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Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts

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Summary

Purpose—To conduct a systematic review and meta-analysis to quantify the incidence of congenital malformations (CMs) and other pregnancy outcomes as a function of in utero anti-epileptic drug (AED) exposure.

Methods—We performed a systematic literature review to identify all published registries and cohort studies of births from pregnant women with epilepsy (WWE) that reported incidence of CMs. Overall incidences were calculated using a random effects model.

Results—The review included 59 studies that met inclusion/exclusion criteria, involving 65,533 pregnancies in WWE and 1,817,024 in healthy women. The calculated incidence of births with CM in WWE [7.08%; 95% CIs 5.62, 8.54] was higher than healthy women [2.28%; CIs 1.46, 3.10]. Incidence was highest for AED polytherapy [16.78%; CIs 0.51, 33.05]. The AED with the highest CM incidence was valproate, which was 10.73% [CIs 8.16, 13.29] for valproate monotherapy.

Conclusions—Results of this systematic literature review suggest that the overall incidence of CMs in children born of WWE is approximately threefold that of healthy women. The risk is elevated for all AED monotherapy and further elevated for AED polytherapy compared to women without epilepsy. The risk was significantly higher for children exposed to valproate monotherapy and to polytherapy of 2 or more drugs when the polytherapy combination included phenobarital, phenytoin, or valproate. Further research is needed to delineate the specific risk for each individual AED and to determine underlying mechanisms including genetic risk factors.

Keywords

Anticonvulsants; Anti-epileptic drugs; Congenital malformations; Pregnancy; Epilepsy; Fetus

Introduction

Most women with epilepsy (WWE) require ongoing antiepileptic drug (AED) therapy during pregnancy in order to avoid the adverse effects of seizures on themselves and their unborn child. However, in utero AED exposure poses a risk of congenital malformations (CMs) to the

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child (Meador et al., 2006). The original reports of AED teratogenicity date from the 1960s (Mullers-Kuppers, 1963), but despite the passage of more than 40 years, many issues remain uncertain. In recent years, AED pregnancy registries have been developed, and there has been a marked increase in registry and cohort studies examining risks posed by AEDs to the unborn child. The main objective of the present investigation was to conduct a systematic review of the literature for all registries and cohort studies of pregnant WWE that report pregnancy outcomes in order to quantify (through meta-analysis) the incidence of CMs and other pregnancy outcomes. Additionally, the incidence of teratogenic effects associated with monotherapy and polytherapy anticonvulsant regimens containing carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproate, was examined where data were available.

In this systematic literature review of all published registries and cohorts of pregnant WWE, we identified and analyzed the incidence of various pregnancy outcomes and teratogenic effects of AEDs. This review summarized relevant literature published between 1970 and 2007 and was further analyzed to quantify the incidence of pregnancy outcomes (healthy births, spontaneous abortions, and most importantly, congenital malformations) in WWE, and to quantify the association of AED and other risk factors with adverse pregnancy outcomes.

Methods

The systematic review methods utilized in this report have been previously described (Cook et al., 1997; Alderson et al., 2004).

Study identification

A comprehensive literature search of MEDLINE (via PubMed) and EMBASE was performed for English language studies published from 1966 through 18 May 2007 (Fig. 1). Our search of MEDLINE was conducted using the following search strategy:

1. carbamazepine OR Carbatrol OR Convulsofin OR Depakene OR Depakine OR Depakote OR Dilantin OR ‘‘Dipropyl Acetate’’ OR Divalproex OR Epitol OR Ergenyl OR Finlepsin OR Lamictal OR lamotrigine OR Neurotol OR phenytoin OR Tegretol OR (Tegretol XR) OR valproate OR valproic OR Vupral OR Epilepsy [MeSH] OR seizure* OR anticonvulsants [MeSH] OR epilepsy OR “petite mal” OR “grand mal” OR clonic OR “status epilepticus” Teratogens [MeSH] OR embryo* OR fetus OR fetal OR fetotoxins OR Embryonic Structures [MeSH] OR Abnormalities [MeSH] OR Pregnancy [MeSH] OR pregnan* OR grava* OR gestation OR maternal.
2. Registries [MeSH] OR registr* OR register* OR Cohort Studies [MeSH].
3. #1 AND #2 AND #3.
4. Limits: English, Human, NOT clinical trials, case reports, editorials, news, or reviews.

A keyword search of EMBASE was performed using a similar strategy to the MEDLINE search. Two additional strategies were used to identify recently published articles that may not have yet been indexed on MEDLINE. The PubMed search included a keyword search for the past 6 months with no limits; and Current Contents® was searched for the past 6 months, using similar search terms. Additionally, the Cochrane Library was searched for any recent systematic review of the subject, which could be a source of further references. A manual check of the reference lists of all accepted studies and of recent reviews and meta-analyses was performed to supplement the above searches and ensure optimal and complete literature retrieval.

Study selection

Study eligibility was determined by two reviewers, who used abstracts of publications and full papers when necessary. Two levels of study screening were performed. Level I screening was performed on abstracts downloaded from the literature searches noted above. At Level I screening, any study with a definite exclusion criterion (as listed below) was rejected. If no definite exclusion criterion was identified, then the full paper was retrieved for closer review. Level II screening was then applied to full papers. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be present for studies to pass Level II screening.

Exclusion criteria

1. Letters, editorials, news, case-reports, commentaries, reviews
2. animal or in vitro studies
3. language other than English
4. study participants were not pregnant WWE
5. no outcomes of interest reported (e.g., incidence of pregnancy outcomes, teratogenic effects, etc.)
6. less than 100 total pregnancies or births in study.

Inclusion criteria

1. Study design: registry or cohort study of pregnant WWE
2. At least 100 total pregnancies or births in study
3. Incidence of pregnancy outcomes (e.g., teratogenic effects, live births, spontaneous abortions, etc.) reported.

