Birth Weight in Offspring of Women with Epilepsy

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INTRODUCTION

Epilepsy is the most common neurologic disorder in pregnant women. The prevalence is 0.2–0.6 percent (1–3). Research on epilepsy and pregnancy has mainly been on treatment with antiepileptic drugs and the risk of congenital malformations (4), and a number of studies have demonstrated an increased risk (5–8). We know less about the effect of epilepsy and antiepileptic drug treatment on preterm delivery and intrauterine growth restriction. Both of these events are frequent, and both are important risk factors for neonatal mortality (9, 10) and for childhood morbidity such as cerebral palsy and cognitive dysfunction (11, 12). Furthermore, the consequences of intrauterine growth restriction seem to go far beyond childhood (13). Until now, the studies on the association between epilepsy and preterm delivery and intrauterine growth restriction have led to no overall conclusions.

Preterm delivery is defined as delivery before 37 completed weeks of gestation (14). Gestational age may be estimated from the last menstrual period, from ultrasound scanning, or from a postnatal assessment (15). Estimates from the last menstrual period may be biased because the incidences of oral contraceptive failure and vaginal bleeding in pregnancy are increased in women with epilepsy (16, 17). On the other hand, the use of ultrasound may overestimate the risk of preterm delivery in women with epilepsy if early fetal growth restriction is more pronounced in women with epilepsy than in healthy women (18, 19).

The most commonly used proxy measure for intrauterine growth restriction is small for gestational age, defined by birth weight below the 10th percentile for the specific gestational age at birth. The 10th percentile is often derived from cross-sectional birth weight for gestational age standards, but standard percentiles vary up to 500 g for term deliveries and may not be specific for gender or race (20). Being small for gestational age may therefore reflect a methodological artifact rather than intrauterine growth restriction.

Low birth weight (birth weight less than 2,500 g) is often used to indicate intrauterine growth restriction. However, low birth weight may be due to a small growth potential in a healthy fetus, preterm delivery, or intrauterine growth restriction. Consequently, low birth weight may be a very poor proxy variable for fetal growth (21, 22), and since preterm delivery and intrauterine growth restriction have different etiologies (23), it seems important to consider these outcomes separately.

The aim of this paper is to provide a critical review of the literature on epilepsy during pregnancy and the risk of preterm delivery and intrauterine growth restriction. We also wish to investigate if an increased risk may be associated with genetic aspects of epilepsy, seizures during pregnancy, antiepileptic drug treatment, or other risk factors.

METHODS

Data source

Searches of MEDLINE from 1968 through 1999 and EMBASE from 1974 through 1999 were performed to identify studies of pregnancy outcome in women with epilepsy (Medical Subject Headings (MESH) terms: epilepsy, pregnancy, pregnancy outcome, congenital malformation, preterm or prematurity, birth weight, low birth weight, fetal growth or fetus growth, anticonvulsants or anticonvulsive agent, carbamazepine, valproic acid, phenytoin, phenobarbitone). Similar searches were conducted in Biosis Previews, Elsevier Biobase, and SciSearch. An additional search of Science Citation Index from 1986 through 1998 was conducted to identify all papers that cited one of three major studies (1, 24, 25), that is, one Continental, one British, and one American study that were all published before 1986. Additional snowball searches were conducted in bibliographies of the initially identified original papers, reviews, and book chapters.

Selection of studies

We included human peer-reviewed studies published in English with information on gestational age or birth weight in children of women with epilepsy. We excluded studies without a nonepileptic comparison group (26–44), studies where comparison of gestational age and birth weight data
was not possible (45–50), studies where measures of growth restriction were left undefined (51, 52), and redundant studies, that is, studies where the same data had been published elsewhere (53). Twenty studies that were described in 26 articles were eligible (1–3, 24, 25, 54–74).

RESULTS

The studies are presented in table 1. Most studies found a slightly higher frequency of preterm delivery, low birth weight, and small for gestational age in women with epilepsy than in the comparison group. For these outcomes, the increased risk ranged up to around twice the risk in the comparison group. The mean birth weight in children of women with epilepsy was reduced in most studies, and the reduction ranged up to around 200 g. However, few of the results were statistically significant.

An increased risk of preterm delivery or intrauterine growth restriction may be due to disease-related factors or other risk factors. Risk factors related to maternal disease include genetic and environmental aspects, seizures during pregnancy, and antiepileptic drug treatment (4, 75). Some authors suggested an interaction between epilepsy and antiepileptic drug treatment (65, 76), but interactions were never tested.

