NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canada

FIRST TRIMESTER ANTICONVULSANT THERAPY AND THE RISK OF CONGENITAL MALFORMATION IN THE OFFSPRING OF WOMEN WITH EPILEPSY

Kenneth Clark Johnson
Department of Epidemiology and Biostatistics
McGill University, Montreal

A Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

June 1992.

ISBN 0-315-87704-9

Canada

Short title of Ph. D. thesis by Kenneth Clark Johnson:

Anticonvulsant therapy and congenital malformation

ABSTRACT

The purpose of this thesis is two-fold: 1) to refine understanding of the relationship between anticonvulsant therapy during the first trimester of pregnancy in women with epilepsy and the risk of congenital malformation among their offspring; and 2) to assess the utility of the Saskatchewan Prescription Drug and Hospital Services databases for studies of maternal drug use and certain reproductive outcomes.

There were two central components to the work--meta-analyses and a record linkage study. Two meta-analyses were performed to quantify and synthesize results of the over 60 published epidemiologic studies concerning anticonvulsant teratogenesis. In the first meta-analysis the malformation risks associated with the use of anticonvulsants in general by women with epilepsy were quantified and clarified. Comparison of the congenital malformation risk among offspring of mothers with epilepsy with first trimester anticonvulsant exposure ("exposed") relative to offspring of non-epileptic parents yielded a summary estimate of relative risk (RR) of 2.6 (95% confidence interval (CI) 2.1-3.2). (All RR's in this abstract are study-stratified Mantel-Haenszel summary estimates.) Congenital malformation risk among the offspring of exposed women with epilepsy compared to unexposed women with epilepsy yielded a summary RR of 2.9 (CI=2.0-4.2). No evidence of increased risk to unexposed women with epilepsy compared to non-epileptic women was evident (RR=0.9, CI=0.5-1.6).

In the second meta-analysis the risks associated with specific types of anticonvulsant therapy were quantitatively synthesized. The analysis demonstrated the inadequacies of many study reports--vague descriptions of methods often restricted assessment of study quality and incomplete reporting of results was largely responsible for restricting the analysis to 31 studies. Women with epilepsy treated with anticonvulsant monotherapy experienced increased risk of congenitally malformed children relative to both unexposed women with epilepsy (RR=1.8, CI=0.8-4.8), and unexposed non-epileptic women (RR=2.5, CI=1.8-4.0). Insufficient data were available to demonstrate statistically

significant differences in malformation risk among specific commonly-used anticonvulsant monotherapies, although phenobarbital and carbamazepine appeared to have the lowest risks. Two-drug therapy was associated with a 20% increase in risk relative to monotherapy, but three-drug therapy was associated with more than twice the risk of one-drug therapy (RR=2.2, CI=1.3-3.7). Although the potential role of confounding by type and severity of epilepsy could not be evaluated, the analysis suggests that avoiding therapy with three or more anticonvulsants during the first trimester would be prudent.

The second component of the thesis was a large record linkage study utilizing information from the databases of Saskatchewan Health. An essentially population-based database of maternal drug use and reproductive outcomes was created which included 104,534 livebirths and 13,685 non-livebirth outcomes occurring between April 1977 and March 1984 linked to 299,152 prescriptions dispensed to the mothers in the year preceding the pregnancy outcome. A study of anticonvulsant use during pregnancy and birth outcome was completed using the created database. The study yielded results with respect to congenital malformation risk generally consistent with the conclusions of the meta-analyses.

Evaluation of the database of maternal drug use and reproductive outcomes raised questions about the utility of Saskatchewan Health's databases for pharmacoepidemiologic research into congenital malformations. A comparison of the Saskatchewan congenital malformation birth prevalences to those in other Canadian hospitalization-based congenital malformation reporting systems suggested that malformations were likely to be significantly underreported in Saskatchewan Health's Hospital Services Plan admission/discharge database. Furthermore, Saskatchewan Health's confidentiality policies resulted in severely limited access to the linked data, making proper epidemiologic analysis most difficult.

RÉSUMÉ

Le but de la présente thèse est de deux ordres : 1) améliorer la connaissance du lien entre le traitement aux anticonvulsivants durant le premier trimestre de la grossesse chez les épileptiques et le risque de malformations congénitales chez leurs enfants; 2) évaluer l'utilité des bases de données sur les médicaments de prescription et les services hospitaliers de la Saskatchewan aux fins des études de la consommation de médicaments par la mère et de certains dénouements de la reproduction.

La tâche comportait deux composantes centrales; une méta-analyse ainsi qu'une étude de couplage de dossiers. On a quantifié et synthétisé, à l'aide de deux méta-analyses, les résultats des 60 études épidémiologiques et plus qui ont été publiées sur la tératogénèse liée à la prise d'anticonvulsivants. La première méta-analyse a permis de quantifier et clarifier le risque dû à l'utilisation d'anticonvulsivants. En comparant le risque de malformations congénitales entre les enfants de mères épileptiques exposées à des anticonvulsivants pendant les trois premiers mois de leur grossesse et les enfants de mères non épileptiques, on a obtenu un risque synthétique (RR) de 2,6 (intervalle de confiance (IC) de 2,1-3,2 à 95 %). (Tous les RR dans cet résumé sont estimés selon la méthode de Mantel-Haenszel par stratification des études.) L'évaluation du risque de malformations congénitales chez la progéniture de femmes épileptiques exposées comparativement à des épileptiques non exposées a donné un risque synthétique de 2,9 (IC=2,0-4,2). On n'a pas mis en évidence d'augmentation du risque pour les femmes épileptiques non exposées comparativement aux femmes non épileptiques (RR=0,9, IC=0,5-1,6).

La deuxième meta-analyse a permis de quantifier le risque dû à differents types specifiques d'anticonvulsivants. Ces analyses ont démontré les imperfections de beaucoup d'études--déscriptions imprécis de methodes ont souvent apporté des restrictions de la qualité des etudes et le reportage incomplet des resultats etait essentiellement responsable pour le restriction de l'analyse a 31 etudes. Les femmes épileptiques

soumises à une monothérapie aux anticonvulsivants ont manifesté un risque accru de malformations congénitales par comparaison aux femmes épileptiques non exposées (RR=1,8, IC=0,8-4,8) et aux femmes non épileptiques non exposées (RR=2,5, IC=1,8-4,0). Les donées étaient insuffisant pour démontrer une grande incidence statistique dans la risque de malformation parmi les monothérapies. Celle au phénobarbital et celle à la carbamazépine ont été associées aux estimations du risque les plus faibles. Le risque lié au traitement basé sur l'administration de deux médicaments était 20% plus élevé que le risque lié à une monothérapie médicamenteuse. Le risque lié au traitement basé sur l'administration de trois médicaments était au moins deux fois plus élevé que le risque lié à une monothérapie médicamenteuse (RR=2,2, IC=1,3-3,7). Bien que on pourait pas évaluer le rôle possible de confusion par sorte et severité de l'epilepsie, l'analyse suggere que l'action d'éviter l'administration de trois médicaments pendant le première trimestre sera prudent.

Dans sa deuxième partie, la thèse a consisté en une étude exhaustive de couplage de dossiers basée sur des données provenant des fichiers du régime de services médico-hospitaliers de la Saskatchewan. On a créé une base de données essentiellement démographique appariant les dénouements de la grossesse et l'usage de médicaments par la mère. Cette base de données comprenait 104 534 naissances vivantes et 13 685 dénouements autres que des naissances vivantes enregistrés entre avril 1977 et mars 1984 et couplés à 299 152 ordonnances délivrées à des mères pendant l'année qui précédait le dénouement de la grossesse. À l'aide de cette base de données, on a étudié l'usage des anticonvulsivants durant la grossesse et les dénouements de la grossesse. Les résultats de l'étude, en ce qui concerne le risque de malformations congénitales, sont compatibles avec les conclusions des méta-analyses.

L'évaluation de la série de données sur les dénouements de la reproduction liés à l'usage de médicaments soulève des questions sur l'utilité des bases de données du régime de services médico-hospitaliers de la Saskatchewan aux fins de la recherche pharmacoépidémiologique sur les anomalies congénitales. Une comparaison de la

prévalence des anomalies congénitales en Saskatchewan avec celle observée dans d'autres systèmes canadiens de déclaration des anomalies congénitales basés sur les hospitalisations donne à penser qu'il est possible que les anomalies soient fortement sous-déclarées dans la base de données sur les admissions et les congés du régime de services médico-hospitaliers de la Saskatchewan. En outre, les règles de confidentialité appliquées par le régime dans cette province réduisent de beaucoup l'accès aux données appariées, rendant des plus difficile toute analyse épidémiologique adéquate.

ACKNOWLEDGEMENTS

I would like to thank Dr. James Hanley, my chief advisor, for his most sensible and thoughtful advice and guidance. I am grateful to the other members of my advisor committee, Dr. Greg Sherman and Dr. Abby Lippman, for their valuable assistance during this thesis.

I would also like to acknowledge Saskatchewan Health and in particular the Saskatchewan Prescription Drug Plan which made data available for this study. The extremely competent and conscientious computing support provided by David Helston of Westbridge Computing (to Saskatchewan Health) was particularly important to the success of this study.

I would like to thank Dr. Don Wigle and the Laboratory Centre for Disease Control for support through this endeavour. I must acknowledge Corrine Stewart who contributed valuable clerical support and uncanny attention to detail. Jocelyn Rouleau deserves thanks, especially for his programming proficiency in developing the confidence band program.

I am indebted to Susan Sinclair and Betty-Anne Daviss for the emotional support they provided. Finally I would like to thank my late father Arthur, and my two children Ami and Grady, who provided the appropriate perspectives to keep this whole undertaking in its rightful place.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CBZ	Carbamazepine
CCASS	Canadian Congenital Anomalies Surveillance System
CHD	Congenital heart disease
CI	Confidence interval
CLN	Clonazepam
DPH	Diphenylhydantoin (phenytoin)
HMRI	Hospital Medical Records Institute
ICD-9	International Classification of Diseases - Ninth Revision
OR	Odds ratio
PHB	Phenobarbitone
PRM	Primidone
RBN	Registered Benefit Number
RR	Relative risk
Rx	Prescription
SHSP	Saskatchewan Hospital Services Plan
SPDP	Saskatchewan Prescription Drug Plan
SUX	Ethosuximide
TRI	Trimethadione
VPA	Valproic acid, valproate

CHAPTER 1. INTRODUCTION AND OBJECTIVES

1.1 Introduction

Research into the teratogenicity of anticonvulsant drugs spans more than 25 years. Over 60 studies of congenital malformations (also referred to as serious congenital anomalies or major birth defects) in the offspring of epileptic women have been published. All anticonvulsants currently in use have been demonstrated to have teratogenic potential in animals and it is generally accepted that the risk of congenital malformation is two to three times greater among the offspring of epileptic women than among the offspring of non-epileptic women. Nevertheless, the roles of anticonvulsant therapy and epilepsy itself in the increased risk of malformation, and the differences in teratogenicity associated with specific anticonvulsant therapies, remain poorly understood.

If understanding of the teratogenic risk of specific anticonvulsant therapies can be improved, the risk experienced by the offspring of epileptic mothers might then be partially alleviated by reducing dosages or by replacing certain anticonvulsants with available alternatives.

Why the meta-analyses?

Individual studies in this field lack the statistical power to convincingly evaluate the teratogenic risk associated with anticonvulsant therapy (Annegers et al., 1974). Neither general reviews of the literature (Nakane, 1980; Janz, 1982; Bossi, 1983; Annegers et al.1983; Kelly, 1984; Dansky and Finnell, 1991) nor reviews of specific anticonvulsants (German et al., 1970; Albengres and Tillement, 1983; Hanson, 1986; Jeavons, 1984; Rosa, 1984; Lammer et al., 1987) have appropriately synthesized the available data to best evaluate the risks associated with epilepsy versus those associated with anticonvulsants. More importantly, little work has been done to synthesize the available

data to compare the differences in malformation risk associated with specific anticonvulsant therapies. By using meta-analytic techniques (Jenicek, 1989) to do a systematic and quantitative synthesis of the numerous studies that have been published, there is the potential to improve the understanding of teratogenic risk.

Why the Saskatchewan record linkage study?