Additionally, all publications in the project were reviewed for availability of separable monotherapy and polytherapy data for the calculation of monotherapy and polytherapy specific CM rates for the drugs of interest. This required both extractable numerators (all CM events for particular drugs) and denominators (all patients exposed to that drug in monotherapy or polytherapy regimens specifically). When data existed in a published study that allowed us to calculate the rate of congenital malformations for at least one of the drugs of interest, it was included for data extraction.

Data extraction

For each eligible study that passed Level II screening, data elements of interest were extracted on the appropriate data extraction forms developed specifically for use in this project. For the monotherapy and polytherapy drug specific calculations of CM, we did not attempt to extract the individual types of CMs by individual drug and drug combinations. One investigator extracted the data from each study, and then a second reviewer (a senior researcher, typically a PhD or physician) independently reviewed each data form against the original paper for completeness and accuracy. Any discrepancies in extracted data were resolved by a consensus conference between the two investigators, with a third party arbitrating disagreements as necessary.

Extraction was attempted for information on pregnancy history including prior number of pregnancies, prior births with CMs, prior abortions, and prior spontaneous abortions, but very little information was available in the published studies and thus is not presented in these results.

Database development

All extracted data were entered into MetaHub®, a relational database of clinical trials and observational studies. Data entry was then 100% verified back to the extraction forms and checked for accuracy and consistency prior to locking the database for analysis. Studies that could not be retrieved by 1 June 2007 (for initial study analysis) were not included in the final dataset.

Statistical analysis

Design, patient, and treatment characteristics of the eligible studies were summarized using basic descriptive statistics. Due to significant heterogeneity in the reporting of numbers of subjects, we created a hierarchical rule for determining the denominators for analysis. Some studies reported the number of pregnant women as a denominator, while others reported the number of pregnancies (total number of potential children for delivery, which accounted for twins, triplets, etc.), and others reported the number of live births (total pregnancies minus the number of intentionally and unintentionally terminated pregnancies). In an effort to create a denominator that could be used across studies for meta-analysis, we used the following hierarchy for the creation of denominators for incidence of pregnancy outcomes: number of pregnancies; if that is not reported, then number of births; and if that is not reported, then number of pregnant women. For baseline characteristics of pregnant women and not their offspring, the above hierarchy was reversed to create a denominator.

All CM information was extracted verbatim from the published study reports. Congenital malformations, as defined by the authors, were captured as both the number of malformations and as the number of births with malformations, where available. After data entry was complete, a clinician reviewed all of the verbatim CM terms and categorized them into clinically meaningful and analyzable categories for analysis.

In the CM-specific analysis for each event or category of events of interest, incidence estimates were meta-analyzed across studies, and weighted by sample size following a Poisson distribution. Heterogeneity in all meta-analyses was examined using Cochran's *Q* statistic. Stratified analyses by type of anti-epileptic medication were conducted where appropriate and feasible. For the monotherapy and polytherapy drug specific analysis, the incidence of births with malformations was more commonly reported/extractable than actual number of events for all the analyses. Due to small numbers of events and the heterogeneity across studies, these incidence rates were not meta-analyzed, but rather the incidence rates were pooled.

The Poisson model was used because it expresses the probability of a number of events occurring in a fixed period of time, assuming that these events occur with a known average rate, and are independent of the time since the last event. Therefore, multiple events (such as a child born with multiple malformations) could be considered as discrete occurrences within a uniform interval of time (9 months of pregnancy). Unlike a raw count incidence score, a Poisson model compensates for large studies that may dominate pooled data. The higher the between-study variation, the less weight a large study will be allowed in the analysis. Consequently, when there is a lack of heterogeneity, the point-estimate of incidence from the random effects mode will equal simple pooled incidence. When the results of each paper vary widely, the point-estimate of incidence from a random effects mode should be expected to change from the point-estimate of the simple calculation of raw incidence. If this variation is significant, caution must be exerted interpreting a point-estimate of incidence from raw data.

Results

Search yields

At Level I screening, 1003 abstracts were reviewed for eligibility, of which 261 full text articles were retrieved for Level II review of inclusion criteria. Of the 261 articles retrieved, 59 primary studies (Meador et al., 2006; Annegers et al., 1978; Artama et al., 2005a; Bertollini et al., 1987; Cunnington and Tennis, 2005; Czeizel et al., 1992; D'Souza et al., 1991; Diav-Citrin et al., 2001; Dravet et al., 1992; Eskazan and Aslan, 1992; Fairgrieve et al., 2000; Fedrick, 1973; Fonager et al., 2000; German et al., 1970; Higgins and Comerford, 1974; Hiilesmaa et al., 1983; Holmes et al., 2001; Hvas et al., 2000; Jick and Terris, 1997; Kaaja et al., 2003; Kallen, 1986; Kaneko et al., 1999; Katz et al., 2001; King et al., 1996; Knight and Rhind, 1975; Koch et al., 1992; Lander and Eadie, 1990; Lindhout et al., 1992; Lowe, 1973; Martin and Millac, 1993; Mastroiacovo et al., 1988; Meischenguiser et al., 2004; Monson et al., 1973; Morrow et al., 2006; Nakane et al., 1980; Niswander and Wertelecki, 1973; Oguni et al., 1992; Olafsson et al., 1998; Omtzigt et al., 1992a; Richmond et al., 2004; Robert et al., 1986; Sabers et al., 1998; Sabers et al., 2004; Samren et al., 1999; Sawhney et al., 1996; Schupf and Ottman, 1997; Shakir and Abdulwahab, 1991; Sonneveld and Correy, 1990; Speidel and Meadow, 1972; Starreveld-Zimmerman et al., 1974; Steegers-Theunissen et al., 1994; Tanganelli and Regesta, 1992; Vajda et al., 2006; Viinikainen et al., 2006a; Waters et al., 1994; Wide et al., 2004; Wilhelm et al., 1990; Wladimiroff et al., 1988; Yerby, 1996) and 36 duplicate reports of patient population studies (Annegers et al., 1988; Artama et al., 2005b; Cunnington, 2004; Tennis and Eldridge, 2002; Reiff-Eldridge et al., 2000; Hiilesmaa et al., 1981, 1985; Wyszynski et al., 2005; Holmes et al., 1994, 2004; Holmes and Wyszynski, 2004; Kaaja et al., 2002; Kallen, 1994; Battino et al., 1999; Canger et al., 1999; Kaneko et al., 1992, 1993, 1988; Battino et al., 1992; Bjerkedal and Bahna, 1973; Lindhout et al., 1984; Nelson and Ellenberg, 1982; Shapiro et al., 1976; Hunt et al., 2006; Nakane, 1979; Omtzigt et al., 1992b, 1993; Tomson, 2006; Vajda and Eadie, 2005; Tomson et al., 2004; Vajda et al., 2003, 2004a,b; Viinikainen et al., 2006b; Pilo et al., 2006; Källín, 2003) were accepted.