Genetic and environmental aspects of maternal epilepsy

Preterm delivery in women with epilepsy and intrauterine growth restriction in their children may be caused by a disease-linked small growth potential, which may be reflected in the mother’s weight and height. Epilepsy may also be related to susceptibility to environmental exposures that are risk factors for preterm delivery or intrauterine growth restriction. It may therefore be difficult to distinguish between genetic factors and other factors related to epilepsy, such as environmental factors.

The disease-linked effect may be estimated from studies of epileptic women without antiepileptic drug treatment, although these women also probably have less severe epilepsy. No study addressed genetic aspects of the association between maternal epilepsy and gestational age at birth, while three studies (58, 65, 68) allowed inference on birth weight. In all three studies, birth weight was reduced in children of women with epilepsy compared with children of healthy women. The results were statistically nonsignificant, and none of the estimates were adjusted for gestational age or potential confounding, although only term deliveries were included in the study by Gaily and Granström (58).

Types of epilepsy are frequently described, but no specific types of epilepsy have been associated with the risk of preterm delivery or intrauterine growth restriction (65, 66).

Seizures during pregnancy

In general, it is estimated that 50 percent of women with epilepsy have an unchanged seizure frequency during pregnancy (77, 78). With good medical compliance, 80 percent seem to have an unchanged, 16 percent an increased, and 4 percent a decreased seizure frequency during pregnancy (77). Poor medical compliance (77, 79) and pharmacokinetic changes during pregnancy (80) may cause lower free antiepileptic drug serum concentrations and thereby an increased seizure frequency. Status epilepticus does not seem to occur more frequently among pregnant than among nonpregnant women with epilepsy (78).

Very few studies investigated the association between the occurrence of seizures during pregnancy and preterm delivery or intrauterine growth restriction, although some provided extensive data on seizures (74). Sawhney et al. (73) reported twice the frequency of low birth weight and small for gestational age in pregnancies where seizures were present compared with women with epilepsy and no seizures during pregnancy. This study was carried out in an Indian population that had a much higher frequency of seizures during pregnancy than found in studies from industrialized countries. Other studies (41, 42) found no association between the occurrence of seizures or an increased seizure frequency and gestational age or birth weight.

Antiepileptic drug treatment

Most antiepileptic drugs increase the risk of major congenital malformations and minor anomalies. Particularly high risk is associated with high-dose treatment, polytherapy, and specific drug combinations such as carbamazepine, valproic acid, and phenobarbital together (76, 81, 82). A specific teratogenic effect has been hypothesized to be associated with metabolites of carbamazepine (66, 81) and valproic acid (76). Most authors conclude that antiepileptic drug treatment is the primary risk factor in the development of congenital malformations (83), and thorough reviews have been published (80, 84–87).

Antiepileptic drugs may cause preterm delivery or intrauterine growth restriction through a drug-induced folate deficiency (72), through a depression of the thyroid function (85, 88), or through epoxid formation (66). Results from studies on antiepileptic drugs and gestational age and birth weight are difficult to compare because prescription practice has changed over time (43, 89). Previously, high-dose polytherapy was used while low-dose monotherapy is now more common as is treatment with carbamazepine and valproic acid instead of with phenobarbital, phenytoin, and primidone (89, 90). There is little human evidence on the use in pregnancy of new antiepileptic drugs such as lamotrigine, gabapentin, oxcarbazepine, and vigabatrin (91).

An increased risk of preterm delivery was found mostly in women treated with an antiepileptic drug, but few studies carried out separate analyses for treated and untreated women (67). Most evidence on the association between antiepileptic drug treatment and birth weight relies on three studies that provided detailed birth weight data for specific monotherapies (56, 65, 68). In all three studies, birth weight was reduced in children of women who received antiepileptic drug treatment, but this reduction was more pronounced than among children of untreated women with epilepsy in only two studies (65, 68). The reduction related to polyther-
apy seemed slightly higher than that related to monotherapy. Some studies addressed the question of drug-specific effects. A number of studies demonstrated a growth-restricting effect of carbamazepine (56, 66), but others found no effect from carbamazepine on fetal growth (58, 65). Other studies found treatment with valproic acid (65), phenytoin (58), and phenobarbital (65, 68) to be associated with reduced birth weight, while others again found no influence by valproic acid (70) and phenytoin (68) on birth weight. Two studies found no relation between the type of drug or the number of drugs in pregnancy and birth weight (67, 72).