In the early 1980's the potential usefulness of Saskatchewan Health's administrative databases as an epidemiologic tool had been recognized (Saskatchewan Health, 1984; Tilson, 1985; Connell et al., 1987). There was particular interest in relation to pharmacoepidemiology, i.e., monitoring the use of prescription drugs in populations and the subsequent occurrence of adverse health outcomes which might be attributable to drug therapy (Lawson, 1984). Five features of the databases contribute to their epidemiologic importance: 1) the Saskatchewan Prescription Drug Plan (SPDP) pays for all Formulary prescription drugs dispensed out-of-hospital to members of the Plan (Saskatchewan Health, 1983), 2) the SPDP covers almost 95% of the province's approximately one million inhabitants, 3) the Saskatchewan Hospital Services Plan (SHSP) pays for all hospitalization costs and also covers about 95% of Saskatchewan inhabitants, 4) Saskatchewan Health has had computerized accounting records for over a decade, and 5) Saskatchewan Health maintains a unique health services number for each individual covered by the plans which is a required individual identifier on each of the Saskatchewan Health databases. Prescription drug use and hospitalizations can thus be rapidly, accurately and inexpensively linked, both within and across databases, a situation essentially unprecedented in a population of almost a million people for so long a period (Tilson, 1985).

The Saskatchewan Health databases provided an opportunity to undertake a large population-based study of anticonvulsant teratogenicity. Hospital ascertained pregnancy outcomes over a seven-year period for an unselected group of women and men using

anticonvulsants could be ascertained; their anticonvulsant prescription history over a several-year period could be established in a prospective manner; the offspring could be followed from birth onwards for hospitalizations; a comparison group of pregnancies of non-epileptic parents could be established in precisely the same manner; and the dataset could be assembled at reasonable cost.

Although the potential of the Saskatchewan databases had been recognized, at the time this study was initiated (1984) very limited use had been made of the databases for epidemiologic study (West et al., 1985). Because databases like those of Saskatchewan Health were set up primarily for administrative as opposed to research purposes, there may be a number of shortcomings for use in epidemiologic research that are difficult to evaluate without in-depth study (Jick, 1985; Shapiro, 1986; Connell et al., 1987; Strom, Carson, 1990). This study was the first to use the drug and hospital databases to do in-depth epidemiologic evaluation of congenital anomalies risk related to prescription drug use.

1.2 General objective

To increase our understanding of the relationship between anticonvulsant therapy during the first trimester of pregnancy among women with epilepsy and the risk of congenital malformation among their offspring.

1.3 Specific aims

The specific aim of the first meta-analysis was:

> To compare the risk of major congenital malformations among the offspring of the following groups: epileptic women treated with anticonvulsants during the first trimester of pregnancy; epileptic women not treated with anticonvulsants during

the first trimester; treated and untreated epileptic men; and non-epileptic parents.

The specific aim of the second meta-analysis was:

To compare the risks of major congenital malformation among the offspring of epileptic mothers associated with specific anticonvulsant therapies during the first trimester of pregnancy.

The specific aims of the Saskatchewan record linkage study were:

1) To compare the risk of congenital malformation among the offspring of: women treated with anticonvulsants during the first trimester of pregnancy; men treated with anticonvulsants during the spermatogenesis period; parents not treated with anticonvulsants.

2) To compare the risks of congenital malformation among the offspring of mothers associated with treatment with specific anticonvulsant therapies during the first trimester of pregnancy.

3) To compare the risks of non-livebirth pregnancy outcomes reported through hospitalization (spontaneous abortion, induced abortion, ectopic pregnancy and stillbirth) in the same manner as for the congenital malformations.

4) To assess the utility of the Saskatchewan Prescription Drug and Hospital Services databases for studies of maternal prescription drug use and reproductive outcome.

1.4 Guide to thesis organization

This thesis is organized into six chapters. Following this introductory chapter, Chapter Two briefly examines the existing state of knowledge, both epidemiologic and experimental, concerning anticonvulsant teratogenicity. Problems inherent to the study of anticonvulsant therapy and birth defect risk are highlighted.

Chapter Three includes the two meta-analyses, each presented as journal articles with self-contained discussions and references; they are analyses that stand alone, quite independent of the record-linkage study that follows. The first meta-analysis improves understanding of the teratogenic risk associated with anticonvulsant therapy in general through the first systematic summary of data from existing studies in a statistically appropriate manner. The second paper provides the first systematic synthesis of the existing epidemiologic literature concerning the risks of major malformation associated with specific anticonvulsant therapies.

Chapter Four describes the study design, record linkage process and data sources used to first create a maternal prescription drug-reproductive outcomes database in Saskatchewan and then to undertake a study of anticonvulsants and reproductive outcomes. Chapter Five presents the results of the record linkage as well as the analysis of the anticonvulsant study.

Chapter Six evaluates the strengths and shortcomings of the Saskatchewan anticonvulsant study and the use of the Saskatchewan databases for adverse reproductive outcome research in general, and finishes with conclusions and recommendations.

Finally, Appendix D is a journal article which describes the confidence band technique which I recently developed to improve the graphic presentation of any series of confidence intervals, such as those presented in the meta-analyses.

1.5 Manuscripts and authorship

(These paragraphs inserted as a requirement of McGill's Faculty of Graduate Studies.)

The candidate has the option, subject to the approval of the Department, of including as part of the thesis the text, or duplicated published text (see below), of an original paper, or papers. In this case the thesis must still conform to all other requirements explained in Guidelines Concerning Thesis Preparation. Additional material (procedural and design data as well as descriptions of equipment) must be provided in sufficient detail (e.g. in appendices) to allow a clear and precise judgement to be made of the importance and originality of the research reported. The thesis should be more than a mere collection of manuscripts published or to be published. It must include a general abstract, a full introduction and literature review and a final overall conclusion. Connecting texts which provide logical bridges between different manuscripts are usually desirable in the interests of cohesion.

It is acceptable for theses to include as chapters authentic copies of papers already published, provided these are duplicated clearly on regulation thesis stationery and bound as an integral part of the thesis. Photographs or other materials which do not duplicate well must be included in their original form. In such instances, connecting texts are mandatory and supplementary explanatory material is almost always necessary.

The inclusion of manuscripts co-authored by the candidate and others is acceptable but the candidate is required to make an explicit statement on who contributed to such work and to what extent, and supervisors must attest to the accuracy of the claims, e.g. before the Oral Committee. Since the task of the Examiners is made more difficult in these cases, it is in the candidate's interest to make the responsibilities of authors perfectly clear. Candidates following this option must inform the Department before it submits the thesis for review.

CHAPTER 2. LITERATURE REVIEW

2.1 Scope of the review

This review will provide background information regarding: epilepsy and treatment with anticonvulsants; the general problems involved in the epidemiologic evaluation of in utero anticonvulsant exposure and teratogenesis; and a summary of the present state of epidemiologic and animal research findings concerning anticonvulsant teratogenicity.

Detailed reviews of the epidemiologic literature (Nakane, 1980; Janz, 1982; Bossi, 1983; Annegers et al., 1983; Kelly, 1984; Dansky and Finnell, 1991) and animal literature (Khera, 1984; Finnell and Dansky, 1991) already exist. The reader is referred to particularly pertinent reviews where applicable.

Results of most of the individual epidemiologic studies have a high degree of uncertainty because of small sample sizes and the low birth prevalence of congenital malformations. Detailed evaluation of study results on a study-by-study basis seemed of limited value. Instead, the author undertook two meta-analyses, presented in Chapter 3 of this thesis, which synthesize the existing literature in a way which addresses the small number problem and several epidemiologic issues not adequately addressed by the existing narrative reviews.

2.2 Epilepsy

The epilepsies are defined as a group of conditions characterized by recurrent seizures, which involve uncontrolled electrical discharge from brain nerve cells (Coatsworth, 1971). There are numerous types of clinical seizures but they are generally classified into three categories - partial seizures (seizures beginning locally), generalized seizures (without local onset), and unclassified epileptic seizures (due to incomplete data). The

cause of epilepsy is often unknown but it may be linked with head injury, brain infection or tumour, blood vessel disturbances, intoxication or chemical imbalance. (Coatsworth, 1971) Accurate figures on population prevalence are difficult to obtain but existing studies suggest a population prevalence in developed countries of between 0.3% and 2% and a prevalence among pregnancies of generally less than 0.5%. (Dansky and Finnell, 1991)

Most individuals with epilepsy are treated with anticonvulsants to control seizure occurrence.(Meadow, 1991) Anticonvulsant efficacy is best defined as a reduction in the seizure frequency and/or severity without undue toxic effects (Coatsworth, 1971). Over 20 antiepileptic drugs have been marketed over the last 80 years (Woodbury et al., 1982), but only a handful have been used regularly in the past three decades. Phenobarbital was first marketed in 1912 in the United States and is still the most commonly used anticonvulsant.(Woodbury et al., 1982) Phenytoin was introduced in 1938 and is also widely used, often in combination with phenobarbital.(Woodbury et al., 1982) Trimethadione was first marketed in 1946 but never gained wide use. Reports of serious teratogenicity (German et al., 1970) have made its use during pregnancy extremely uncommon. Primidone, introduced in 1954, and ethosuximide, introduced in 1960, are used to a lesser degree. Valproic acid has been used as an anticonvulsant since 1968 in Europe and since 1978 in North America.(Lammer et al., 1987) Carbamazepine is the most recently introduced anticonvulsant, available since 1974.

General recommendations guide the appropriate choices of anticonvulsant drugs for different seizure types.(Young et al., 1982) However, the recommendations have varied among countries and over time as have the prescribing patterns. An anticonvulsant rarely used in one country may be the drug of choice in another (Bertollini et al., 1987). Therapy recommendations are hampered by the lack of scientific rigour that has characterized much of the research done to evaluate anticonvulsant efficacy--there have been few properly controlled randomized clinical trials (Gram et al., 1982; Beghi et al., 1986). Reviews of anticonvulsant therapy (Coatsworth, 1971; Gram et al., 1982; Smith

et al., 1983) concur with the opinion of Beghi et al. who suggest that "antiepileptic drug selection is still based on fashion, market pressures and individual experience rather than on sound scientific considerations"(1986).

An anticonvulsant treatment regime that will control seizures varies by patient, and the process of finding that regime is one of trial and error. Beghi et al. also suggest that "The choice of appropriate drug seems to be dictated more by clinical toxicity than by truly greater efficacy since there is no evidence of significant differences in efficacy among the major anticonvulsants such as phenytoin, phenobarbital, carbamazepine and primidone." A recent trial of carbamazepine, phenytoin, phenobarbital and primidone monotherapy showed that approximately 80% of patients were adequately managed on any one of these anticonvulsants. (Beghi et al., 1986)

2.3 Epilepsy and pregnancy

During pregnancy, seizure frequency often changes. Existing studies suggest that seizure frequency increases in 25% of pregnant women, decreases in another 25% and is unchanged in the remaining 50% of women.(Schmidt, 1982; Hopkins, 1987) Non-compliance to drug therapy by women worried about the possible teratogenic effects of the anticonvulsants is apparently a major reason for increased seizures.(Schmidt, 1982) Meadow suggests that an increase in the number of seizures is twice as likely if the fetus is male (1991). Drug metabolism is altered in several ways during pregnancy resulting in declining serum levels of anticonvulsants as pregnancy proceeds, even when dose is increased (Schmidt, 1982). There seems to be a general consensus that anticonvulsant therapy should be continued during pregnancy to minimise the likelihood of seizures that might threaten the safety of the mother and fetus.(Janz, 1982; Annegers et al., 1983)

2.4 Problems in the epidemiologic evaluation of anticonvulsant teratogenesis

Epidemiologic study and evaluation of the relationship between epilepsy, anticonvulsant medication, and increased teratogenesis has been difficult for a number of reasons (Annegers et al., 1974; Bossi, 1983) including the following:

1. Low prevalence of epilepsy

Because of the low population prevalence of epilepsy (0.5 to 2.0 percent), studies have generally found only three to five births to epileptic women among every thousand births in the population. This makes the follow-up approach of studying a population often impractical as the identification of suitably sized groups of reproductive-aged women is expensive. Either a very large base population must be chosen, or many years of data collection will be required to obtain a follow-up group which confers an acceptable amount of statistical power.

2. Low prevalence of congenital malformations

Serious malformations affect only about 3% of infants in the general population. Specific birth defects are quite rare (heart defects 5.8 cases/1000 births, oral facial clefts 1.65 cases/1,000 births, spina bifida 0.84 /1,000 births - Canadian Congenital Anomalies Surveillance System data, 1978-1988).

For rare outcomes the case-referent (case-control) study (Rothman, 1986) has generally been chosen as the most practical method in epidemiology to reveal exposure-outcome associations. Drug exposure information is retrieved retrospectively and the potential exists for recall bias when a drug has become suspect and drug exposure is ascertained from memory or incomplete records. If the drug causes a specific type of malformation, the association may be difficult to detect in studies that include all types of malformations. If the drug is a

relatively rare cause of the specific malformation, its identification from a case-referent study is uncertain as large study groups will be needed.