Study characteristics

The 59 primary studies (*k*) included 102 separately extractable treatment arms (*t*) (Table 1). There were 10 studies published between 1970 and 1979 ($t = 16$), seven studies published from 1980 to 1989 ($t = 11$), 25 studies published between 1990 and 1999 ($t = 41$), and 17 studies published from 2000 to 2006 ($t = 34$). Thirty-five studies ($t = 63$) were based in Europe, 11 ($t = 19$) in North America, three were multi-continental ($t = 4$), and 10 studies ($t = 16$) were conducted in places other than Europe or North America or on multiple continents. Fourteen studies were industry sponsored ($t = 24$). There were 11 studies ($t = 11$) that had separately reported monotherapy AED treatment groups, seven studies ($t = 7$) that had separate polytherapy AED treatment groups, 25 studies ($t = 27$) with WWE not treated with AEDs, and 50 studies ($t = 57$) with treatment groups that had mixtures of monotherapy and polytherapy treated patients. Nineteen studies ($t = 20$) included data that could be extracted for both WWE and those who did not have epilepsy. Commonly, these were population cross-sectional studies where case finding for pregnancies complicated with epilepsy was done in the context of a mandatory country-wide registry or multiple hospital records. There were seven studies ($t = 7$) with treatment arms containing 1000 or more pregnancies in WWE, five ($t = 5$) with 501–1000 pregnancies in WWE, and eight ($t = 8$) with 301–500 pregnancies in WWE.

Patient characteristics

There were 25 studies that reported the mean age of pregnant WWE; the mean age of the WWE was 29.1 years. Of all the WWE studied who received AEDs, there were 57.1% treated with AED monotherapy and 26.3% treated with polytherapy.

Incidence of Congenital Malformations and Other Pregnancy Outcomes. Pregnancy outcomes are detailed in Table 2 for the following categories: healthy births, still births, spontaneous abortions, elective abortions, elective abortions due to CMs, the number of births with CMs, the total number of CMs, and perinatal deaths. Significant heterogeneity across treatment arms ($p < 0.01$) was detected for most analyses. For pregnancies in all WWE, CMs were estimated as 8.42 total events per 100 pregnancies (95% confidence inferval [CI] = 6.73, 10.11) and 7.08 births with CM per 100 pregnancies (95% CI = 5.62, 8.54). Differences in CM rates for births and total events are due in part to the fact that different studies contribute information to each rate, and only a few studies had data for both. These estimates were more than 2.5 times higher than those for healthy women ($p < 0.05$). Rates of births with CMs were numerically higher for women treated with AED polytherapy (16.78%; 95% CI = 0.51, 33.05) compared to women treated with AED monotherapy (10.12%; 95% CI = 1.96, 18.28). Rates of total CMs were significantly higher ($p < 0.05$) for polytherapy (9.84%; 95% CI = 7.82, 11.87) than monotherapy (5.30%; 95% CI = 3.51, 7.09).

The data were stratified over four categories of women. WWE were typically identified in studies by clinical diagnosis or diagnosis code. AED use was not sufficient to infer that a woman had epilepsy. The broad category of WWE contained unknown proportions of monotherapy, polytherapy, and unexposed pregnant WWE. Monotherapy and polytherapy subgroups were analyzed separately when the treatment regimen(s) were clear. The non-epileptic category was derived from comparison groups that could be extracted separately from those with epilepsy. Typically, they represent a population of baseline risk—a hospital matched control or a government birth or medication registry. AED users without epilepsy were excluded from these analyses.

Incidence of individual congenital malformations

The numbers of CMs are detailed in Table 3 according to the following organ systems: alimentary, cardiovascular, dermatologic, genital, urinary, lung (pulmonary), and musculoskeletal systems. In addition, specific malformations were also grouped as “ear, neck, or face”, “neural tube defects”, “neurological”, “palmer crease”, “chromosomal”, “any syndrome”, or “miscellaneous”. Malformations within an organ system were elaborated if data permitted.

For all those children of WWE, the most common malformations were cardiovascular defects (Poisson point-estimate = 1.77 per 100 pregnancies; 95% CI = 1.39, 2.25; $t = 59$) followed by musculoskeletal defects (1.48 per 100 pregnancies; 95% CI = 1.14, 1.92; $t = 59$). When compared to healthy women, the WWE group had significantly higher rates of hernia, ear/neck/face, cleft lip, and spina bifida ($p < 0.05$). The polytherapy AED group had significantly higher rates of ear/neck/face and cleft lip compared tothe monotherapy AED group. Across groups, there seemed to be a trend in the incidence for specific malformations with higher rates in children of WWE compared to healthy women, and there was also a trend for higher rates in children of women treated with AED polytherapy to be higher than monotherapy. However, this trend was not always seen when individual malformations were considered separately.