Other risk factors

Maternal characteristics that may be associated with birth weight include maternal age, parity, race, marital status, smoking habits, drug use, previous intrauterine growth restriction, hypertension, height, prepregnancy weight, and pregnancy weight gain (92, 93). Offspring characteristics known to affect birth weight include multiple birth, congenital malformations, and infant gender (93). If the presence of these characteristics differs between women with epilepsy and healthy women, differences in birth weight for gestational age may be explained by these characteristics rather than by factors related to maternal epilepsy.

Pregnant women with epilepsy were younger and more often primiparous than women without seizure disorders (59). There is too little evidence to suggest a difference in maternal weight and height, but midparental height was confounding one study of birth weight in children of women with epilepsy (58). Women with epilepsy were of lower social status and more often single than the general pregnant population (24, 57, 72). Yerby et al. (25) found a reduction from 2.8 to 2.3 in the relative risk of low birth weight after adjustment for marital status in women with epilepsy compared with a random sample of healthy women. There is no evidence to suggest a different distribution of smoking habits or alcohol consumption than in the general population. On the other hand, no study reported or adjusted for lifestyle factors in the analyses of gestational age or birth weight. A number of studies addressed the relation between antiepileptic drug use and folate, but no study investigated the association between serum folate levels in women with epilepsy and gestational age or birth weight of their children.

Most studies reported an increased frequency of congenital malformations in children of women with epilepsy, but only one study excluded malformed children before the analyses of birth weight (65). A finding of decreased birth weight in children of women with epilepsy may therefore be caused by an increased frequency of congenital malformations.

DISCUSSION

Most studies of pregnant women with epilepsy and offspring gestational age and birth weight showed an increased risk of preterm delivery, low birth weight, and small for gestational age (table 1). However, few of the results were statistically significant. The lack of statistical significance could be due to small sample sizes. If the results were due to random variation, one would expect more studies to show a decreased risk of preterm delivery or reduced birth weight in women with epilepsy. It therefore appears that women with epilepsy carry an increased risk of infant preterm delivery and reduced birth weight compared with women without chronic disease, but several problems have to be taken into account.

A meta-analysis with a pooled risk estimate is impossible to carry out. The study populations varied from general populations and register-based samples to highly selected hospital populations; women with epilepsy were therefore not comparable among studies. Different selection of comparison groups caused differences in results, for example, individual matching by age, parity, social class, and place of delivery versus random population samples. Gestational age and birth weight were analyzed as categorical or continuous variables but often without providing frequencies or standard deviations; thus, assigning weights to each study result was impossible. Finally, the risk estimates failed to show homogeneity across populations, which is essential for pooling of results (94).

Study design

A number of authors (44) have proposed that differences in study design could in part explain the conflicting results. All identified studies were follow-up studies that defined the study objects by their exposure, that is, whether they had epilepsy or not. The studies could be categorized into prospective, historical, and register-based studies (table 1). Prospective studies identified women with epilepsy before or during pregnancy, while historical studies established the cohorts after delivery, that is, after the pregnancy outcome was known. Register-based studies used medical birth registers and were thus historical, but they differed from other historical studies because they provided no data on antiepileptic drug treatment.

Prospective and historical studies were carried out in neurologic or obstetric settings. There was no correspondence between the epidemiologic study design and the setting, although historical studies with review of maternal medical or obstetric records were most common.

Cohorts with historical identification of women with epilepsy, that is, when the pregnancy outcome was known, may have included more women with severe disease. Ascertainment from neurologic departments probably resulted in more women with severe disease and medical treatment, whereas women with mild epilepsy were not included in these studies or were included in the comparison group. Consequently, the results may be generalized only to women with severe disease and antiepileptic drug treatment. It is not clear whether the differences in study design contributed to the differences in the results of the studies. Stratification by design into historical, prospective, and register-based studies revealed no consistent pattern in the results. Any difference in results may thus be random or due to other factors not accounted for in the studies.
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<tr>
<th>Study</th>
<th>Country or state, setting, study period</th>
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<td>Pre-term delivery (risk ratio)</td>
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<td>Niel et al., 1983 (62) Israel, obstetric, 1971–1980</td>
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<td>172 Match 1/1: age, parity, time of delivery</td>
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<td>Jones et al., 1989 (66) California, teratogen registry, 1979–?</td>
<td>54 Prospective No Yes 0 69</td>
<td>70 Random, no drug treatment, 0-30 ml of alcohol per week</td>
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<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
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<td>Waters et al., 1994</td>
<td>California, special clinic, 1987–1990</td>
<td>174</td>
<td>Prospective</td>
<td>No</td>
<td>No</td>
<td>355 Random hospital database sample, healthy women</td>
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<td>Steegers-Theunissen et al., 1994</td>
<td>Netherlands, obstetric, 1972–1992</td>
<td>119</td>
<td>Prospective</td>
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<td>No</td>
<td>106 Random, no genetic disorder, no treatment</td>
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<td>India, obstetric, 1987–1994</td>
<td>157</td>
<td>Historical</td>
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<td>Yes</td>
<td>471 Match 3/1: age, parity, time of delivery</td>
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<td>Yes</td>
<td>39,211 Total database</td>
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</table>