3. **Differences in malformation ascertainment**

Congenital anomaly birth prevalence rates vary with the intensity and duration of follow-up. As the follow-up strategies used in the epidemiologic studies of anticonvulsants and congenital anomalies have varied, the studies are not strictly comparable (Annegers et al., 1974). In addition, the criteria may vary among observers as to what constitutes a serious anomaly. Analysis of minor anomalies, except in situations where appropriate referent groups are used and there is strict adherence to blinding of the person examining the children, is open to serious questions about reproducibility.

4. **Difficulties in separating drug and disease effects**

Even if a statistical association can be demonstrated between drug use and the appearance of fetal damage, a causal connection does not necessarily exist. As anticonvulsants are used almost exclusively for epilepsy and as active epilepsy is usually treated with one or more anticonvulsants, it is difficult to separate drug effects from disease effects.

5. **Confounding by type and severity of epilepsy**

Epilepsy is not a specific disease. The term is used to describe a variety of seizure patterns which vary widely in type, severity, and underlying cause.

"In general, type, number, dosage, and serum levels of drugs will be more or less related to the type, the severity and the frequency of maternal seizures and the etiology of maternal epilepsy. Therefore, an association between drug exposure and congenital anomalies may merely reflect a causal relation between the

maternal disease and the congenital anomalies. Such a causal relation may exist in two different ways. The maternal epilepsy may have a metabolic basis and seizures may cause metabolic derangements with teratogenic influences on the embryo and fetus. Secondly, genetic factors can play a role as far as epilepsy itself is genetically linked or associated with congenital malformations". (Lindhout, 1985)

6. **Epilepsy clinic data and generalizability**

Most studies have used epilepsy clinics as the study base. Epileptics attending clinics are not likely to be representative of the epileptic population as a whole as they tend to be those patients with the most severe epilepsy (Nakane, 1980). Thus, results of these studies may not be generalizable beyond this group.

7. **Inadequate sample sizes**

As a consequence of the difficulties involved in assembling substantial numbers of births following in utero anticonvulsant exposure, the vast majority of published studies have inadequate statistical power to allow strong inferences from the data. Table 2.4.1 summarises the sample sizes of the more than 50 follow-up studies of anticonvulsant teratogenicity found in the medical literature. More than 50% of the studies include fewer than 100 births to women with epilepsy treated with anticonvulsants during the first trimester of pregnancy and would therefore generate only a small number of cases, even if one was only interested in the overall rate of serious malformations. Only 2 of the 22 prospective studies include more than 200 births and only 5 of the 35 retrospective studies include more than 300 births; even these larger studies are relatively small for birth defect evaluation.

The consequences of these difficulties led a prominent researcher in the field to comment that:

"The investigator whose aim it is to identify teratogenic risk factors in drug treated maternal epilepsy, and to accomplish prevention of drug-induced congenital disorders, is confronted with complex problems of study design and interpretation. Not less difficult is the task of the general practitioner and medical specialists who have to counsel and to treat the individual epileptic woman of child bearing age."(Lindhout, 1985)

Table 2.4.1

Summary of sample sizes for follow-up studies* of anticonvulsants and birth defect risk – number of livebirths among women with epilepsy treated with anticonvulsants during the 1st trimester

Sample size-- number of livebirths following 1st trimester anticonvulsant therapy for epilepsy	Retrospective	Prospective	Total	(%)
<100	15 **	14	29	(50.9%)
100–199	10	6	16	(28.1%)
200–299	5	0	5	(8.8%)
300–399	1	1	2	(3.5%)
400–499	1	0	1	(1.8%)
500–599	3	0	3	(5.3%)
600–699	0	1	1	(1.8%)
Total***	35	22	57	(100.0%)

* Studies listed here are referenced in the meta-analyses in Chapter 3.

** number of studies

*** There were 4 record linkage studies where anticonvulsant treatment data was not available. These are not included in this table.

2.5 Findings from epidemiologic studies

2.5.1 Anticonvulsants and major malformations

An association between maternal anticonvulsant use and increased risk of orofacial clefts (cleft lip and cleft palate) was initially reported by Meadow (1968). A number of subsequent studies provided further evidence of this relationship as well as suggesting a relationship between maternal anticonvulsant treatment and congenital heart defects.

It is now well established that the children of epileptic mothers exposed to anticonvulsants in utero have a higher frequency of congenital anomalies than those of non-epileptic parents (Meadow, 1968; Nakane, 1980; Bossi, 1983). The major studies of offspring of epileptic women have suggested a two- to three-fold increase in anomalies, notably congenital heart defects, cleft lip and/or cleft palate, and syndromes of dysmorphia and mental retardation (Nakane, 1979; Bossi, 1983). Table 2.5.1 summarises the major findings of the epidemiologic studies of anticonvulsant teratogenicity. A detailed review of the epidemiologic evidence was recently published by Dansky and Finnell (1991).

Offspring of epileptic fathers have been the subject of limited study, but there are indications that the frequency of major malformations in this group is lower than in offspring of epileptic mothers but consistently higher than among children of non-epileptic parents (Janz, 1982).

Although the studies consistently demonstrate a risk of heart and cleft defects, the relationship of specific anticonvulsants (i.e. drug specificity) to major malformation risk remains poorly understood (Dansky and Finnell, 1991). A study may have adequate power to demonstrate excess risk for major anomalies with anticonvulsant exposure in general. However, when the study group is then split into the four or five different

anticonvulsants with which different women will be treated, singly or in various combinations, statistical evaluation of all but the most common exposures becomes exceedingly difficult.

The role of genetic and environmental etiologic factors in the elevated risk of facial clefts and congenital heart defects in children of parents with epilepsy has recently been reviewed in detail by Friis (1989). Although the amount of study in the area is quite limited, the author suggests that genetic factors are of minor importance for the etiology of facial clefts in the offspring of epileptic parents and the existing literature does not suggest a genetic association between congenital heart defects and epilepsy.

Table 2.5.1

Summary of the findings of epidemiologic studies of anticonvulsant drug teratogenesis

	Anti-Epileptic Drugs	PHB	DPH	PRM	VPA	CBZ	TRI	SUX
Elevated Risks Observed								
Major Malformations	*** RR 2-3	*	*	*				
Cleft lip +- palate	*** RR 4-13	*	*	*				
Congenital heart defects	*** RR 3-8	*	*				*	
Skeletal defects	**							
Spina bifida					** RR 10-20	** RR 6-14		
Dysmorphic features (syndromes)								
Cranio-facial defects	*** RR 2-3	**	**	*	*	*	*	
Digital	*** RR 2-3	**	**	*	*	*	*	
Growth Retardation	**					*		
Mental Retardation	**	*	*					

1. PHB – Phenobarbital; DPH – Phenytoin; PRM – Primidone; VPA – Valproic acid; CBZ – Carbamazepine; TRI – Trimethadione; SUX – Ethosuximide
2. ***reported in most studies; **reported in several studies; * reported in a few studies
3. RR – A range of Relative Risks reported in the literature is presented where risk has been evaluated for a substantial number of births with in utero exposure. Risk is compared with that of the general population.

2.5.2 Polytherapy and major malformations

There is some evidence that maternal anticonvulsant polytherapy, as opposed to monotherapy, is associated with a relatively higher risk of anomalies in the offspring (Hill et al., 1974; Nakane, 1980; Lindhout et al., 1984). Nakane et al. (1979) reported an association between the number of different types of anticonvulsants taken and the malformation rate in a large sample of epileptic women in Japan often medicated with several anticonvulsants. Women who took one anticonvulsant during the first trimester gave birth to offspring with a malformation rate of 4% (4/93), and women treated simultaneously with two, three, or four or more anticonvulsants experienced malformation rates among their offspring of respectively 5% (12/232), 11% (21/187), and over 20% (22/118).

Specific combinations of antiepileptic drugs have been subject to only limited systematic investigation with respect to their teratogenic potential (Lindhout et al., 1984). In most studies there are only a few women treated with any specific combination of anticonvulsants. As a result, little evaluation can be made of anomaly risk and authors have often not even presented the numbers of women exposed to specific anticonvulsant combinations. Lindout et al. (1984) examined the combination of carbamazepine, phenobarbital and valproic acid in 151 live born infants exposed to antiepileptic drugs during pregnancy. They hypothesised that interaction between the anticonvulsants resulting in expoxidation of carbamazepine might result in a teratogenic effect.

2.5.3 Anticonvulsants and minor anomalies

As the studies of major malformation risk were being reported during the 1970's, reports started to appear suggesting a link between specific anticonvulsants and an elevated risk of a number of minor facial abnormalities and abnormalities of the fingers and toes

including a short nose with flat bridge, epicanthus, ptosis, low set, abnormally formed ears, wide set eyes, a large mouth with protruding lips, and hypoplasia of the nails or the distal phalanges.(Speidel and Meadow, 1972; Hill et al., 1974; Hanson and Smith, 1975; Hanson et al., 1976; Dansky et al., 1982)

These minor anomalies were reported by different authors to be associated with hydantoin (phenytoin), with phenobarbital, and with trimethadione and were labelled as fetal syndromes bearing the incriminated drug's name (Janz, 1982). However other reports suggested that these anomalies were not drug specific (Janz, 1982). Much of the information about the relation between minor anomalies and anticonvulsant treatment in early pregnancy came from case reports, without proper referent groups and/or proper blinding of the observers to the anticonvulsant status of the mother.(Annegers et al., 1983) As the evaluation of many of these anomalies is highly subjective, the results of such study can be highly misleading and highly variable. In a dozen studies, the observed rates of these dysmorphic features among the offspring of treated epileptic women have varied between 6 and 46 percent.(Bossi, 1983)

The observation of increased occurrence of these minor anomalies has raised a number of potentially important but as yet unanswered concerns. It has been suggested that the pattern of anomalies may be associated with growth deficiency and mental deficiency.(Janz, 1982) These minor anomalies may also be associated with an increased probability of occurrence of major anomalies. On the other hand these anomalies may be related to epilepsy per se, they may recur in families or they could be related to other features such as socioeconomic status.(Janz, 1982) Gaily et al., (1988) recently reported on a blinded systematic study of minor malformations in 121 five year-old children of epileptic mothers, the mothers themselves and a control group of children and mothers. They found a significant excess of minor anomalies considered characteristic of hydantoin syndrome in the children of epileptic mothers and in the epileptic mothers compared with the non-epileptic control group, suggesting a genetic link to epilepsy. The risks of developmental disturbances were also much lower than in some earlier reports of fetal

hydantoin syndrome.

2.5.4 Valproate and spina bifida

An association between in utero exposure to valproic acid and spina bifida was initially reported in France in 1982 by Robert and Guibaud (1982). They performed a case-control study using spina bifida cases reported through the Rhone-Alps birth defect surveillance system as cases and other structural malformations reported in the surveillance system as controls. The study found that there had been in utero exposure to valproic acid among 9 of 146 spina bifida cases, but in utero exposure in only 21 of the 6,616 control anomalies, yielding a relative risk of 20.6 (95% CI 8.2-47.9) for spina bifida with valproic acid exposure. When the analysis was restricted to 71 women with maternal epilepsy the high risk persisted (RR 17.1, 95% CI 2.1-76.9).

Attempts to replicate the finding in other countries were limited by the fact that valproic acid had not been widely used outside France and Italy. A case-control study from Italy (Mastroiacovo et al., 1982) and a Dutch report (Lindhout and Meinardi, 1984), although based on small numbers, found evidence suggesting similarly high relative risks. A thorough review of valproic acid teratogenicity was published by Lammer et al. in 1987 which details the case reports and case series, the case-control studies, the cohort studies and the experimental animal studies.

To address the small numbers problem, Lindhout and Schmidt (1986) sent questionnaires to 18 groups doing prospective cohort studies of birth outcome among women with epilepsy to ask them about spina bifida and/or anencephaly in relation to first trimester anticonvulsant exposure, in particular valproic acid. Thirteen groups shared data with the authors allowing them to assemble information on 2,332 infants born to women with epilepsy. Eleven of the 2,111 infants exposed in utero during the first trimester to any anticonvulsant had spina bifida and one additional infant had anencephaly. There were

2 cases of spina bifida and 1 anencephaly case among the 120 women taking valproic acid only (2.5%), 3 spina bifida cases among the 273 women taking valproic acid and other anticonvulsants (1.0%), and 6 spina bifidas among the 1,718 women on other anticonvulsants (0.35%).

The authors convincingly argue that the results are unlikely to have been seriously skewed by potential biases that could have been introduced by selective response to the questionnaire or differences in background incidence of neural tube defects in the different population studies. They conclude that "The results confirm that valproic acid exposure during the first trimester is casually associated with a considerably increased risk of neural tube defects of 1.5% (95% confidence limits 0.42-3.00%)."

