NEURAL TUBE DEFECT RATES FOLLOWING IN UTERO EXPOSURE TO VALPROIC ACID
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ABSTRACT

Women who are problem drinkers often have psychiatric co-morbidities or epilepsy, for which valproic acid may be prescribed. It is critical to acknowledge that some medications may add teratogenic risk to the one induced by ethanol. Valproic acid is one such example. There is inconsistency in the literature concerning prevalence of fetal neural tube defects following maternal valproic acid (VPA) use. Various prevalence rates, ranging from 1% up to 5-6%, have been quoted in the literature. A meta-analysis is required to establish the exact prevalence.

Neural tube defects (NTDs) are serious malformations caused by failure of the neural tube to properly fuse. NTDs lead to stillbirth, neonatal death and severe disabilities.1 The occurrence of neural tube defects, specifically spina bifida, in the fetus was linked to maternal VPA therapy as early as 1982.2 VPA is not only a first-line treatment for epilepsy, but has also found wider use in controlling other paroxysmal disorders such as bipolar disorder, migraine and trigeminal neuralgia.3-5 These chronic illnesses are relatively widespread in women of childbearing age.5-9 As such, a potential pregnancy must be considered when seeking treatment with VPA. Extensive use of VPA may significantly increase the risk of fetal NTDs in the general population and requires education about this risk. Furthermore, given that 50% of pregnancies are unplanned,10 it is imperative that not only pregnant women but all women of childbearing potential be aware of the potential risk for fetal NTDs caused by VPA.

Factors to Consider

It is important to note that neural tube defects are known to have multifactorial etiology, of which one factor is folate deficiency.11 VPA interferes with folic acid metabolism, thereby potentially raising the risk of NTDs. Supplementation with folic acid has been found to substantially reduce the risk of occurrence and of recurrence of NTDs in the fetus when 0.412 to 0.8 mg13 and 4 mg14 was administered, respectively. Confounding factors such as history of previous pregnancies in which a neural tube defect occurred (genetic predisposition)15 and folate supplementation must be considered in any study aiming to link NTDs with VPA use. Also, epidemiological factors relating to geography and ethnicity have been implicated as contributors to the prevalence of NTDs16 and must be considered.

Valproic Acid and Prevalence of Neural Tube Defects (NTDs)

Since 1982, various case reports and studies have been reported implicating that valproic acid increased the risk of NTDs in offspring of VPA-treated pregnancies.17-19 However, the exact prevalence of NTDs in newborns of women undergoing valproic acid therapy remains unclear. A comparison of methodologies is required to ascertain whether the conclusions drawn in these studies can be generalized. Several examples which exemplify the discordance between published prevalence rates will be discussed.

A case-control study based on data collected by a birth defects surveillance system in Lyon, France2,20 reported that 6.2% of mothers of infants with spina bifida had used VPA during their pregnancy and calculated an odds ration of 20.6 for the association of spina bifida with VPA. In a valproic acid teratogenicity update, Lammer et al.21 reviewed this and other studies and concluded the prevalence rate of fetal NTDs after maternal valproic acid exposure to be between 1-2%.

Prieto et al.22 published a letter which questioned the statistical analysis performed for
the aforementioned case-control study\textsuperscript{2,20}; their recalculation yielded a prevalence rate of 3.4%.

Omtzigt et al.\textsuperscript{23} performed a prospective cohort study on 92 mother-child pairs and described incidence of spina bifida among all valproic acid-exposed offspring at 5.4% when twins were considered concordantly and 6.3% when twins were taken separately. The incidence rate presented by Omtzigt et al. is considerably higher than had been previously reported. Demographics as well as VPA dosage were considered as confounders, but folate supplementation was not mentioned.

The prospective study performed by Omtzigt et al.\textsuperscript{23} defined 1000 mg/day as the threshold VPA dosage, above which an increased risk for spina bifida must be considered. This makes the dosage specification essential for studying valproic acid teratogenicity, since dosages as low as 400 mg/day, with a range of 400-2000 mg/day, were reported among the 9 cases of spina bifida after valproic acid exposure in the French case-control study.\textsuperscript{2,20}

The most recent study of infants exposed in utero to VPA monotherapy was published in 2005\textsuperscript{24} and is based on data collected by the North American anti-epileptic drug pregnancy registry. Of the 149 VPA-exposed mothers considered in the primary analysis, 16 (10.7%) gave birth to children with major malformations, as compared to the 2.9% rate associated with other antiepileptic drugs. Of the total of 16 major malformations, 3 were spina bifida. Of note, the three cases were among VPA-exposed mothers who took the daily recommended dose of folic acid supplement in the periconceptional period or as part of prenatal multivitamins. Thus, the protective effect of folate supplementation came under scrutiny\textsuperscript{25} with respect to the timing and extent of supplementation, raising the question of the need for folate throughout pregnancy versus around conception and during organogenesis only.

Recently, a meta-analysis of controlled cohort studies with first trimester exposure to VPA, concluded the following: based on almost 1000 exposed babies reported in 13 cohort studies (5-14), exposure to VPA was associated with a relative risk of 2 for major malformation (95% CI 1.33-2.99) when compared to all other antiepileptic drugs. When compared to the general population of healthy controls, the relative risk was 4.37 (95% CI 2.84-6.71).\textsuperscript{26}

**Conclusion**

Practitioners should inform women on increased malformation risk of valproic acid when used in early pregnancy, especially at high doses.

REFERENCES


Neural tube defect rates following in utero exposure to valproic acid


