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Malformation Rates in Children of Women with Untreated Epilepsy

A Meta-Analysis

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Abstract

Background: It is widely quoted that women with epilepsy have a higher than baseline risk for giving birth to a child with malformations, independent of the effects of antiepileptic drugs.

Objective: To determine, based on available evidence, if epilepsy *per se* represents a teratogenic risk. To systematically review all studies investigating the occurrence of major malformation rates among children of treated or untreated women with epilepsy and non-exposed controls who do not have epilepsy.

Methods: A meta-analysis, using a random effects model, was conducted of all cohort and case-control studies reporting malformation rates in children of women with epilepsy exposed or unexposed to antiepileptic drugs compared with that of children of nonepileptic women. Medline (1966–2001), EMBASE, the Cochrane database as well as REPROTOX (an information system on environmental hazards to human reproduction and development) databases were accessed.

Results: We found ten studies reporting results of untreated epilepsy (n = 400) and their non-epileptic healthy controls (n = 2492). Nine out of ten studies also reported results on 1443 patients exposed to antiepileptic drugs and their 2526 unexposed healthy controls. The risk for congenital malformations in the offspring of women with untreated epilepsy was not higher than among nonepileptic controls (odds ratio [OR] = 1.92; 95% CI 0.92–4.00). There was evidence of publication bias, thus with bias removed the OR was 0.99 (95% CI 0.49–2.01). In contrast, the offspring of epileptic women who received antiepileptic drugs had higher incidences of malformation than controls (OR 3.26; 95% CI 2.15–4.93).

Conclusion: Our study does not support the commonly held view that epilepsy *per se* represents a teratogenic risk. Our study suggests that this view is the result of a publication bias, with several small (<100 participants) positive studies leading to a premature conclusion.

It is estimated that one million women of childbearing age currently have a diagnosis of epilepsy in the US[1] and women with epilepsy account for 0.5% of all pregnancies.[2] Mounting evidence suggests that over the past decade there has been an increase in perinatal risks, associated with pregnant women who have epilepsy, for both mother and child.[3] All commonly used antiepileptic drugs have

been associated with an increased risk for major malformations in both animal and human studies.

It has been speculated that a genetic predisposition of the mother's epilepsy results in the susceptibility to anticonvulsant-related teratogenicity.[4] The frequency and severity of seizures can also play a role in causing an adverse outcome. There is a widely cited view that epilepsy *per se* may contribute to an adverse outcome.[5] A potential interaction between genetic and environmental components makes it difficult to attribute an adverse outcome to any single factor.[6,7]

While some studies have suggested a characteristic pattern of anomalies resulting from antiepileptic drug therapy during pregnancy,[8,9] others have implicated epilepsy itself as an associative factor in the occurrence of malformations.[10,11] Although a role for epilepsy in teratogenicity has been suggested, conflicting results have made it difficult to counsel patients and their families when they are planning pregnancy.

In order to better define the extent to which epilepsy contributes to the development of congenital malformations, we systematically reviewed the literature and conducted a meta-analysis of all studies that investigated the rates of malformations among offspring of untreated pregnant women with epilepsy compared with those of treated epileptic women and nonepileptic controls.

Methods

Data Sources and Study Selection

A search of the literature was conducted for studies reporting the association of untreated epilepsy with pregnancy outcome. The following OVID (4.3.0) databases (and relevant segment dates) were searched electronically by a professional librarian: Medline (1966–2001), EMBASE, the Cochrane database as well as REPROTOX (an information system on environmental hazards to human reproduction and development) [key words were: malformations, epilepsy, pregnancy, antiepileptic drugs, untreated epilepsy]. Teratology text references, the references in the bibliographies of all the included studies and review articles that were identified by the search strategy were searched manually. Controlled human population studies, both cohort and case control, in all languages were selected.

Objective

The objective was to determine if epilepsy *per se* represents a teratogenic risk, using available evidence. To systematically review all studies reporting on major malformation rates among children of treated or untreated women with epilepsy and non-exposed controls.

Inclusion Criteria

The inclusion criteria in this meta-analysis were studies that reported pregnancy outcomes for women with epilepsy (defined using the International League Against Epilepsy criteria)[12] who were untreated with antiepileptic drugs and included comparison groups comprising children of women without epilepsy and not exposed to antiepileptic drugs.