2.5.5 Carbamazepine and spina bifida

Carbamazepine came under suspicion as a cause of spina bifida shortly after valproate was implicated. Twelve cases of spina bifida had been observed among 60 infants with birth defects exposed in utero to carbamazepine (Sullivan and McElhatton, 1975; Sullivan and McElhatton, 1977). After further case reports of spina bifida following carbamazepine exposure were reported to the Federal Drug Adminstration in the United States, Rosa (1991) decided to examine the association more closely by conducting his own study using Michigan Medicaid data as well as collecting data from other existing cohort studies. By combining information from the 20 cohort studies that he was able to locate which included epileptic women with carbamazepine exposure during pregnancy, Rosa found the following: 9 cases of spina bifida among 612 women treated with valproic acid (but not carbamazepine) during pregnancy; 9 cases of spina bifida among 984 women following carbamazepine (but not valproic acid) exposure; but only 6 cases of spina bifida following 4,489 pregnancies with exposure to other anticonvulsants.

These findings lead Rosa to conclude that exposure to carbamazepine (without concurrent exposure to valproic acid) carries a 1% risk of spina bifida--a relative risk of 13.7 (95% CI 5.6-33.7) compared to the expected background rate in the populations studied. The Mantel-Haenszel weighted relative risk of spina bifida after carbamazepine exposure in the studied cohorts was five times higher than after exposure to anticonvulsant drugs other than valproic acid (RR 5.2 (95% CI 2.0-13.8), and 40% lower than with valproic acid (RR 0.6; 95% CI.2-1.7).

2.5.6 Other disorders

A number of other disorders besides major malformations and dysmorphic features have been associated with prenatal exposure to anticonvulsant drugs. These include mental retardation, growth retardation in the prenatal and postnatal period, neoplasia, seizures and transient postnatal dysfunction (Dansky and Finnell, 1991).

2.6 Experimental findings from animal studies

Animal studies provide a useful adjunct to epidemiologic studies because they allow researchers to experiment under controlled conditions, facilitating the development of testable hypotheses and elucidation of mechanisms. At the same time meaningful extrapolation of teratogenicity from animal studies to the human situation has important limitations, particularly the following: 1) extreme insults to pregnant animals are likely to cause malformed offspring but are unlikely to represent the human situation (Fraser, 1959); 2) a drug that is teratogenic in one species of animal is often not teratogenic in other animal models; 3) a drug that is not demonstrably teratogenic in animals may be teratogenic in man and 4) a drug that is demonstrably teratogenic in animals may not be a human teratogen.(Fraser, 1964) Furthermore, experimental studies may suffer from shortcomings including inadequate power, improper selection of dose, lack of proper control groups and unnatural routes of drug administration.(Wilson and Fraser, 1977)

Over 60 animal studies examining anticonvulsant teratogenicity have been reported in the literature over the last 25 years. A thorough review of the experimental evidence on the teratogenicity of selected anticonvulsant drugs was recently published by Finnell and Dansky (1991). Because of the limitations of reproductive toxicology mentioned above, the extensive literature in the area, and this recent detailed review, the summary here is limited to highlighting the major experimental findings.

Table 2.6.1 provides a brief overview of the published experimental research into anticonvulsant teratogenicity. Because individual defects are rare and may easily occur in excess in any one study by chance, it is not surprising that the anticonvulsants most studied would also have the widest spectrum of anomalies that had been observed to be elevated. Several factors likely contribute to decisions about which anticonvulsants are most studied, in particular the results of the earliest animal experiments and the focus of concerns raised in human studies. Only phenytoin, phenobarbital and valproic acid have received particular attention in the experimental research.

Phenytoin

Phenytoin has been the most studied anticonvulsant and study has been concentrated in rodents, primarily mice. The research on phenytoin has focused almost exclusively on the ability of phenytoin to induce orofacial clefts (Finnell and Dansky, 1991). The experiments in mice have clearly demonstrated susceptibility to cleft palate in a number of strains of mice (Harbison and Becker, 1969; Harbison and Becker, 1970; Gibson and Becker, 1968; Staples, 1972; Mercier-Parot and Tuchman-Duplessis, 1974; Fritz et al., 1976; Miller and Becker, 1975; Paulson et al., 1979) and also marked differences in strain susceptibility (Gibson and Becker, 1968). The association has also been demonstrated in the rat (Harbison and Becker, 1972).

Decreased fetal growth has been reported to be associated with phenytoin in a number

of the studies, while a variety of other congenital malformations have been reported less often to be increased with phenytoin.

A mouse model with spontaneous seizures, controlled with chronic phenytoin demonstrated a relationship with the overall malformation rate in the offspring that was heavily dose dependent. Anomalies observed included renal, ocular, cardiac defects, abnormal digits, but cleft palates were observed only at the highest dose level.(Finnell, 1980)

In both of the studies of mice which compared several of the more common anticonvulsants, phenytoin was found to be the most teratogenic. (Sullivan and McElhatton, 1975; Sullivan and McElhatton, 1977; Kao et al., 1979) Primidone and phenobarbital were modestly teratogenic, while clonazepam, ethosuximide and carbamazepine showed little teratogenic potential.

A variety of hypotheses have been put forth to explain phenytoin's teratogenic effect including phenytoin's interference with folate metabolism and that phenytoin may be metabolized to a reactive intermediate, although which enzymatic pathway and metabolite is controversial. Despite concerted effort by a number of researchers, however, the mechanism by which phenytoin exerts teratogenic effect is still unknown.(Finnell and Dansky, 1991)

Phenobarbital

Although phenobarbital is more widely used for the treatment of epilepsy than phenytoin and is often used in therapy in conjunction with phenytoin, it has received remarkably little attention in experimental work compared to phenytoin (Finnell and Dansky, 1991). As well, there has been little experimental research involving the combination of the two drugs or other anticonvulsant combinations.(Finnell and Dansky, 1991) Phenobarbital

was found to increase major malformations in mice in one study, particularly cleft palate, neural defects and skeletal defects. However, in another study, administering the same dose intraperitoneally instead of orally did not produce a teratogenic effect. A study of rats did not find an effect at the doses examined.

Valproic Acid

Valproic acid is the only other anticonvulsant that has received much attention in experimental research. Valproic acid has demonstrated a teratogenic potential in the mouse, rat, rabbit and rhesus monkey.(Nau and Hendrickx, 1987) Several studies have found a relationship between anterior neural tube defects and valproate in mice but the relationship has not been found in the single studies of rabbits and monkeys or the two studies with rats. Widely differing strain susceptibility in mice and the formation of neural tube defects has been observed suggesting a strong genetic component.(Finnell, 1992; Finnell et al., 1988; Finnell et al., 1986; Seller et al., 1979) In humans concern has focused on posterior neural tube defects, but these defects have not been replicated in the animal studies to date.(Finnell and Dansky, 1991) Skeletal anomalies have been the most commonly reported malformations across different types of animal studies of valproic acid.(Finnell and Dansky, 1991)

Table 2.6.1

Summary of experimental animal studies of anticonvulsant drug teratogenesis

	Phenytoin			Valproic acid				Phenobarbital		Carbamazepine		Primidone		Trimethadione	
	Mouse	Rat	Cat	Mouse	Rat	Monkey	Rabbit	Mouse	Rat	Mouse	Rat	Mouse	Rat	Mouse	Rat
Number of studies	43	8	1	9	2	2	1	6	1	4	1	2	0	1	1
Elevated Risks Observed															
Cleft palate	•••	••	•	•				•		•		•		•	
Cleft lip	•		•												
Decreased fetal growth	••	••		•	•			•		•	•				
Neural defects	•	•		•••				•							
Teratogenic effects	••			•	•			••		•	•	•		•	
Renal defects	•	•													
Skeletal defects	•	•		•	•	•	•	•							
Cranio-facial defects	•	•			•	•									
Spina bifida	•														
Cardiac anomalies	•				•	•			•						•
Tracheo-esophageal fistulas	•														
Urogenital	•				•										
Limb defects			•		•										

•••reported often; ••reported in some studies; •reported

2.7 Conclusion

This brief review of the literature has attempted to demonstrate the complexities involved and the limitations in knowledge related to the evaluation of the potential teratogenicity of anticonvulsant therapy during pregnancy. The situation confronted by researcher and practitioner in this field are appropriately summarised as follows:

> "Despite numerous studies in which associations have been described, it still remains obscure to what extent anticonvulsant drugs are the cause of abnormalities in the offspring of epileptic women, and whether changes in prescription policy may contribute to prevention." (Lindhout, 1985)

This thesis will attempt to fill gaps in the existing knowledge in two ways:
First, the problems involved in assembling data on large numbers of births to women with epilepsy have severely limited the number of studies with the statistical power to adequately evaluate anticonvulsant risk. Saskatchewan Health's databases provide the potential to undertake one of the largest studies of anticonvulsant teratogenicity to date, with perhaps 500 women exposed to anticonvulsants during the first trimester of pregnancy. The study will be prospective in nature and because the study will be essentially population based it should have more generalizability than the many existing clinic-based studies. Furthermore, useful comparison groups of offspring of fathers dispensed anticonvulsants, and of offspring of women not taking anticonvulsants can be assembled in precisely the same way.

Second, the inadequate power of most of the existing studies has greatly hampered understanding of the teratogenic risk associated with anticonvulsants. By quantitatively synthesizing the results of existing studies in a statistically appropriate way and at the same time presenting the data in ways that allow maintenance of individual study integrity, one should be able to gain new insights into the existing data that neither the individual studies nor existing narrative reviews can provide. Meta-analytic techniques

offer a systematic approach for summarising the results of the more than 60 published studies.

CHAPTER 3. META-ANALYSES

3.1 Introduction

In this chapter two meta-analyses of the existing epidemiologic studies of anticonvulsant teratogenicity are presented. As self-contained research quite separate from the Saskatchewan component of the thesis and as a natural progression from the literature review in Chapter Two, they are presented in journal article format in this chapter with their own discussions and references. The first meta-analysis compares the risk of major malformation among the offspring of epileptic women treated with anticonvulsants during the first trimester of pregnancy with the risk among offspring of mothers without first trimester anticonvulsant therapy. The second meta-analysis compares the malformation risks associated with various anticonvulsant therapies.

Meta-analysis (also referred to as systematic overview, research synthesis, or integrative research review) is a set of techniques used to provide a systematic quantitative overview of the existing research concerning a specific issue.(Jenicek, 1989) Central to the concept is the use of the single study as the individual unit of statistical analysis (Greenland, 1989). Literature reviews tend to describe the results of existing studies and provide a subjective and not necessarily reproducible evaluation of the literature. "A meta-analysis tends to address sharper questions, usually with quantitative answers." (Louis et al., 1985). In meta-analysis criteria are developed for finding studies, evaluating study quality and deciding on which studies will be included in the analysis. The intention is to make the overview such that independent researchers using the same criteria would be likely to produce similar results if they were to overview the same research question. A meta-analysis may contribute to a literature review, but review papers are generally wider in scope than meta-analyses. (Louis et al., 1985)

Meta-analysis originally developed in the 1970's in the field's of psychology and education, when researchers realized the shortcoming of the narrative approach, even

when done quite carefully. A seminal work on the meta-analytic technique in psychology and education by Light and Smith was published in 1971. "Classical meta-analysis" attempted to bring together as many published and un-published research studies on a subject as possible, without taking into consideration issues of study quality, to assess the effectiveness of treatments, programs and interventions (Jenicek, 1989). Important books on meta-analysis were written by Glass et al.(1981) and Light and Pillemer (1984).

As the techniques of meta-analysis started to gain currency in medical research during the 1980's it became apparent that studies concerning a specific medical question were often much more heterogeneous in design than studies to answer a question in the social sciences and that the quality of individual studies and cross-study heterogeneity needed to be given careful consideration if meta-analytic techniques were to be appropriately applied in medicine. At the same time it was recognized that "a meta analysis can lead to stronger inferences about a subject" because "by taking account of information on the same topic from many sources, a meta-analysis can increase the statistical and scientific credibility of a result, partly because of the variety of sites and circumstances represented." (Louis et al., 1985) A number of papers have appeared in recent years that address the issues involved in applying meta-analysis techniques to the review of epidemiologic literature. (Louis et al., 1985; Chalmers et al., 1987; Jenicek, 1989; Greenland, 1989)

A number of meta-analyses have now been published in the field of epidemiology, in particular for evaluating the results of randomized controlled trials of health care (Chalmers et al., 1989; Early Breast Cancer Trialists' Collaborative Group, 1990) but also for overviewing observational research (Wald et al., 1986; Longnecker et al., 1988). The anticonvulsants-birth defects issue seemed suited to meta-analysis because 1) there existed a large number of quite small studies each with very limited statistical power and 2) although the settings and designs varied, the basic approach of almost all studies was similar--a follow-up approach to studying hospital-ascertained birth outcomes for a series women with epilepsy whose anticonvulsant therapy had been recorded during pregnancy.