Incidence of congenital malformation by treatment

The incidence of CM was calculated as either number of affected births or total events and stratified by AED treatment exposure and individual treatment combinations in Table 4. Incidence rates were stratified for the five drugs that had at least five eligible and extracted treatment groups: carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproate. Several drugs, including oxcarbazepine, were originally intended to be included, but due to lack of published eligible studies were not included in the formal analyses. Individual

treatments were examined as monotherapy, polytherapy with the drug of interest and any one other AED treatment, and also with at least two other AED treatments.

The highest rates of births with CMs were seen for valproate (10.73%; 95% CI = 8.16, 13.29) and phenytoin (7.36%; 95% CI = 3.60, 11, 11). Carbamazepine (4.62%; 95% CI = 3.48, 5.76), phenobarbital (4.91%; 95% CI = 3.22, 6.59), and lamotrigine (2.91%; 95% CI = 2.00, 3.82) were slightly lower. The rate for valproate was significantly higher than the rate for healthy women.

The highest rates of births with CM for polytherapy regimens including the individual drugs plus one other AED were seen for phenytoin (11.47%; 95% CI = 6.65, 16.30), phenobarbital (9.19%; 95% CI = 5.88, 12.50), and valproate (9.79%; 95% CI = 7.57, 12.02). For most individual drugs, the rate of malformations was approximately doubled when comparing monotherapy rates to polytherapy with the addition of another AED to the individual drug. The highest rate for polytherapy regimens including the individual drugs plus any two or more other AEDs was valproate with 25.00% (95% CI = 5.97; 44.03). The rates for phenobarbital, phenytoin, and valproate plus one other AED were significantly higher when compared to healthy women. The same drugs (phenobarbital, phenytoin, and valproate) were also noted to have significantly higher rates of CMs when combined with two or more other AEDs compared to healthy women. The numbers of patients and treatment arms in this analytical summary were notably low.

Discussion

Over the last few years, a large amount of new information has become available on the incidence of CMs in pregnant women exposed to AEDs. We identified 59 registries and cohort studies that had the primary objective of examining this issue. For WWE, the incidence of births with a CM was estimated to be 7.08% [95% CIs = 5.62, 8.54] according to the Poisson meta-analytic model. This incidence was significantly greater and over three times higher than for healthy women, who had an incidence of 2.28% [95% CIs = 1.46, 3.10]. Although not statistically significant, the number of malformed births for polytherapy tended to be higher than monotherapy. The incidence of births with CMs in monotherapy groups was estimated to be 10.12% [95% CIs = 1.96, 18.28] and in polytherapy groups incidence was 16.78% [95% CIs = 0.51, 33.05]. This pattern of risk was also evident when we examined CMs as total events rather than as births. Total events were fewest in healthy mothers (3.27%; CIs = 1.37, 5.17), roughly double in WWE (8.42%; 95% CIs = 6.73, 10.11), and also significantly increased ($p < 0.05$) in the polytherapy group (9.84%; 95% CIs = 7.82, 11.87), which was more than 1.5 times higher than the rates for monotherapy.

The most common defects in babies of mothers without epilepsy were malformations of the cardiovascular system, in particular ventricular septal defects. Muscular skeletal defects and urinary malformations were less common, but still prominent. In almost every category, more defects were detected in babies born to WWE than in babies born to those without epilepsy. Cardiovascular and musculoskeletal systems were still the most common types of CMs, but some rare defects became much more common. For example, defects of the ear, neck, and face were significantly greater and increased 7.8-fold in offspring of WWE compared to those without epilepsy. Cleft lip was also significantly increased in offspring of WWE. Spina bifida, the lowest defect category for offspring of mothers without epilepsy, was 14.7-fold higher for those children born to WWE.

In most categories, exposure to monotherapy or polytherapy demonstrated non-significantly higher incidences of CMs than unexposed births. The incidence of ear/neck/face defects and cleft lip were significantly increased in both monotherapy and polytherapy groups. In some

body systems, no increases were apparent. For example, the incidence was similar (e.g., urinary) or even non-significantly lower (e.g., alimentary) in monotherapy-exposed births versus unexposed births. Likewise, children exposed to polytherapy had a numerically lower mean incidence of alimentary defects than children born to all WWE and mothers without epilepsy.

Data was collected from births exposed to carbamazepine, lamotrigine, phenobarbital, phenytoin, or valproate. The highest overall incidence of malformations (as both births and total events) occurred in pregnancies exposed to valproate. When AEDs were compared in monotherapy groups, valproate continued to show the highest incidence of malformed births. When the drugs of interest were compared in polytherapy groups, valproate again continued to demonstrate higher incidence of malformed births.

The observation of increased CMs in WWE compared to healthy women could be related to AED exposure or to underlying genetic differences in the two groups. Findings show that CMs are greater for polytherapy, vary across AEDs, exhibit dose-dependent effects in several human studies, and occur in controlled animal studies. They indicate that AEDs do play an important role in the CMs observed in children of WWE. Nevertheless, teratogens act on a susceptible genotypes, so individual genetic differences likely modulate the risk imposed by AEDs. It is also quite possible that other unidentified confounding factors such as patient age, disease severity, or prior pregnancies with congenital malformations, may also provide some insight into the differences in CM risk for exposed and unexposed patients as well as the risk across varying AEDs. This review could not address those issues since individual patient data (as opposed to study level results) would be required to examine those relationships.

It should be noted that heterogeneity was noted in most analyses, and this was likely caused in part by varying definitions of teratogenic outcome as well as differences in exposure. Thus, it is difficult to come to firm conclusions with regard to the precise magnitude of difference between active treatment(s) and non-treatment. However, due to the magnitude of the overall effect, and the general consistency in direction of effect across the studies, we are comfortable in inferring that congenital malformation risk is significantly higher in the those patients treated with AEDs as opposed to not treated.