Convulsive disorders due to other aetiologies (e.g. post-traumatic) were not included. When data were available, genetic disorders (e.g. chromosomal abnormalities and disorders due to single gene mutation) and positional deformity or deformations (e.g. congenital dislocation of hip) were not considered to be major malformations.

Exclusion criteria consisted of non-controlled studies, studies reporting on women exposed to other known teratogens or diseases, and papers not separating treated from untreated patients with epilepsy.

One reviewer screened all the abstracts, titles, and, if necessary, full reports for inclusion in this review. Based on this preliminary screening, studies were chosen for detailed review by two reviewers who applied the selection criteria and decided independently which studies should be included in the final analysis. In cases of disagreement between the two reviewers, the decision was made based on the assessment of a third reviewer. There was no blinding of authors or results. When multiple studies reported data for the same populations or subpopulations, only the study reporting the more comprehensive data was included.

Data Extraction and Synthesis

Using structured data collection forms, two reviewers extracted data independently and entered it into 2 × 2 tables. Discrepancies were resolved by discussion. All data entries were double-checked manually.

We used the Cochrane Review Manager software (Revman 4.1) to calculate the pooled odds ratio (OR) and 95% CI, assuming a random-effects model.

Two analyses were conducted. The first compared the rates of malformations in offspring of women with epilepsy who did not take antiepileptic drugs during the first trimester with those in offspring of controls who did not have epilepsy. The second compared the rates of malformations in children of women who had epilepsy and were treated with antiepileptic drugs with the rates in children of controls who did not have epilepsy.

Results

The search generated 2615 titles, of which 287 abstracts in all languages were selected for further analysis. A total of 74 articles were selected for complete review. Ten of these studies met the inclusion criteria and were included in the analysis, including five prospective cohort studies, four case control studies and one study using both prospective and retrospective design.[11,13-21] Sixty-four studies were excluded. The list of excluded papers can be provided by the authors. We included ten studies reporting the results of untreated epilepsy (n = 400) and their non-epileptic healthy controls (n = 2492). Nine out of ten studies also reported on 1443 pregnancies of women exposed to antiepileptic drugs and 2526 healthy non-epileptic unexposed women. The difference in the number of controls is due to matching.

The risk for congenital malformations in the offspring of women with untreated epilepsy was not higher than that in the offspring of controls who did not have epilepsy (OR 1.92; 95% CI 0.92–4.00) [figure 1]. The studies were not heterogeneous (p for heterogeneity = 0.80). In contrast, the offspring of women treated with antiepileptic drugs had a significantly higher incidence of major malformations than the offspring who did not have epilepsy (OR 3.26; 95% CI 2.15–4.93) [figure 2]. The studies were not heterogeneous (p for heterogeneity = 0.87).

Funnel plots of the data were made, with sample size plotted against the natural log of each OR. Figure 3 reveals the possibility of publication bias, since there were no small studies with negative results. We then adjusted the plot by inserting pseudo-values representing unpublished studies of