3.2 Meta-analysis of the Risk of Congenital Malformation in the Offspring of Women with Epilepsy: A Graphical Presentation

META-ANALYSIS OF THE RISK OF CONGENITAL MALFORMATION IN THE OFFSPRING OF WOMEN WITH EPILEPSY: A GRAPHICAL PRESENTATION

KENNETH C. JOHNSON B.E.S. 1

GREGORY J. SHERMAN Ph.D. 1

1. Diseases of Infants and Children Division,
Bureau of Chronic Disease Epidemiology,
Laboratory Centre for Disease Control

ABSTRACT

A meta-analysis was performed to consolidate and quantitatively summarise the epidemiologic evidence concerning the association between anticonvulsant therapy during the first trimester of pregnancy in women with epilepsy and the risk of congenital malformation among the offspring. The meta-analysis made use of data from published reports of 37 epidemiologic studies. A comparison of congenital malformation risk among offspring of epileptic mothers with first trimester anticonvulsant exposure ("exposed") relative to offspring of non-epileptic parents yielded a study-stratified Mantel-Haenszel summary estimate of the relative risk (RR) of 2.6 (95% confidence interval (CI) 2.1-3.2). Congenital malformation risk among the offspring of exposed epileptic women relative to unexposed epileptic women yielded a summary risk of 2.9 (CI=2.0-4.2). For cleft lip and/or palate and for congenital heart anomalies, summary risks for offspring of exposed epileptic women relative to offspring of non-epileptic women were 10.9 (CI=7.3-23.5) and 8.4 (CI=3.9-15.7), respectively. No evidence of increased malformation risk to unexposed epileptic women compared to non-epileptic women was evident (RR=0.9, CI=0.5-1.6).

INTRODUCTION

Epidemiologic research into the teratogenicity of anticonvulsant drugs spans more than 25 years and encompasses over 60 studies. Nevertheless, the role of anticonvulsants in the increased risk of birth defects among offspring of epileptic mothers remains poorly understood[1,2]. Problems inherent in studying anticonvulsant teratogenicity[2,3] coupled with difficulties associated with combining results from disparate studies[1] have limited our understanding of anticonvulsants' teratogenic risk.

Individual studies in this area have generally lacked sufficient statistical power to convincingly evaluate risk. Literature reviews have failed to adequately quantify the existing data on the risks offspring of exposed epileptic mothers experience relative to the offspring of natural comparison groups (e.g. unexposed epileptic mothers, epileptic fathers, and non-epileptic parents). For example, few of the individual studies or reviews have presented confidence limits and have thus failed to indicate the degree of precision of point risk estimates.

In four recently published reviews of the literature[2,4-6], summary measures of birth defect risk for specific epileptic exposure groups were created by simply pooling numerators and denominators from individual studies, a method which has been noted to be inappropriate[7,8]. The authors of another recent review[9] suggested that individual studies were not strictly comparable because of differences in definitions of anomalies as well as in the type, extent and duration of follow-up and avoided quantitative summarization.

In this paper a meta-analytic approach focusing on graphical presentation of relative risks and confidence intervals for individual studies was adopted to compare congenital anomaly risk between the offspring of epileptic women and other parents. By using the graphical approach, we were able to concisely summarize the results of a large number of studies in a way that facilitates observation of patterns of risk, while maintaining individual study integrity.

MATERIALS AND METHODS

The National Library of Medicine's computerized English-language databases from 1966 to March 1990 were searched using MEDLINE for papers describing studies of anticonvulsant use by epileptic women and congenital anomalies in their offspring. The search employed the terms "abnormalities, drug induced", in combination with the word "anticonvulsants". References from the located papers as well as from five recent reviews[2,4-6,9] were also used to identify studies.

Epidemiologic studies reporting on congenital anomaly risk in the offspring of epileptic women were deemed eligible for inclusion in this analysis. Both retrospective and prospective studies were considered for inclusion but case reports were not. Studies reporting rates of congenital anomalies in the offspring of epileptic mothers and in the offspring of epileptic fathers or non-epileptic parents were considered for this analysis. Studies reporting on women with epilepsy taking anticonvulsants during the first trimester ("exposed epileptic women") and women with epilepsy not on anticonvulsant therapy during the first trimester ("unexposed epileptic women") were also considered.

Although we were interested in the occurrence of major congenital anomalies, few papers presented specific information about the criteria used to define the type and severity of malformations studied. Studies published before 1980 typically described the outcome of interest as "congenital malformations", subsequently the terms "major" and "minor" anomalies came into increasing use. We included studies employing terms such as "congenital malformations", "serious anomalies", and "serious physical disfigurements". If the report distinguished "major" from "minor" anomalies we included data on only the major anomalies. Studies reporting only on minor anomalies, dysmorphisms or the occurrence of anticonvulsant "syndromes" were not eligible for inclusion.

Establishing the quality of a number of the individual studies was difficult. First, the description of the methods and materials was often short and vague. Second, details

required to judge the quality of routine birth records and the extent of birth defect ascertainment were frequently lacking. Third, we could not establish that those examining infants had been blinded to epilepsy or anticonvulsant status in the vast majority of retrospective or prospective studies. On the other hand, about 95% of the studies we located were of a follow-up design, a design not generally perceived to be as open to serious bias as the case-referent (case-control) design. Typically the studies involved following up all the women attending a clinic for epilepsy, or the births of an entire population. In consideration of the above factors and the problems of small sample size that plague many of the studies, we decided to evaluate the methodological strength of individual studies on a simple relative ranking of unacceptable, "uncertain" (U), "adequate" (A) or "sound" (S), present the results for all studies not labelled unacceptable, and contrast the results obtained from all acceptable studies with those labelled "sound".

The following criteria were used to evaluate the quality of individual follow-up studies:

1) a medical diagnosis of epilepsy;

2) medical record evidence of the anticonvulsant use in the first trimester;

3) anomaly ascertainment (intensity of search) that appeared to be independent of anticonvulsant exposure; and

4) loss to follow-up that appeared independent of anticonvulsant exposure.

The methodological quality of case-control studies was evaluated using criteria one and two above plus the following:

a) for studies involving community controls, choice of controls that would indicate that had they been diagnosed with a major malformation they would have been selected as cases;

b) data collected for cases and controls in a similar manner;

c) the same exclusion criteria applied to cases and controls; and

d) if an interview was involved, the interviewer was blinded to case-control status.

Study methodological quality was evaluated by one of the authors (KCJ) without examining study results and where a decision on quality was unclear a consensus was reached between authors. Follow-up studies were categorized as follows. Studies that clearly met the first four criteria were labelled "sound". Studies that appeared to meet the first four criteria, but where the details were sketchy, or that appeared sound but did not meet criteria one or two, were rated "adequate". Studies that provided too little information to evaluate whether criteria were met were labelled "uncertain". Studies clearly not meeting criteria three or four were excluded. Case-control studies not meeting criteria a), b) and c) were excluded. Case-control studies meeting all the criteria set for case-control studies were labelled "sound"; if criteria one or two was not met the study was labelled "adequate"; and if some methodological details were unclear the study was labelled "uncertain".

Data from acceptable studies performing any of the following comparisons were abstracted: mothers with epilepsy versus mothers without epilepsy, exposed mothers with epilepsy versus mothers without epilepsy and exposed mothers with epilepsy versus non-exposed mothers with epilepsy. For each two-group comparison, within study estimates of the relative risk (RR) and exact 95% CI were calculated using the odds ratio and exact 95% CI routines available in EGRET[10]. With rare outcomes like birth defects, odds ratios provide a close approximation of the RR. Because many of the studies included were small, exact calculations of 95% CI were preferable and were available in EGRET for odds ratios but not for RR's. Using odds ratios also allowed direct inclusion of case-control studies in summary estimates.

Once all of the within-study RR estimates and 95% CI's had been calculated for a comparison, the individual risk estimates were ordered by 95% CI width, and the risks and CI's plotted using a log scale[11]. Estimates of the summary RR and associated exact 95% CI were also calculated[10] using the Mantel-Haenszel procedure[12], in which risks from individual studies are weighted according to their precision (i.e. inversely to the

variance of the odds ratio). When no congenital anomalies were reported in a study for one of the exposures being compared, the RR for that comparison was either undefined or zero and the study was not plotted, because of its low information value and the visual distraction caused by very wide CI's, although the comparison did contribute to the RR summary estimate.

The graphical approach to study synthesis and presentation allows one to maintain individual study integrity thus avoiding the explicit assumption of homogeneity required for statistical summarisation. It allows one to evaluate the degree of heterogeneity among studies, the role of study quality and the contributions of specific studies to summary estimates. The role of study quality was assessed by comparing the results obtained from all "acceptable" studies with the results of the subset of acceptable studies labelled "sound". The homogeneity of the RR's was evaluated by examining each graph for a common area where all the confidence intervals overlapped, which would indicate study homogeneity.

RESULTS

Reports on 61 analytic epidemiologic studies of birth defects in the offspring of epileptic mothers were identified[3,13-69] as well as three case-control studies of drug exposure and birth defects[24,70,71]. Thirty-nine studies [14-22,24-31,34,36,39,40,43,44,46,47,49-51,54,56,58,61-63,65,67] reported on at least two of the comparison groups of interest but two did not meet the design criteria[18,26]. Appendix 3.2.1 summarises the design characteristics and Table 3.2.1 summarises the results of the 37 studies used in the analysis. Among the 37 included studies 21 (57%) received a methodological quality assessment of "sound".

In Figure 3.2.1, the risk of congenital anomalies among offspring of mothers with epilepsy is compared to that among offspring of non-epileptic mothers. Studies reporting separately on livebirths to exposed and unexposed epileptic women were compared using exposed women only. All 20 point risk estimates were greater than 1.0. The lower 95%

confidence limit exceeded 1.0 in nine of the ten studies with the most precise estimates of risk. The 16 studies in which exposed epileptic women could be specified, yielded a Mantel-Haenszel summary risk of 2.6 (95% CI 2.0 - 3.1).

Figure 3.2.2 compares exposed and unexposed epileptic mothers. The exposed epilepties generally experienced higher risk than the unexposed epileptics; 11 of the 14 risk estimates were greater than one. The 95% CI around all of these estimates, however, were wide because of the small numbers of unexposed epileptics. A Mantel-Haenszel summary risk estimate of 2.8 (95% CI 2.0 - 4.2) was calculated.

Unexposed epileptics and non epileptic controls are compared in Figure 3.2.3. The plot provides no evidence that unexposed epileptics were at increased risk compared to non-epileptic controls; the summary risk estimate is 0.9 (95% CI 0.5 - 1.6). Restriction of the analyses to studies given a methodological quality assessment of "sound" did not materially change the results in any of the above comparisons.

The seven studies which compared the offspring of mothers with epilepsy and fathers with epilepsy yielded a summary risk of 2.0 (95% CI 1.5-2.7). (See Figure 3.2.4.) Six of seven point estimates were above 1.0. The composition of the comparison groups varied among these studies. Generally, exposed and unexposed epileptics were not distinguished, or exposed mothers were compared to exposed and unexposed fathers, diluting the precision of the comparison. Furthermore, the two studies producing the most precise risk estimates were given the methodological quality assessment of "uncertain".

Congenital heart defects and cleft lip and/or palate are generally considered the two types of major malformations elevated in association with the use of anticonvulsants. Data on these two malformation types are presented in Table 3.2.2 and risks for epileptic women and non-epileptic women compared in Figures 3.2.5 and 3.2.6. Among the five studies reporting heart defects for treated epileptics, three of the relative risks are over eight.

The summary point estimate is 8.4 (95% CI 3.9-15.7). The four studies which include all epileptic women present a less extreme picture although two of the confidence intervals do not include 1.0. All eleven studies which reported cleft lip and/or palate for offspring of both epileptic and non-epileptic women reported risks of cleft lip and/or palate above one. Over half of the individual 95% CI did not include 1.0. The summary risk estimate was 10.9 (95% CI 7.3 - 23.5). Two of the studies that did not receive the "sound" methodological assessment had the highest cleft palate and/or lip risk estimates; removing the uncertain studies somewhat reduces the risk estimate.

Only one heart defect and two cleft lip and/or palates were reported for the offspring of the unexposed epileptic women precluding meaningful comparisons between exposed and unexposed epileptic women.

DISCUSSION

There is strong, consistent evidence that the offspring of epileptic women with first trimester anticonvulsant exposure experience a two- to three-fold increase in congenital anomalies in comparison to a similar non-epileptic control population not exposed to anticonvulsants. High risks of congenital heart defects and cleft lip and/or palate contribute to the increased risk among the offspring of exposed epileptic women.