In this review, duplication in study reporting was actively reviewed, and studies (or study report years) were clearly not included when identified as duplicate reporting of the same study (and patients). Even with this vigilance, there is no assurance that a patient could not have been included in the reporting of multiple individual studies. For example, a patient could be included in both a national pregnancy registry as well as other ad hoc pregnancy registries such as those set up to track patients exposed to specific AEDs. This could result in multiple reports of both exposed patients as well as congenital malformations. There is no clear way to identify how often this occurs, but the consistency in the observed rates of congenital malformations seen across individual studies, by drug and by mono- and polytherapy provide some assurance in the acceptability in these results.

In conclusion, this systematic review using pooled incidences and meta-analyses demonstrates that epilepsy during pregnancy is associated with a higher incidence of malformations when compared to a healthy cohort. AED polytherapy exhibited higher overall adverse outcomes than monotherapy. Individual CM types were significantly elevated in children of WWE for ear/neck/face, cleft lip, and spina bifida. Across AEDs, valproate was associated with the highest risk of malformations. The risk of CMs in children exposed to AED should be communicated as part of the routine informed consent process for WWE who are prescribed AEDs and are of childbearing potential. The communication of these risks should be placed in the context that most children born to WWE are normal. Further, the teratogenetic risk of

AEDs should be balanced against the inherent risk due to seizures. Future research should seek to determine the exact teratogenic risks attributable to each individual AED and to delineate the mechanisms underlying AED-induced teratogenesis.

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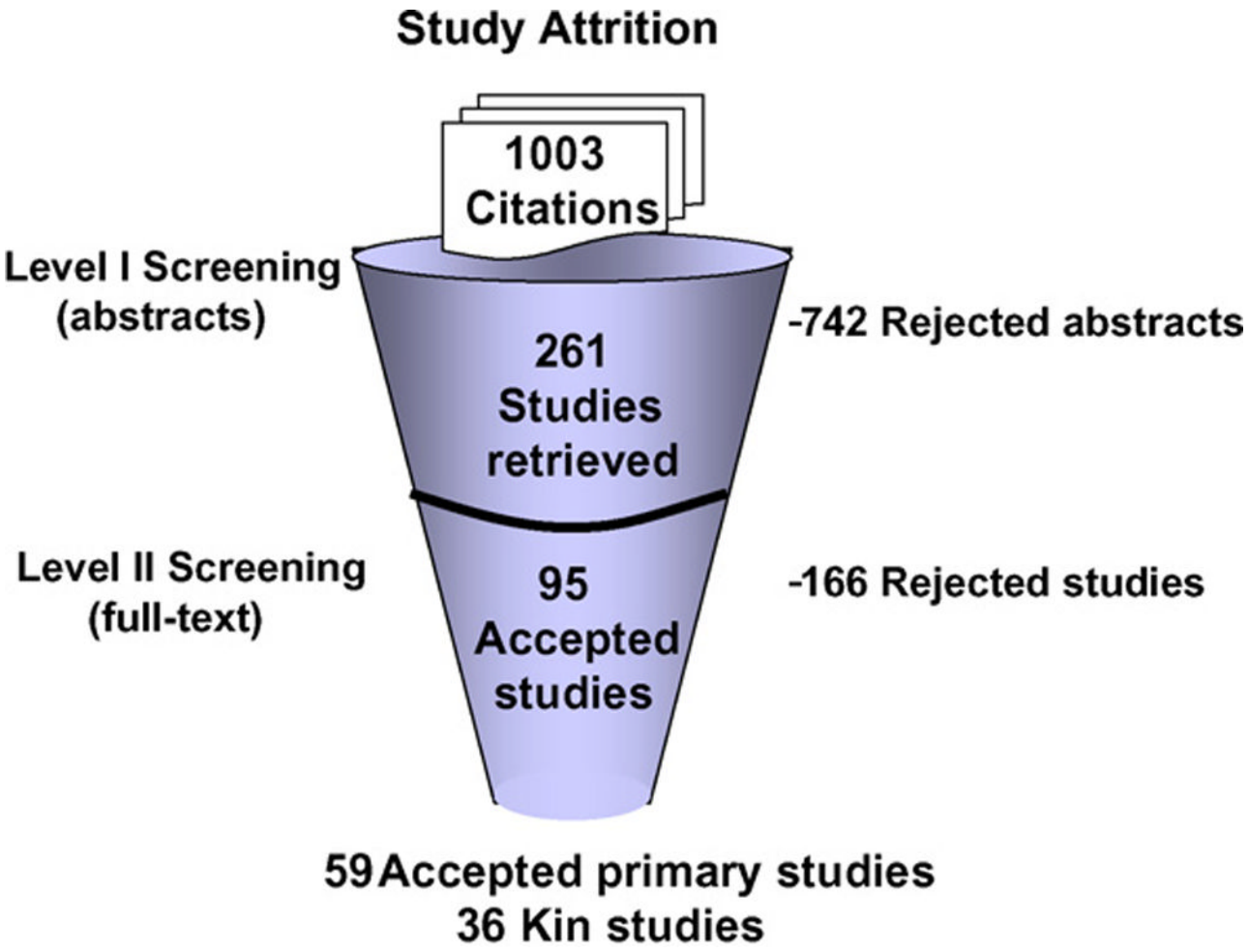

Figure 1.
Study attrition.