* Differences in mean gestational age and mean birth weight are reported for children of all women with epilepsy compared with children of women in the comparison group (↑, decreased gestational age or birth weight; ↓, increased gestational age or birth weight), as are the risk ratios. All risk ratios are relative risks.
† Indicates that the distribution of epilepsy type and occurrence of seizures and seizure frequency were described.
‡ Monotherapy fraction is the fraction of treated women who received monotherapy.
§ LWB, low birth weight; SGA, small for gestational age.
Definition of epilepsy

Few studies provided specific definitions of epilepsy, such as the World Health Organization criteria (56) and the criteria of the International League Against Epilepsy (69). Four studies defined the exposure by antiepileptic drug treatment (54, 62, 64, 66), and one of these studies (66) failed to report on the presence of epilepsy in treated women. Five studies reported confirmation of the epilepsy diagnosis by a neurologist (55, 61, 65, 72, 74), whereas the remaining studies failed to provide information on the validity of the diagnosis. Most studies excluded women with onset of disease during pregnancy, but these women were included in at least two studies (73, 74). Thus, different subgroups of women with epilepsy were enrolled, but it is unclear whether this affected the results.

Comparison group

Most studies used a random sample of the background population for comparison, while some used individually matched controls. In general, the use of individually matched controls limits interpretation regarding potential confounders and common background factors. In particular, matching by social status may introduce an unadjustable selection bias if social status is affected by epilepsy. The direction and magnitude of this bias are unknown because unadjusted risk estimates cannot be calculated. Women with chronic diseases other than epilepsy were included in the comparison group in some studies (54, 61, 67, 71), which may bias the results toward no effect.

Outcome measures

In most studies, the method to estimate gestational age was not described, and it is therefore not clear to what extent the results related to gestational age may be biased. It is also unclear whether a reduced mean birth weight or an increased risk of low birth weight or small for gestational age reflects a true increase in the risk of intrauterine growth restriction. The majority of studies reported a reduction of head circumference in children of women with epilepsy. This could be due to proportionate intrauterine growth restriction, but only two studies investigated body proportions in children of women with epilepsy, and both studies combined birth weight with body length. Sonneveld and Correy (67) found no difference in the mean ponderal index between children of women with epilepsy and children of controls, while Gaily and Granström (58) found a slight reduction of the ponderal index in children of treated as well as untreated women with epilepsy relative to healthy controls.

Confounding

Part of the results may be due to confounding from maternal age, parity, and social status and from congenital malformations of the newborn. There is insufficient evidence on the impact of lifestyle factors and folate deficiency on gestational age and birth weight in children of women with epilepsy.

In general, most of the studies reviewed had one or more of the above-mentioned limitations. Furthermore, small samples and poorly described methods increased the risk of random errors. Three large studies used carefully described methods and were less prone to systematic errors. The study from the Collaborative Perinatal Project (61) thoroughly described the study group, but the assessment of gestational age was inaccurate. The Finnish cohort (56–58) had a closely monitored study group and valid gestational ages based on ultrasound scannings. The Dutch multicenter study (72) enrolled women with epilepsy before conception and provided detailed information on maternal characteristics. The methodological strengths in these three cohorts increase the confidence in their results that support the overall conclusion from all the studies in the review (table 1).

CONCLUSIONS

We reviewed the literature on gestational age and birth weight in children of women with epilepsy. There is some evidence that women with epilepsy are at increased risk of preterm delivery. The risk may be increased only in women who receive antiepileptic drug treatment. With respect to birth weight, most evidence suggests that women with epilepsy give birth to children with reduced birth weight. The birth weight reduction may be due to more preterm deliveries, to a reduced growth potential in children of women with epilepsy, or to intrauterine growth restriction. It appears that birth weight is reduced in children of treated as well as untreated women with epilepsy. Particularly high risk intrauterine growth restriction may be associated with antiepileptic drug treatment, but firm conclusions related to any specific drug-induced growth restriction seem unjustified. No specific pattern of intrauterine growth restriction in children of women with epilepsy has been identified.

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