There is no evidence that epileptic women not exposed to anticonvulsant drugs during the first trimester are at increased risk of having children with congenital malformation. The summary risks were almost identical when exposed epileptics were compared to unexposed epileptics and to non-epileptics. No difference in risk was apparent in direct comparisons of unexposed epileptic mothers and non-epileptic mothers.

Publication bias, which arises if studies with positive results are more likely to be published and thus a biased set of studies is available for analysis, is a central concern

in meta-analysis[72,73]. However, the likelihood of publication bias may be less than in other areas of study because the question of anticonvulsant teratogenicity is multi-faceted. Unlike randomized controlled trials of a specific therapy which often result in a positive or a negative answer to a single question, epidemiologic studies of anticonvulsant teratogenicity have generally examined the risks of a variety of anticonvulsant therapies and have lacked the statistical power to evaluate the risk of any particular therapy.

A more important problem in this field may be selective reporting of the exposure and outcome. It seems quite possible that specific outcomes would be more likely to have been reported where a high risk was encountered. For example, although 19 studies compared exposed epileptics with non-epileptic controls, in only 10 could the rates of heart defects be extracted for both groups. If it happened that heart defect rates were not reported or not properly reported where no substantial increase in risk was observed (i.e. not including number of livebirths and number of heart defects for both epileptic and non-epileptic groups), then it is possible that there was no substantial increase in heart defect risk in nine of the nineteen comparison studies. If this were the case it would temper the heart defect results that have been presented and would tend to indicate that either the summary risk was overestimated or that two different phenomena were being observed[7].

Other reviewers have argued that studies are not directly comparable because of differences in study design, base population, outcome ascertainment, length of follow-up, etc. As Greenland has pointed out[7], the homogeneity assumpti nderlies statistical summarization of individual study results--and implicitly underlies most narrative reviews--will rarely be tenable in non-experimental epidemiological research. He argues that the question at issue is whether the variation due to differences in covariates, bias and exposure ascertainment is small enough relative to other sources of variation to be reasonably ignored. It is clear that length of follow-up, as well as the range of congenital anomalies studied will result in substantial variation in the observed anomaly rates, but this does not mean that intra-study relative risks will necessarily be

heterogeneous. In the comparisons we have plotted, the anomaly risk for exposed epileptic women was consistently higher than the comparison group, be it unexposed epileptic women ,epileptic fathers or non-epileptic parents. This elevated risk was observed regardless of the follow-up strategy, anomaly definition or study population, suggesting that the heterogeneity introduced by these factors is not overwhelming the observed effect. Furthermore, the major effect of combining studies with different outcome measurement and definition will be to decrease precision of the estimates.

The "odd man out" technique[74] has been suggested as a statistically valid way of forming summary confidence intervals for between five and ten heterogeneous studies. However, we employed the Mantel-Haenszel technique because it provides a summary point estimate, can be used regardless of the number of studies summarized, maintains a constant p-value (0.05), and uses information from studies that can not be plotted (i.e. risk was zero or undefined because of null numerators). Where they could be compared, the "odd man out" intervals substantially agreed with the Mantel-Haenszel estimates.

The choices of inclusion and exclusion criteria regarding study design, execution, and presentation are subjective in meta-analyses[7,75]. We chose to limit criteria for several reasons. First, unlike most epidemiologic meta-analyses, which combine clinical trials to answer a very specific question[73], our intent was exploratory--to quantify the existing published literature and examine the risk patterns. Second, strict criteria would have eliminated almost all studies. For example, few reports mentioned whether or not those examining children for anomalies were blinded to the mother's epilepsy status or anticonvulsant use. Third, for all the potential flaws in individual studies, the shortcomings in reporting and heterogeneity between studies, "a reasonable person" will have to tolerate a certain degree of ambiguity and be influenced by the weight of evidence.

The meta-analysis does not help to resolve the issue of potential confounding by the type of epilepsy, the severity of epilepsy, or familial disposition to both seizures and certain

types of congenital malformations. Few of the published studies provided estimates of malformation risk stratified by any of these factors. In an area where individual studies lack statistical power and a synthesis of data from different studies is necessary to mitigate this problem, it is important that study results are presented, stratified on potential confounders.

Comparison of exposed epileptic mothers to other control groups is only one aspect of assessing the teratogenicity of anticonvulsant drug use. With strong evidence of a two- to three-fold increase in risk among offspring of exposed epileptic women relative to non-epileptic women, together with general agreement that epileptic women remain on anticonvulsants during pregnancy[76], one important focus for future research would be a quantitative summarisation of congenital anomaly risk associated with specific anticonvulsant therapies.

Table 3.2.1

Results of 37 studies reporting on the incidence of malformations in the offspring of epileptic mothers and a comparison group*

AUTHORS	YEAR	COUNTRY	ASC**	ALL EPILEPTIC MOTHERS		EXPOSED EPILEPTIC MOTHERS		UNEXPOSED EPILEPTIC MOTHERS		REFERENCE POPULATION		EPILEPTIC FATHERS***	
				LB	CA****	LB	CA	LB	CA	LB	CA	LB	CA
RETROSPECTIVE STUDIES													
JANZ and FUCHS	1964	GFR		345	5	225	5	130	0				
MARONI and MARKOFF	1969	GFR		35	1	21	1	14	0				
ELSHOVE and VAN ECK	1971	NL		65	10	65	10			11,986	221		
WATSON and SPELLACY	1971	USA	Y	51	3	51	3			50	0		
SPEIDEL and MEADOW	1972	UK	Y	383	17	324	17	59	0	442	7		
BJERKEDAL and S BAHNA	1973	NORWAY	Y	375	17					112,328	2,471		
FEDRICK	1973	UK	Y	217	30	198	28	19	2	649	36		
KOPPE et al	1973	NL	Y	192	13	125	11	67	2	12,175	462		
LOWE	1973	UK	Y	245	12	134	9	111	3	31,632	865		
MILLAR and NEVIN	1973	IRE	N	110	7	110	7			32,227	1,235		
NISWANDER and WERTELECKI	1973	USA	Y	413	17					345,584	9,216		
STARREVELD-ZIMMERMANN et al	1973	NL		297	22	279	20	18	2				
BARRY and DANKS	1974	AUSTRALIA		93	13	73	13	20	0				
KNIGHT and RHIND	1975	UK		140	6	97	4	43	1	69,000	2,484		
SHAPIRO et al	1976	FINLAND	Y	2,784	8					2,784	2		
WEBER et al	1977	FR		655	25	569	23	86	2	5,011	110		
ANNEGERS et al	1978	USA	Y	259	21	177	19	82	2	748	26	234	9

** ASC = ascertainment of congenital anomalies in non-epileptic controls, if Y (Yes), indicates that the same methods, sources and follow-up was used as for the offspring of the epileptic mothers

*** exposed and unexposed epileptic fathers except Meyer (exposed only)

**** LB = live births; CA = congenital malformations

(continued)

Table 3.2.1 (continued)

AUTHORS	YEAR	COUNTRY	ASC**	ALL EPILEPTIC MOTHERS		EXPOSED EPILEPTIC MOTHERS		UNEXPOSED EPILEPTIC MOTHERS		REFERENCE POPULATION		EPILEPTIC FATHERS***	
				LB	CA****	LB	CA	LB	CA	LB	CA	LB	CA
MAJEWSKI et al	1980	GFR		111	24	93	21	18	3				
NAKANE et al	1980	JAPAN		638	63	478	55	129	3				
BECK-MANNAGETTA et al	1982	GFR		397	61	268	53	129	8			371	41
BJERKEDAL	1982	NORWAY	Y	3,879	170					3,879	136		
DANSKY et al	1982	CANADA				88	14	46	3			100	1
KOCH et al	1982	GFR		34	4	32	4	2	0				
LINDHOUT et al	1982	NL		165	16	151	15	14	1				
SATISH and KALAYANARAN	1984	INDIA				32	N/S	43	N/S	89	N/S		
KALLEN	1986	SWEDEN				548	20	93	4				
ROBERT et al	1986	FRANCE				147	8	35	0				
PROSPECTIVE STUDIES													
SOUTH	1972	UK	Y	31	2	22	2	9	0	7,865	190		
KUENSSBERG and KNOX	1973	UK	Y	48	3	48	3			14,620	447		
GOUJARD et al	1974	FR	Y	42	1	39	1	3	0	12,691	219		
SHAPIRO et al	1976	USA	Y	305	20	102	5			49,977	1,373	396	18
BOSSI et al	1982	ITALY		49	4	46	4	3	0				
GRANSTROM and HIILESMAA	1982	FINLAND	N	147	7	134	7	16	0				
HILL et al	1982	USA	Y	59	11	59	11			252	5		
KOCH et al	1982	GFR		109	11	89	9	20	2	43	2	19	3
MIYAKOSHI and SEINO	1984	JAPAN				123	20	9	0				
KANEKO et al	1988	JAPAN				97	5	15	0				

** ASC = ascertainment of congenital anomalies in non-epileptic controls, if Y (Yes), indicates that the same methods, sources and follow-up was used as for the offspring of the epileptic mothers

*** exposed and unexposed epileptic fathers except Meyer (exposed only)

**** LB = live births; CA = congenital malformations

N/S not specified

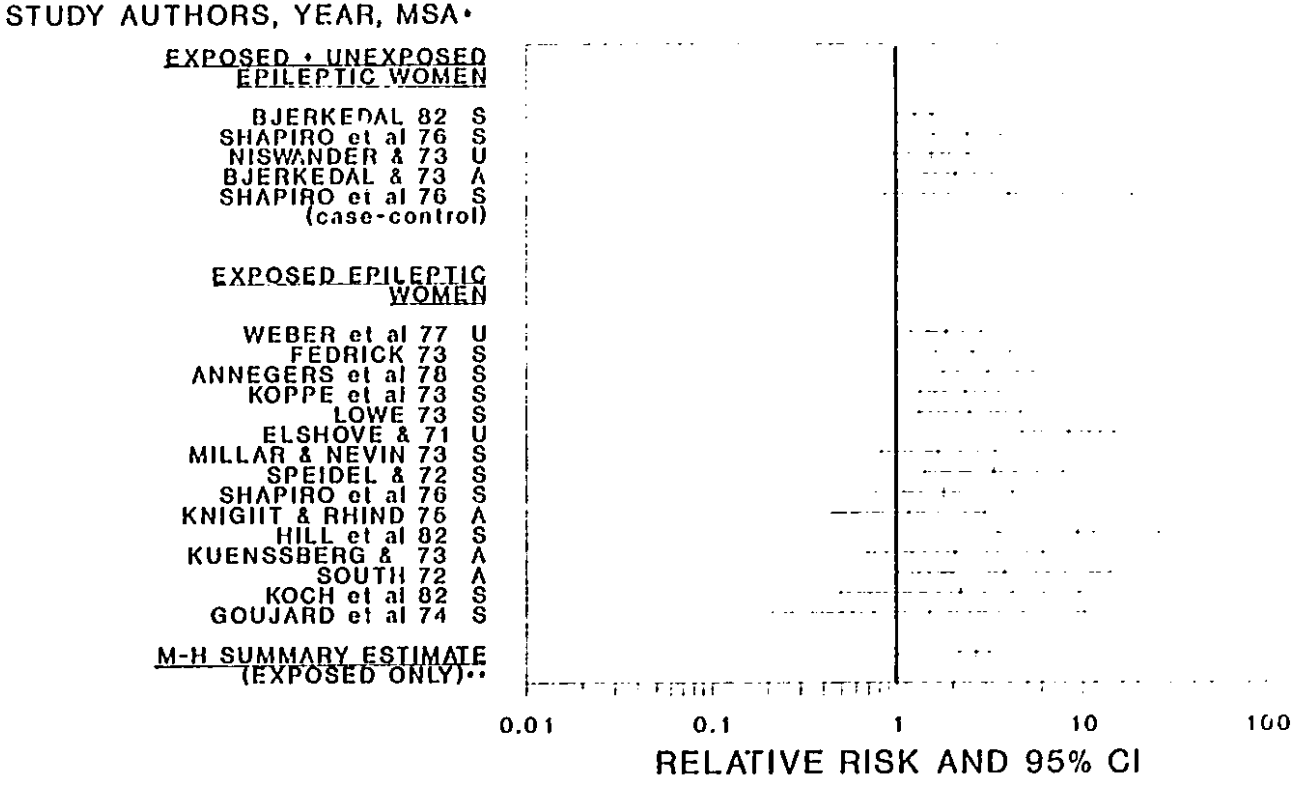
Table 3.2.2 Congenital heart defects and cleft lip and/or palate in the offspring of epileptic and non-epileptic women