Table 1

Study characteristics

All studies	***k***	***t***	**# Births**
Total	59	102	1,871,218
Publication year			
1970–1979	10	16	85,532
1980–1989	7	11	2,511
1990–1999	25	41	1,629,999
2000–2006	17	34	153,176
Study location			
North America	11	19	250,430
Europe	35	63	1,615,235
Other	10	16	3,310
Multi-continental	3	4	2,243
Industry sponsored			
Yes	14	24	10,234
No/NR	45	78	1,860,984
Type of therapy[a]			
Monotherapy	11	11	6,806
Polytherapy	7	7	1,780
No AEDs	25	27	196,945
Mixed/NR	50	57	1,665,687
Number of MWE[b]			
None	19	20	1,807,486
1–99	15	20	1,330
100–200	23	24	3,522
201–300	17	18	4,453
301–500	8	8	3,722
501–1000	5	5	3,629
1000 or more	7	7	47,076

k = number of primary studies. *t* = number of treatment arms reporting characteristic. # Births = total number of births in groups reporting characteristic. AED = anti-epileptic drug. NR = not reported.

[a] Many groups had mixed mono- and polytherapeutic regimens; there were others that were not specified.

[b] Per treatment arm MWE= mothers with epilepsy.

Table 2

Incidence of congenital malformations and other pregnancy outcomes[a]

	t	# Events/# of pregnancies	Raw incidence[b]	Incidence—Poisson result[c]	*t*	# Events/# of pregnancies	Raw incidence[b]	Incidence—Poisson result[c]
All women with epilepsy[d]					Women without epilepsy[d]			
Healthy births	65	26,248/28,114	93.4%	**88.83 [86.45, 91.22]**	11	1,643,419/1,659,392	99.0%	94.74 [91.68, 97.81]
Stillbirths	32	115/9,163	1.3%	1.07 [0.73, 1.41]	11	2,154/271,687	0.8%	0.69 [0.28, 1.10]
Spontaneous abortions	27	615/8,690	7.1%	**4.65 [2.57, 6.73]**	4	115/874	13.2%	11.75 [7.60, 15.90]
Elective abortions	26	435/9,596	4.5%	2.53 [0.81, 4.26]	4	35/874	4.0%	3.84 [0.87, 6.81]
Elective abortions due to malformation	21	32/6,518	0.5%	0.38 [0.17, 0.59]	3	3/2,206	0.1%	0.16 [0.00, 0.45]
Births with congential malformation	79	2,276/56,035	4.1%	**7.08 [5.62, 8.54]**	16	6,105/315,381	1.9%	2.28 [1.46, 3.10]
Congential malformations (total events)	57	1,032/13,685	7.5%	**8.42 [6.73, 10.11]**	9	4,487/108,084	4.2%	3.27 [1.37, 5.17]
Perinatal deaths	32	108/7,012	1.5%	**1.30 [0.90, 1.71]**	5	1,190/195,550	0.6%	0.67 [0.45, 0.90]
	t	# Events/# of pregnancies	Raw incidence[b]	Incidence—Poisson result[c]	*t*	# Events/# of pregnancies	Raw incidence[b]	Incidence—Poisson result[c]
Monotherapy[d]					Polytherapy[d]			
Healthy births	9	5,630/5,992	94.00%	87.92 [78.99, 96.85]	7	1,612/1,780	90.60%	82.66 [66.59, 98.73]
Stillbirths	2	5/120	4.20%	3.13 [0.00, 8.00]	–	–	–	–
Spontaneous abortions	2	3/463	0.60%	5.25 [0.00, 18.26]	1	0/284	0.00%	0.00 [0.00, 0.49]
Elective abortions	3	4/786	0.50%	2.46 [0.00, 8.33]	1	3/284	1.10%	1.06 [0.00, 2.25]
Elective abortions due to malformation	3	1/786	0.10%	0.14 [0.00, 0.41]	1	3/284	1.10%	1.06 [0.00, 2.25]
Births with congential malformation	10	320/6,266	5.10%	10.12 [1.96, 18.28]	7	151/1,780	8.50%	16.78 [0.51, 33.05]
Congential malformations (total events)	7	111/2,352	4.70%	5.30 [3.51, 7.09]	4	82/833	9.80%	**9.84 [7.82, 11.87]**
Perinatal deaths	2	14/586	2.40%	**2.39 [1.15, 3.63]**	1	6/288	2.10%	2.08 [0.43, 3.73]

t = number of treatment arms reporting characteristic.

[a]Most meta-analytic rates were significant for the test of heterogeneity.

[b] Raw # events per 100 pregnancies.

[c] Point-estimate of incidence and 95% CIs from the Poisson model meta-analysis.

[d] Many groups had mixed mono- and polytherapeutic regimens; there were others that were not specified Bolded results are statistically significant, $p < 0.05$, when compared to women without epilepsy.

Table 3a

Incidence of individual congenital malformations for women with and without epilepsy: Poisson meta-regression results[a]

