Morris JK, Wald NJ. Quantifying the decline in the birth prevalence of neural tube defects in England and Wales. J Med Screen. 1999; 6(4):182–185. [PubMed: 10693061]

Nau H. Valproic acid-induced neural tube defects. Ciba Found Symp. 1994; 181:144–152. discussion 152-160. [PubMed: 8005022]

Rieder MJ. Prevention of neural tube defects with periconceptional folic acid. Clin Perinatol. 1994; 21(3):483–503. [PubMed: 7982331]

Robert E, Pradat E, Laumon B. Ovulation induction and neural tube defects: a registry study. Reprod Toxicol. 1991; 5(1):83–84. [PubMed: 1807541]

Rosano A, Smithells D, Cacciani L, Botting B, Castilla E, Cornel M, Erickson D, Goujard J, Irgens L, Merlob P, Robert E, Siffel C, Stoll C, Sumiyoshi Y. Time trends in neural tube defects prevalence in relation to preventive strategies: an international study. J Epidemiol Community Health. 1999; 53(10):630–635. [PubMed: 10616675]

Schreiber E, Johnson JE, Plotz EJ, Weiner M. Studies with 14C labeled clomiphene citrate. Clin Res. 1966; 14:287.

Shaw GM, Todoroff K, Finnell RH, Lammer EJ. Spina bifida phenotypes in infants or fetuses of obese mothers. Teratology. 2000; 61(5):376–381. [PubMed: 10777833]

Singh M, Singhi S. Possible relationship between clomiphene and neural tube defects. J Pediatr. 1978; 93(1):152. [PubMed: 650331]

Stromberg B, Dahlquist G, Ericson A, Finnstrom O, Koster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. Lancet. 2002; 359(9305):461–465. [PubMed: 11853790]

van der Put NM, Eskes TK, Blom HJ. Is the common 677C-->T mutation in the methylenetetrahydrofolate reductase gene a risk factor for neural tube defects? A meta-analysis. Qjm. 1997; 90(2):111–115. [PubMed: 9068801]

Werler MM, Louik C, Shapiro S, Mitchell AA. Ovulation induction and risk of neural tube defects. Lancet. 1994; 344(8920):445–446. [PubMed: 7914567]

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. Am J Epidemiol. 2000; 152(9):823–828. [PubMed: 11085393]

Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics. 2005; 116(3):580–586. [PubMed: 16140696]

Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA. 2003; 290(20):2677–2684. [PubMed: 14645309]

Ylikorkala O. Letter: Congenital anomalies and clomiphene. Lancet. 1975; 2(7947):1262–1263. [PubMed: 53754]

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2012 July 29.

Table 1

Univariate odds ratios of demographic and infertility variables for spinal neural tube defects in a population of term and near-term infants born at Kaiser Permanente Northern California, 1994–1997.

	Cases (N = 18)		Controls (N = 1608)				
	N	(%)	N		OR	95% CI	P value
Maternal age							
< 20	2	11%	129	8%	1.6	0.2–7.1	0.55
20–34	12	67%	1222	76%	Reference	–	–
≥35	4	22%	257	16%	1.6	0.4–5.3	0.42
Maternal Race							
White	12	67%	852	53%	Reference	–	–
Black	1	6%	209	13%	0.4	0.01–2.9	0.40
Hispanic	3	17%	338	21%	0.6	0.1–2.4	0.48
Asian	1	6%	209	13%	0.3	0.01–2.4	0.28
Other	1	6%	64	4%	1.2	0.02–8.0	0.89
Infant Characteristics							
Male gender	8	44%	836	52%	0.8	0.3–2.1	0.54
Gestational weeks (mean ± SD)		39.1 ± 1.3		39.5 ± 1.3			0.15
Birth weight (mean grams ± SD)		3348 ± 545		3499 ± 494			0.20
Infertility							
History of infertility *	4	22%	96	6%	4.3	1.01–14.0	0.02
Infertility medication prior to delivery	4	22%	48	3%	10.9	2.5–36.7	0.001
Periconception[#] clomiphene citrate exposure	3	17%	32	2%	11.7	2.0–44.8	0.004

[a]The periconception window is defined as 60 days before to 15 days after the date of conception.

*The four case mothers with history of infertility had ovarian dysfunction (3) and female infertility NOS (l).