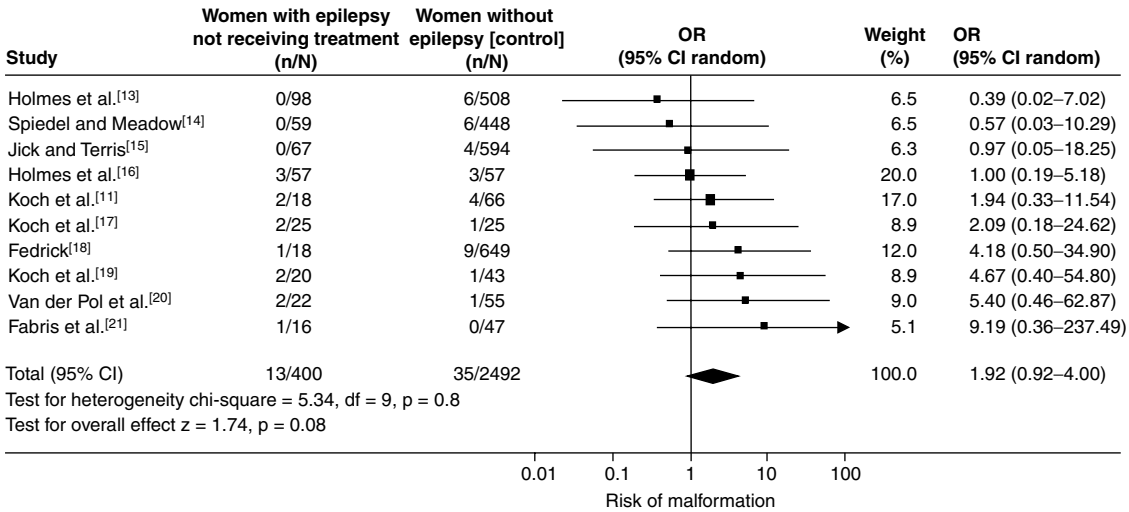

Fig. 1. Major malformations in offspring of women with untreated epilepsy and healthy controls. **n** = number of offspring with malformations; **N** = total number of offspring; **OR** = odds ratio.

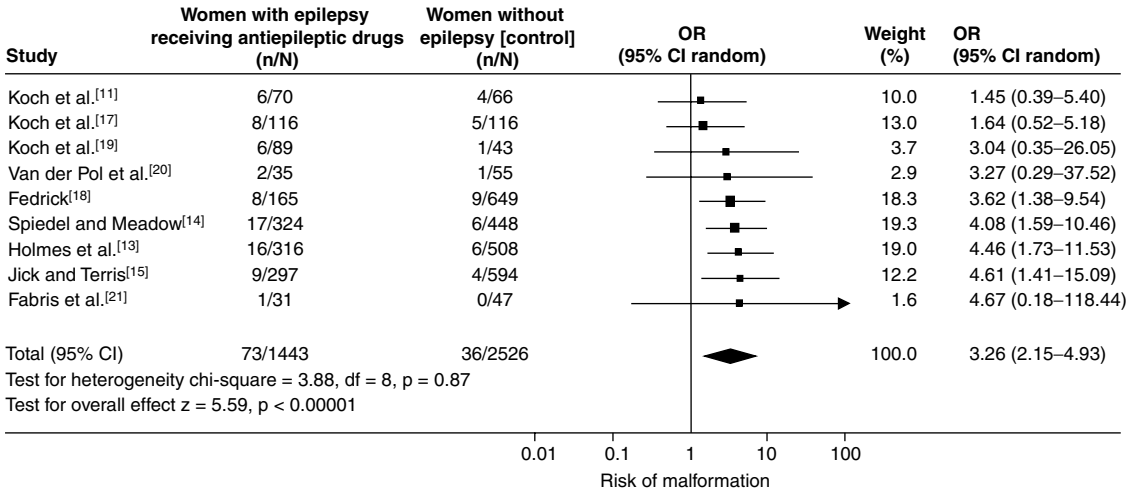

Fig. 2. Major malformations in offspring of epileptic mothers treated with antiepileptic drugs and in healthy controls. **n** = number of offspring with malformations; **N** = total number of offspring; **OR** = odds ratio.

equal size but opposite results for those studies with a sample size of <100. Figure 4 depicts the funnel plot of the adjusted data. The summary OR decreased to 0.99 (95% CI 0.49–2.01) from 1.92 (95% CI 0.92–4.00), suggesting that there really is no difference in malformations in children of untreated women with epilepsy versus children of women without epilepsy. On the other hand, the plot for treated mothers (not shown) showed no such publication bias.

Sensitivity analyses revealed no significant differences between cohort and case control studies for comparisons of the offspring of antiepileptic drug-treated epileptic women with the offspring of nonepileptic controls and comparisons of the offspring of untreated women with epilepsy with the offspring of nonepileptic controls.

Our study had a power of 78% to detect a significant (α error rate = 0.05) difference in the rate of malformations between untreated epileptic women and nonepileptic control. A total of 54 more studies of average size including 15 505 more patients would be needed to show such effect to be significant.

Discussion

Our findings did not confirm an increase in rates of major malformations among children of untreated epileptic women compared with that among children of nonepileptic controls. This information is reassuring for women with epilepsy who do not need to take antiepileptic drugs. It is also important for women with specific types of epilepsy and their physicians, who may choose to discontinue antiepileptic drugs during the first trimester in order to reduce the risks of major malformations. The teratogenic risk associated with antiepileptic drugs appears to be 4–8%, approximately 2–3 times greater than the general obstetric population.[22] Presently there is no consensus regarding which anticonvulsant drug is the safest for the patient's unborn child.