	All women with epilepsy[b]					Women without epilepsy[b]				
	t	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]	*t*	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]
Alimentary	37	124	11,616	1.07	.88 [.62–1.27]	4	519	82,224	.63	.63 [.55–.73]
Hernia	20	56	6,534	.86	**.76 [.47–1.21]**	3	265	82,084	.32	.32 [.25–.42]
Diaphragmatic hernia	6	6	2,326	.26	.27 [.07–.96]	1	1	141	.71	.71 [–]
Inguinal	13	35	4,001	.87	.73 [.43–1.26]	–	–	–	–	
Umbilical	1	4	983	.41	.41 [.–.]	1	1	184	.54	.54 [–]
Ventral hernia	3	3	683	.44	.44 [.04–5.27]	–	–	–	–	
Cardiovascular	59	296	16,617	1.78	1.77 [1.39–2.25]	6	522	82,729	.63	1.06 [.27–4.23]
Atrial septal defect	11	17	3,201	.53	.53 [.31–.91]	1	1	184	.54	.54 [–]
Coarctation	4	5	1,247	.40	.40 [.10–1.66]	–	–	–	–	–
Patent ductus arteriosis	9	11	2,453	.45	.45 [.22–.90]	–	–	–	–	–
Tetrology	8	10	2,678	.37	.37 [.18–.79]	–	–	–	–	–
Transposition	3	3	1,072	.28	.28 [.02–3.36]	1	1	184	.54	.54 [–]
Ventricular septal defect	24	48	6,283	.76	.76 [.57–1.03]	4	6	487	1.23	1.23 [.34–4.52]
Chromosomal	19	21	7,002	.30	.30 [.19–.47]	3	194	82,426	.24	.24 [.17–.32]
Dermatologic	9	25	3,242	.77	.59 [.16–2.13]	1	1	184	.54	.54 [–]
Nails	5	16	1,624	.99	.66 [.06–7.57]	–	–	–	–	–
Ear/neck/face	61	294	55,984	.53	**1.16 [.85–1.58]**	5	2,164	1,581,816	.14	.15 [.11–.19]
Cleft lip	55	226	55,086	.41	**.82 [.59–1.16]**	5	2,164	1,581,816	.14	.15 [.11–.19]
Ear	8	8	1,953	.41	.41 [.18–.95]	–	–	–	–	–
Face	22	69	5,929	1.16	1.04 [.61–1.78]	–	–	–	–	
Genital	22	58	8,479	.68	.66 [.48–.92]	–	–	–	–	–
Lung	9	10	3,235	.31	.31 [.15–.64]	–	–	–	–	–
Miscellaneous	18	60	6,290	.95	.62 [.23–1.65]	1	1	106	.94	.94 [–]
Musculoskeletal	59	248	16,045	1.55	1.48 [1.14–1.92]	3	906	82,006	1.10	1.10 [.96–1.27]
Club foot	29	46	6,462	.71	.68 [.46–1.01]	–	–	–	–	–
Fingers/toes	35	77	9,777	.79	.79 [.55–1.12]	1	1	106	.94	.94 [–]
Hips	21	50	5,655	.88	.91 [.64–1.30]	–	–	–	–	–

	All women with epilepsy[b]					Women without epilepsy[b]				
	t	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]	*t*	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]
Skull	10	17	3,320	.51	.52 [.28–.96]	1	1	141	.71	.71 [–]
Neural tube defects	46	125	21,871	.57	.75 [.55–1.02]	6	1,303	1,694,959	.08	.20 [.04–.98]
Anencephaly	11	10	3,612	.28	.28 [.14–.56]	2	94	82,242	.11	.11 [.03–.42]
Microcephaly	14	23	3,247	.71	.71 [.45–1.11]	2	387	82,242	.47	.47 [.25–.90]
Spinal	7	8	1,397	.57	.57 [.24–1.36]	1	1	140	.71	.71 [–]
Spina bifida	27	67	16,201	.41	**.58 [.38–.88]**	3	817	1,612,589	.05	.04 [.01–.17]
Hydrocephalus	12	23	3,813	.60	.59 [.32–1.09]	–	–	–	–	–
Meningocele	3	3	938	.32	.32 [.03–3.84]	–	–	–	–	–
Myelomeningocele	5	6	1,376	.44	.44 [.14–1.35]	–	–	–	–	–
Neurological	14	36	3,895	.92	.88 [.52–1.47]	2	190	81,781	.23	.23 [.09–.58]
Ptosis	6	6	1,528	.39	.39 [.14–1.12]	–	–	–	–	–
Palmar crease	3	5	706	.71	.76 [.06–9.89]	–	–	–	–	–
Any syndrome	9	20	3,044	.66	.50 [.15–1.67]	1	1	22	4.55	4.55 [–]
Urinary	42	109	12,582	.87	.85 [.63–1.14]	4	604	82,897	.73	.73 [.64–.83]

t = number of treatment arms reporting characteristic.

[a] Most meta-analytic rates were significant for the test of heterogeneity.

[b] Many groups had mixed mono- and polytherapeutic regimens; there were others that were not specified.

[c] Raw # events per 100 pregnancies.

[d] Point-estimate of incidence and 95% CIs from the Poisson model meta-analysis.

[e] Confidence intervals not given for studies with only one treatment arm, bolded results are statistically significant, $p < 0.05$, when compared to women without epilepsy.

Table 3b

Incidence of individual congenital malformations for monotherapy and polytherapy: Poisson meta-regression results[a]

	Monotherapy[b]					Polytherapy[b]				
	t	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]	*t*	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]
Alimentary	6	9	3,548	.25	.25 [.09–.73]	4	4	833	.48	.48 [.10–2.36]
Hernia	2	2	1,530	.13	.13 [.00–1043.15]	1	1	288	.35	.35 [–]
Diaphragmatic hernia	1	1	1,256	.08	.08 [–]	1	1	288	.35	.35 [–]
Inguinal	2	2	597	.34	.34 [.00–2673.09]	–	–	–	–	–
Umbilical	–	–	–	–	–	–	–	–	–	–
Ventral hernia	–	–	–	–	–	–	–	–	–	–
Cardiovascular	8	49	3,619	1.35	2.02 [.83–4.91]	5	41	868	4.72	4.16 [.63–27.40]
Atrial septal defect	–	–	–	–	–	1	2	284	.70	.70 [–]
Coarctation	1	1	323	.31	.31 [–]	–	–	–	–	–
Patent ductus arteriosis	1	1	263	.38	.38 [–]	1	2	284	.70	.70 [–]
Tetrology	–	–	–	–	–	1	1	288	.35	.35 [–]
Transposition	1	1	441	.23	.23 [–]	1	1	284	.35	.35 [–]
Ventricular septal defect	2	4	463	.86	.86 [.00–496.05]	1	1	284	.35	.35 [–]
Chromosomal	2	5	1,494	.33	.33 [.00–98.28]	1	2	180	1.11	1.11 [–]
Dermatologic	–	–	–	–	–	–	–	–	–	–
Nails	–	–	–	–	–	–	–	–	–	–
Ear/neck/face	8	22	3,706	.59	**.71 [.25–1.98]**	5	31	868	3.57	**2.92 [.37–22.71]**
Cleft lip	7	20	3,432	.58	**.71 [.21–2.44]**	5	27	868	3.11	**2.18 [.22–21.60]**
Ear	–	–	–	–	–	1	1	284	.35	.35 [–]
Face	1	2	274	.73	.73 [–]	1	2	284	.70	.70 [–]
Genital	3	13	1,828	.71	.71 [.22–2.35]	2	6	468	1.28	1.28 [.01–229.46]
Lung	–	–	–	–	–	–	–	–	–	–
Miscellaneous	3	17	1,614	1.05	.96 [.00–399.40]	3	20	503	3.98	.81 [.00–9030.85]
Musculoskeletal	8	44	3,909	1.13	1.21 [.50–2.92]	4	25	833	3.00	2.83 [1.16–6.90]
Club foot	4	6	1,001	.60	.60 [.16–2.20]	3	6	653	.92	.79 [.05–12.79]
Fingers/toes	4	15	1,675	.90	.90 [.39–2.04]	3	5	545	.92	.92 [.13–6.28]
Hips	4	14	1,791	.78	.85 [.26–2.83]	3	8	549	1.46	1.30 [.12–13.92]

	Monotherapy[b]					Polytherapy[b]				
	t	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]	*t*	# Events	# Pregnancies	Raw incidence[c]	Incidence—Poisson result[d,e]
Skull	2	4	1,579	.25	.25 [.00–145.48]	–	–	–	–	–
Neural tube defects	7	19	3,683	.52	.65 [.21–2.02]	3	10	752	1.33	.96 [.06–15.19]
Anencephaly	2	2	539	.37	.37[.00–2960.87]	–	–	–	–	–
Microcephaly	1	1	98	1.02	1.02 [–]	1	1	284	.35	.35 [–]
Spinal	1	1	274	.36	.36 [–]	1	1	284	.35	.35 [–]
Spina bifida	3	10	1,565	.64	.92 [.03–29.77]	3	4	752	.53	.53 [.06–4.57]
Hydrocephalus	1	3	274	1.09	1.09 [–]	1	1	284	.35	.35 [–]
Meningocele	–	–	–	–	–	–	–	–	–	–
Myelomeningocele	–	–	–	–	–	1	2	284	.70	.70 [–]
Neurological	1	1	22	4.55	4.55 [–]	–	–	–	–	–
Ptosis	–	–	–	–	–	–	–	–	–	–
Palmar crease	–	–	–	–	–	–	–	–	–	–
Any syndrome	1	1	22	4.55	4.55 [–]	–	–	–	–	–
Urinary	6	34	3,574	.95	1.04 [.36–3.03]	3	3	503	.60	.52 [.00–81.56]

t = number of treatment arms reporting characteristic.

[a] Most meta-analytic rates were significant for the test of heterogeneity.

[b] Many groups had mixed mono- and polytherapeutic regimens; there were others that were not specified.

[c] Raw # events per 100 pregnancies.

[d] Point-estimate of incidence and 95% CIs from the Poisson model meta-analysis.

[e] Confidence intervals not given for studies with only 1 treatment arm, bolded results are statistically significant, $p < 0.05$, when compared to women without epilepsy.

Table 4

Meta-analyzed incidence of congenital malformations by AED exposure[a]

Treatment	Malformations (total events)		Births with malformations[b]	
	t (*n*)	% [95% CI]	*t* (*n*)	% [95% CI]
Women without epilepsy	9 (108,084)	3.27 [1.37, 5.17]	16 (315,381)	2.28 [1.46, 3.10]
Monotherapy				
Carbamazepine	24 (4,411)	4.62 [3.48, 5.76]	9 (544)	**5.68 [3.71, 7.65]**
Lamotrigine	5 (1,337)	2.91 [2.00, 3.82]	3 (600)	1.55 [0.00, 3.48]
Phenobarbital	14 (945)	4.91 [3.22, 6.59]	4 (126)	5.90 [0.00, 13.46]
Phenytoin	16 (1,198)	7.36 [3.60, 11.11]	5 (289)	5.48 [2.80, 8.16]
Valproate	19 (2,097)	**10.73 [8.16, 13.29]**	6 (217)	**17.64 [5.25, 30.03]**
Polytherapy—2 drugs				
Carbamazepine + 1 other	25 (942)	7.10 [3.71, 10.49]	9 (279)	1.89 [0.00, 5.14]
Lamotrigine + 1 other	5 (599)	5.59 [1.11, 10.08]	3 (388)	8.67 [0.00, 22.61]
Phenobarbital + 1 other	19 (603)	**9.19 [5.88, 12.50]**	4 (51)	16.40 [0.00, 34.09]
Phenytoin + 1 other	18 (720)	**11.47 [6.65, 16.30]**	3 (52)	6.49 [0.00, 21.75]
Valproate + 1 other	14 (694)	**9.79 [7.57, 12.02]**	3 (124)	18.64 [0.00, 39.78]
Polytherapy—3 drugs or more				
Carbamazepine + 2 or more others	4 (70)	8.57 [1.99, 15.16]	–	–
Lamotrigine + 2 or more others	–	–	–	–
Phenobarbital + 2 or more others	6 (221)	**14.57 [8.81, 20.33]**	–	–
Phenytoin + 2 or more others	9 (276)	**14.27 [8.95, 19.60]**	–	–
Valproate + 2 or more others	2 (20)	**25.00 [5.97, 44.03]**	–	–

t = number of treatment arms reporting characteristic. *n* = number of patients reporting characteristic. CI = 95% confidence interval. %=*n*/*N*.

[a] Most meta-analytic rates were significant for the test of heterogeneity, bolded results are statistically significant, $p < 0.05$, when compared to women without epilepsy.

[b] The rates for births with malformations may be higher than the rates of total events due to the fact that different studies contribute information to each rate and only a few studies contribute data to both.