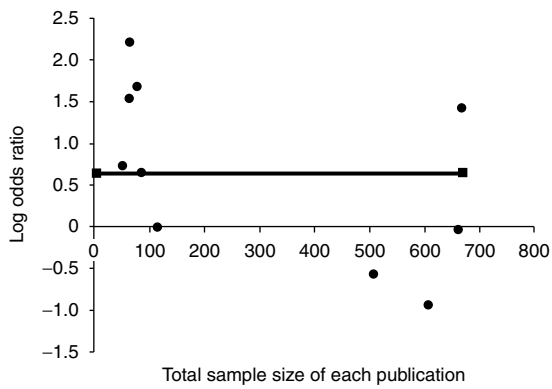

Fig. 3. Funnel plot of publications[11,13-21] (included in this meta-analysis) that compared major malformations in offspring of untreated women with epilepsy with that of offspring of women without epilepsy. The solid black line represents the pooled odds ratio.

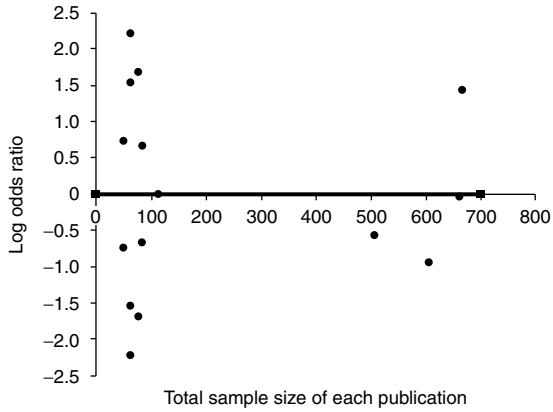

Fig. 4. Adjusted funnel plot after removal of the possibility of publication bias of publications[11,13-21] (included in this meta-analysis) that compared major malformations in offspring of untreated women with epilepsy with that of offspring of women without epilepsy. The plot was adjusted by inserting pseudo-values representing unpublished studies of equal size but opposite results for those studies with <100 participants. The solid black line represents the pooled odds ratio.

Moreover, a number of factors exist that may affect the teratogenic potential of an antiepileptic medication, such as the number of co-administered drugs, drug dose, time of exposure, pharmacokinetics and differences in metabolism.[23,24] However, with increased severity of epilepsy, there is usually an increase in drug dose, and more common use of polytherapy.

The majority of selected studies did not report the type, duration, or severity of epilepsy. Furthermore, information about clinical indications for treatment discontinuation and seizure-free periods was not reported by the majority of studies. Another potential shortcoming of our study is its inability to account for the effects of seizures during pregnancy. Seizure frequency has been shown to increase by 17–37% during gestation.[25,26] Several mechanisms have been attributed to an increase in seizure activity including pregnancy-induced changes in antiepileptic drug pharmacokinetics, increased stress, higher levels of estrogen and drug regimen adherence problems. The occurrence of status epilepticus may result in fetal death in a substantial number of cases, as well as pose the risk for maternal death.[27]

Untreated epileptic women who are pregnant may represent those having a less severe form of epilepsy with lower frequencies of seizures and hence lower frequencies of malformations are observed in their offspring.[7] This hypothesis is supported by the fact that women treated with polytherapy may have more severe forms of epilepsy.[23]

On the other hand, women with untreated epilepsy may not necessarily have milder forms of the disorder. Other forms (e.g. temporal lobe) may be equally severe, but do not result in tonic-clonic seizures, and may be tolerable in the mother without harming the fetus. The present study was unable to determine whether that was the case because of incomplete reporting of the exact nature of the epilepsy by the original authors. Equally important, it will be critical to assess the potential role of paternal epilepsy in future studies.

The funnel plot presented in figure 3 clearly shows that small studies (e.g. with <100 participants) were all positive, (e.g. showing an association between maternal epilepsy and increased malformation rate). It is very important to address such bias, and this is done by including in the analysis 'mirror image' results plotted on the 'negative' side. Such analyses, correcting for the bias produced by small sample size, further balances the overall result of the whole group of studies.

Another potential difficulty is bias against publications of negative trials (the 'file drawer' syndrome). However, in this particular case, unpublished negative cohorts, if they exist, would strengthen the result of a lack of effect of untreated epilepsy on malformation rates of offspring.

In conclusion, our study does not support the commonly held view that epilepsy *per se* represents a risk for increased congenital malformations. We suggest that the current literature on the topic suffers from publication bias, which produces distortion. More studies are needed to control for the type, severity, and frequency of seizure disorders on teratogenic risk.

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References

1. Devinsky O, Yerby M. Women with epilepsy: reproduction and effects of pregnancy on epilepsy. Neurol Clin 1994; 12: 479-95
2. Yerby MS. Pregnancy and epilepsy. Epilepsia 1991; 32 Suppl. 6: s51-9
3. Martin PJ, Millac PAH. Pregnancy, epilepsy, management and outcome: a 10-year perspective. Seizure 1993; 2: 277-80
4. Janz D. On major malformations and minor anomalies in the offspring of parents with epilepsy: review of the literature. In: Janz D, Dam M, Richens A, et al., editors. Epilepsy, pregnancy, and the child. New York: Raven Press, 1982: 211-22
5. Majewski F, Steger M, Richter B, et al. The teratogenicity of hydantoins and barbiturates in humans, with considerations on the etiology of malformations and cerebral disturbances in the children of epileptic parents. Int J Biol Res Pregnancy 1981; 2 (1): 37-45
6. Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades. 2: human studies. Reprod Toxicol 1991; 5 (4): 301-35
7. Nulman I, Laslo D, Koren G. Treatment of epilepsy in pregnancy. Drugs 1999; 57 (4): 535-44
8. Jones KL, Lacro RV, Johnson K, et al. Patterns of malformations in the children of women treated with carbamazepine during pregnancy. N Engl J Med 1989; 320: 1661-6
9. Clayton-Smith J, Donnai D. Fetal valproate syndrome. J Med Genet 1995; 32: 724-7
10. Nulman I, Scolnik D, Chitayat D, et al. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy medications. Am J Med Genet 1997; 68: 18-24
11. Koch S, Gopfert-Geyer I, Jager-Roman E, et al. Antiepileptika wahrend der schwangerschaft. Dtsch Med Wochenschr 1983; 108: 250-7
12. International League Against Epilepsy, Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1990; 30: 389-99
13. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001; 344: 1132-8
14. Spiedel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and newborn. Lancet 1972; 21: 839-43
15. Jick SS, Terris BZ. Anticonvulsants and congenital malformations. Pharmacotherapy 1997; 17: 561-4
16. Holmes LB, Rosenberger PB, Harvey EA, et al. Intelligence and physical features of children of women with epilepsy. Teratology 2000; 61: 196-202
17. Koch S, Losche G, Jager-Roman E, et al. Major and minor birth malformations and antiepileptic drugs. Neurology 1992; 42 Suppl. 5: 83-8
18. Fedrick J. Epilepsy and pregnancy: a report from the Oxford Record Linkage Study. BMJ 1973; 2: 442-8
19. Koch S, Hartmann A, Jager-Roman E, et al. Major malformations in children of epileptic parents: due to epilepsy or its therapy? In: Janz D, Dam M, Richens A, et al., editors. Epilepsy, pregnancy and the child. New York: Raven Press, 1982: 313-5
20. Van der Pol MC, Hadders-Algra M, Huisjes HJ, et al. Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. Am J Obstet Gynecol 1991; 164: 121-8
21. Fabris C, Licata D, Stasiowska B, et al. Il neonato da madre epilettica: rischio malformativo ed auxologico. Pediatr Med Chir 1989; 11: 27-32
22. Yerby M. Pregnancy, teratogenesis and epilepsy. Neurol Clin 1994; 12: 749-71
23. Kaneko S, Otani K, Fukushima J, et al. Teratogenicity of antiepileptic drugs: analysis of possible risk factors. Epilepsia 1988; 29: 459-67
24. Kaneko S, Fukushima Y, Sato T, et al. Teratogenicity of antiepileptic drugs: a prospective study. Jpn J Psychiatry Neurol 1986; 40: 447-50
25. Byrne B. Epilepsy and pregnancy. Ir Med J 1997; 90: 173-4
26. Lopes-Cendes I, Andermann E, Candes F, et al. Risk factors for changes in seizure frequency during pregnancy of epileptic women: a cohort study [abstract]. Epilepsia 1992; 33 Suppl. 3: 57
27. Donaldson JO. Neurologic disorders of pregnancy. In: Reece EA, Hobbins JC, Mahoney MJ, et al., editors. Medicine of the fetus and mother. Philadelphia (PA): JB Lippincott, 1992: 1097-102

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