AUTHORS	CONGENITAL HEART DISEASE				CLEFT LIP AND/OR PALATE			
	ALL EPILEPTIC MOTHERS	EXPOSED EPILEPTIC MOTHERS	UNEXPOSED EPILEPTIC MOTHERS	REFERENCE POPULATION	ALL EPILEPTIC MOTHERS	EXPOSED EPILEPTIC MOTHERS	UNEXPOSED EPILEPTIC MOTHERS	REFERENCE POPULATION
RETROSPECTIVE STUDIES								
JANZ and FUCHS						3		
MARONI and MARKOFF								
ELSHOVE and VAN ECK		2				5		27
WATSON and SPELLACY						0		0
SPEIDEL and MEADOW		6		1		3		1
BJERKEDAL and S BAHNA					4			675
FEDRICK	2			5		1		0
KOPPE et al						1		20
LOWE						1		49
MILLAR and NEVIN						2		70
NISWANDER and WERTELECKI	5			1,624		3		518
STARREVELD-ZIMMERMANN et al		4	0			4	1	
BARRY and DANKS								
KNIGHT and RHIND		3		379		2		76
SHAPIRO et al case-control								
WEBER et al	10			24	6			7
ANNEGERS et al		8	0	4		4	0	
MAJEWSKI et al								
NAKANE et al		14				15	0	
BECK-MANNAGETTA et al								
BJERKEDAL	11			12	13			7
DANSKY et al		6	1			3	0	
KOCH et al								
LINDHOUT et al								
SATISH and KALAYANARAN		1	0	1				
KALLEN		7	0			2	1	
ROBERT et al								

Table 3.2.2 (continued)

AUTHORS	CONGENITAL HEART DISEASE				CLEFT LIP AND/OR PALATE			
	ALL EPILEPTIC MOTHERS	EXPOSED EPILEPTIC MOTHERS	UNEXPOSED EPILEPTIC MOTHERS	REFERENCE POPULATION	ALL EPILEPTIC MOTHERS	EXPOSED EPILEPTIC MOTHERS	UNEXPOSED EPILEPTIC MOTHERS	REFERENCE POPULATION
PROSPECTIVE STUDIES								
SOUTH						2		10
KUENSSBERG and KNOX						0		30
GOUJARD et al		1		38				
SHAPIRO et al						1		50
BOSSI et al								
GRANSTROM and HIILESMAA								
HILL et al		3		0		1		0
KOCH et al								
MIYAKOSHI and SEINO								
KANEKO et al								

Figure 3.2.1 Congenital anomaly risk among offspring of epileptic women relative to offspring of non-epileptic women

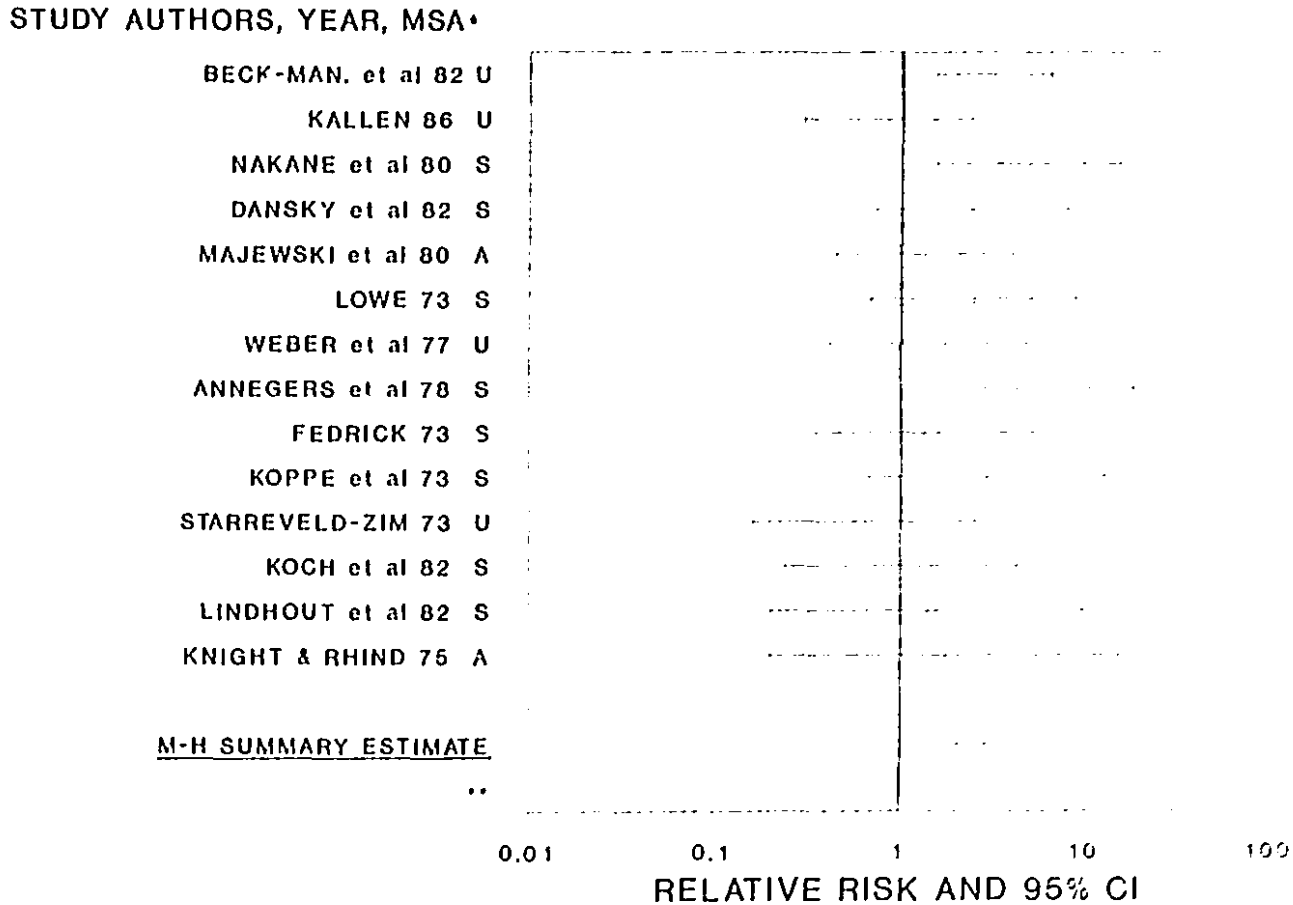


Confidence intervals ordered by width.

* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

**M-H estimate summarizes data from the 15 plotted studies of exposed epileptics and 1 study not plotted because the relative risk was undefined. Un-plotted study:
exposed epileptics - 3 malformations among 51 live births (3/51);
non-epileptic women - 0 malformations among 50 live births (0/50).

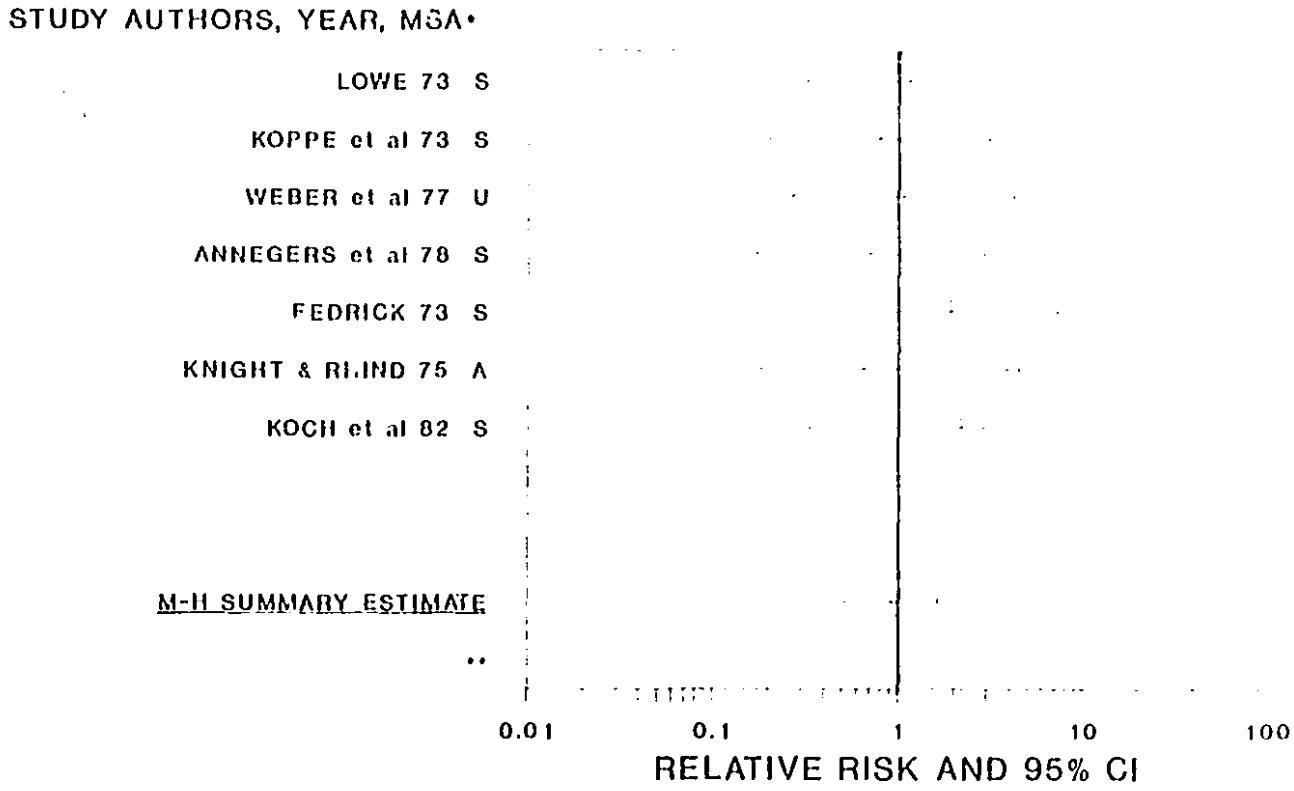
Figure 3.2.2 Congenital anomaly risk among offspring of exposed epileptic women relative to offspring of unexposed epileptic women



* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

**M-H estimate summarizes data from the 14 plotted studies and 12 studies not plotted because the relative risk was undefined. See Table 3.2.1 for data. Totals for 12 un-plotted studies:
exposed epileptic women - 79 malformations among 1,283 live births;
unexposed epileptic women - 0 malformations among 315 live births.

Figure 3.2.3 Congenital anomaly risk among offspring of unexposed epileptic women relative to offspring of non-epileptic women

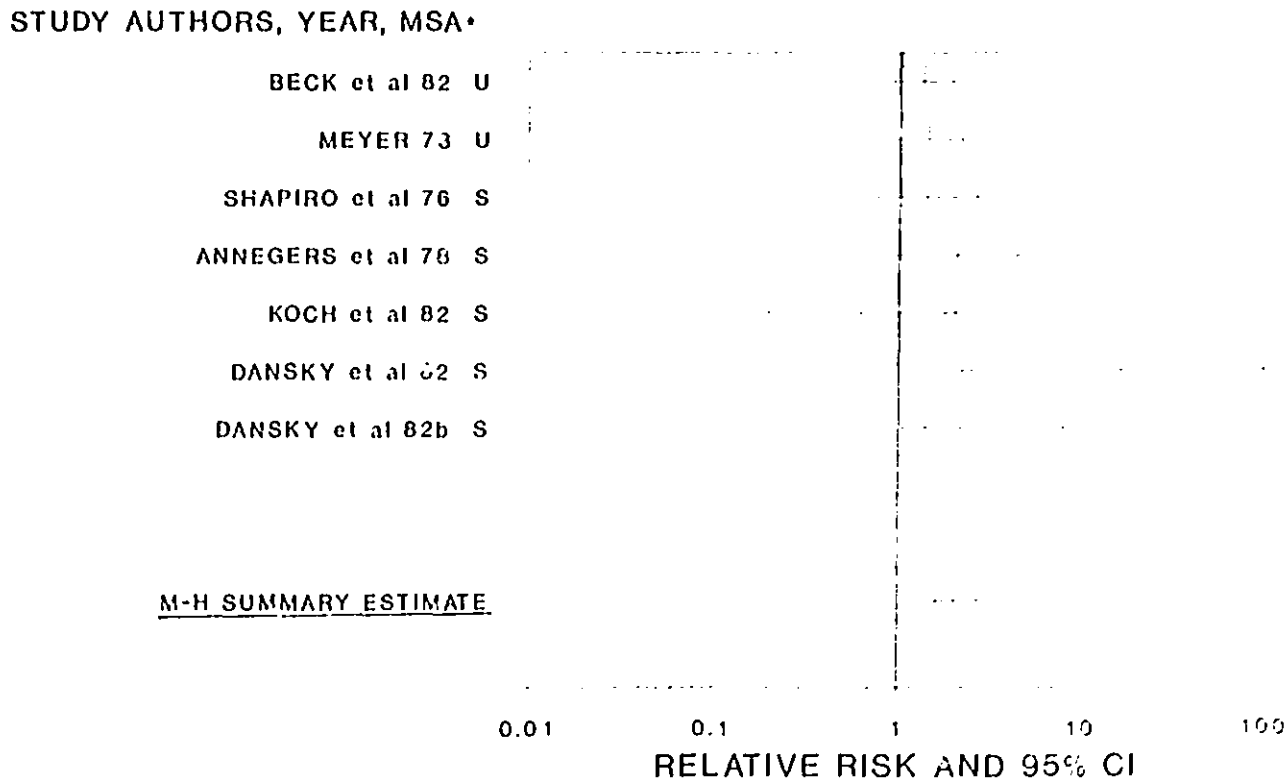


Confidence intervals ordered by width.

* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

**(see Figure 1) M-H estimate includes 3 un-plotted studies: unexposed 0/59, 0/9, 0/3; non-epileptic 7/442, 190/7865, 219/12691.

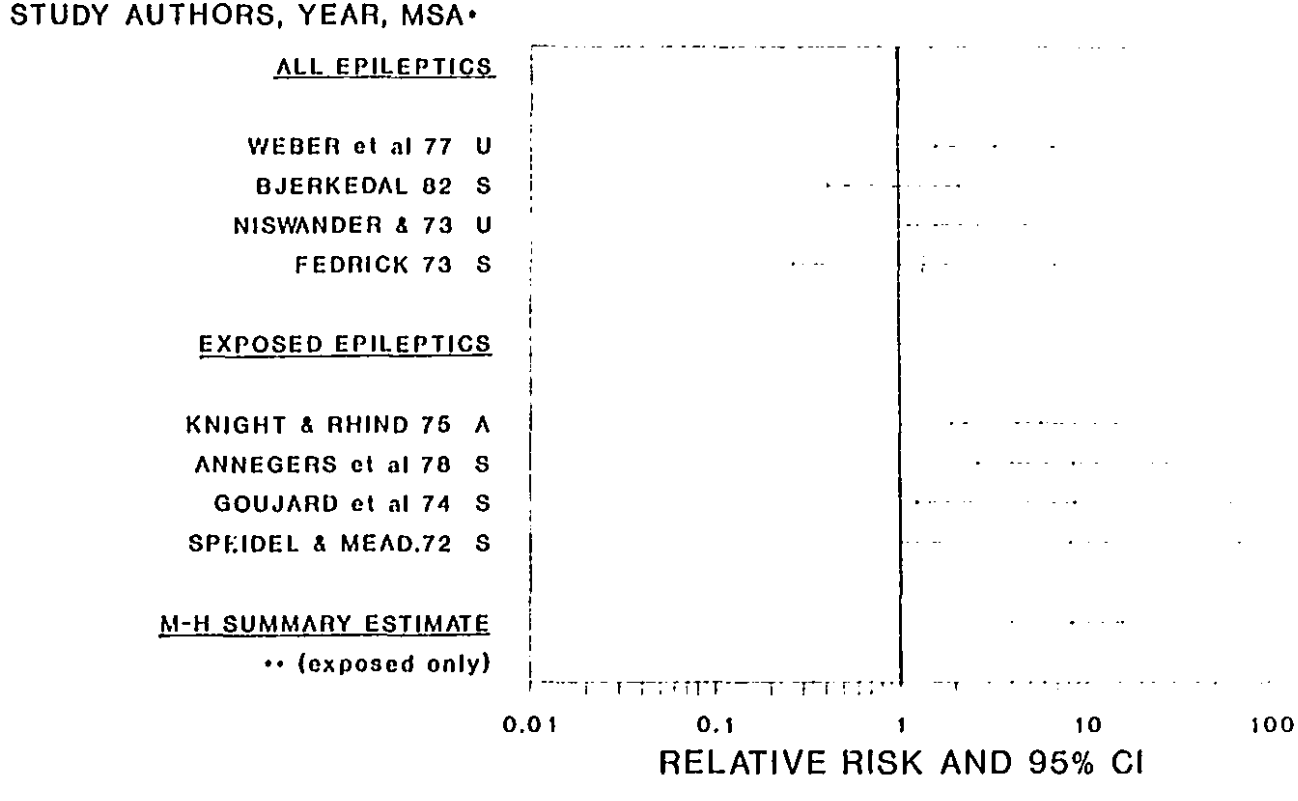
Figure 3.2.4 Congenital anomaly risk for offspring of epileptic mothers relative to epileptic fathers



Confidence intervals ordered by width.

* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

Figure 3.2.5 Congenital heart disease among offspring of epileptic women relative to offspring of non-epileptic women

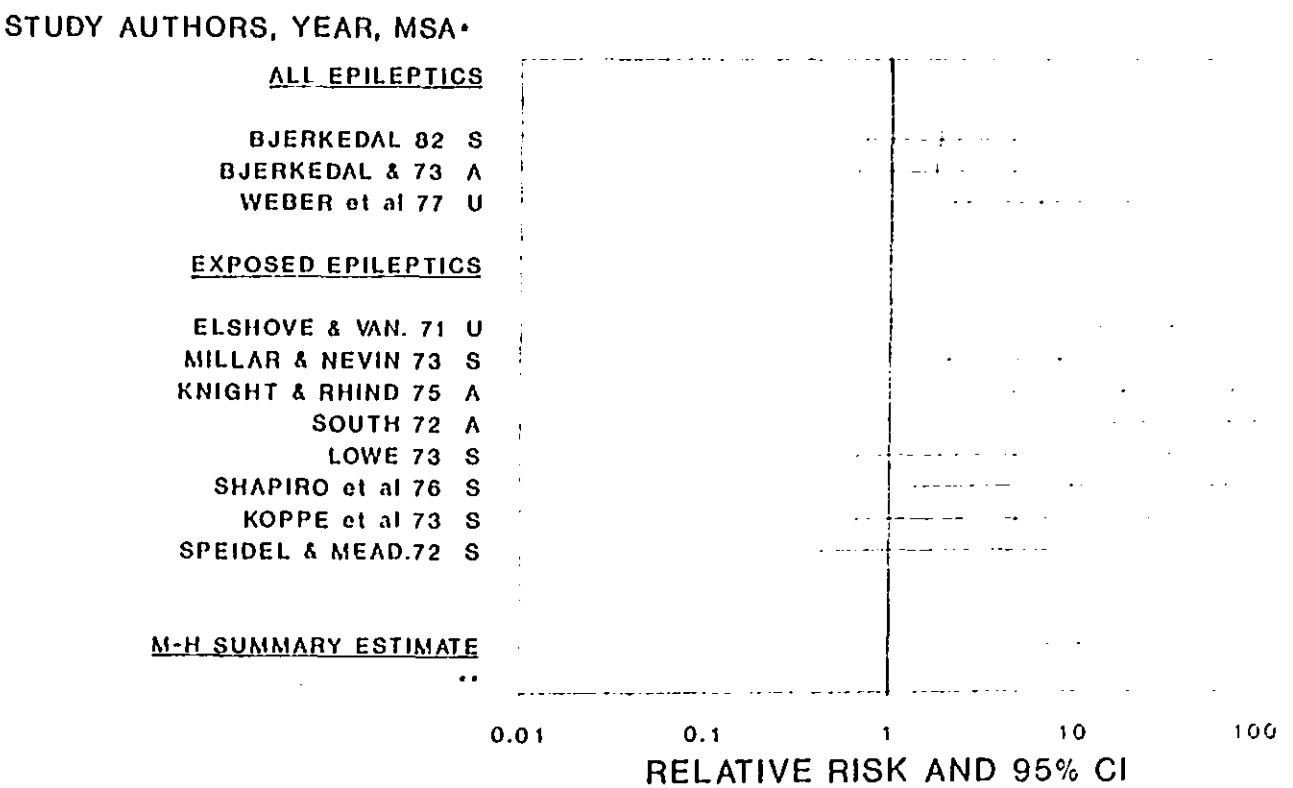


Confidence intervals ordered by width.

* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

**(see Figure 1) M-H estimate includes 1 un-plotted study: exposed epileptic 3/89; non-epileptic 0/43.

Figure 3.2.6 Cleft lip and/or palate among offspring of epileptic women relative to offspring of non-epileptic women



Confidence intervals ordered by width.

* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

** (see Figure 1) M-H estimate includes 3 un-plotted studies: exposed epileptic 1/59, 0/48, 1/198 ; non-epileptic 0/25, 30/14620, 0/649.

REFERENCES

1. Annegers JF, Hauser WA. Teratogenicity of anticonvulsant drugs. Res Publ Assoc Res Nerv Ment Dis 1983; 61:239-48.

2. Bossi L. Fetal effects of anticonvulsants. In: Morselli PL, ed. Antiepileptic Drug Therapy in Pediatrics. New York City: Raven Press, 1983:37-64.

3. Annegers JF, Elveback LR, Hauser WA, Kurland LT. Do anticonvulsants have a teratogenic effect? Arch Neurol 1974; 31:364-373.

4. Nakane Y. The teratological problem of antiepileptic drugs. Folia Psychiatrica et Neurologica 1980; 34:277-287.

5. Janz D. On major malformations and minor anomalies in the offspring of parents with epilepsy: review of the literature. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:211-222.

6. Kelly TE. Teratogenicity of anticonvulsant drugs. I: Review of the literature. Am J Med Genet 1984; 19:413-434.

7. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9:1-30.

8. Rothman KJ. Modern Epidemiology. Boston/Toronto: Little, Brown and Company, 1986.

9. Annegers JF, Kurland LT, Hauser WA. Teratogenicity of anticonvulsant drugs. In: Ward AA, Penry JK, Purpura D, eds. Epilepsy. New York City: Raven Press, 1983:239-248.

10. Mauritsen R. EGRET. Seattle, Washington: Statistics and Epidemiology Research Corporation 1990.

11. Galbraith RF. A note on graphical presentation of estimated odds ratio from several clinical trials. Stat Med 1988; 7:889-894.

12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Natl Cancer I 1959; 22:719-748.

13. Melchior JC, Svensmark O, Trolle D. Placental transfer of phenobarbitone in epileptic women, and elimination in newborns. Lancet 1967; 2:860-861.

14. Watson ID, Spellacy WN. Neonatal effects of maternal treatment with the anticonvulsant drug diphenylhydantoin. Obstet Gynecol 1971; 37:881-885.

15. Fedrick J. Epilepsy and pregnancy: a report from the Oxford Record Linkage Study. Brit Med J 1973; 2:442-448.

16. Koppe JG, Bosman W, Oppers VM, Spaans F, Kloosterman GJ. Epilepsie en aangeboren afwijkingen. Ned T Geneesk 1973; 117:220-224.

17. Lowe CR. Congenital malformations among infants born to epileptic women. Lancet 1973; 1:9-10.

18. Meyer JG. The teratological effects of anticonvulsants and the effects on pregnancy and birth. Eur Neurol 1973; 10:179-190.

19. Millar JH, Nevin NC. Congenital malformations and anticonvulsant drugs. Lancet 1973; 1:328.

20. Starreveld-Zimmerman AAE, van der Kolk WJ, Meinardi H, Elshove J. Are anticonvulsants teratogenic? Lancet 1973; 2:48-49.

21. Barry JE, Danks DM. Anticonvulsants and congenital abnormalities [letter]. Lancet 1974; 2:48-49.

22. Hill RM, Verniaud WM, Horning MG, McCulley LB, Morgan NF. Infants exposed in utero to antiepileptic drugs. Am J Dis Child 1974; 127:645-653.

23. Hanson JW, Myrianthopoulos NC, Harvey MAS, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976; 89:662-668.

24. Shapiro S, Slone D, Hartz SC, Rosenberg L, et al . Anticonvulsants and parental epilepsy in the development of birth defects. Lancet 1976; 2:272-275.

25. Nakane Y, Okuma T, Takahashi R, Sato Y, et al . Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: A report of a collaborative study group in Japan. Epilepsia 1980; 21:663-680.

26. Dieterich E, Steveling A, Lukas A, Seyfeddinipur N, Spranger J. Congenital anomalies in children of epileptic mothers and fathers. Neuropaediatrie 1980; 11:274-283.

27. Majewski F, Raff W, Fischer P, Huenges R, Petruch F. [Teratogenicity of anticonvulsant drugs (author's transl)]. Dtsch Med Wochenschr 1980;

105:719-723.

28. Bossi L, Battino D, Boldi B, Caccamo ML, et al . Anthropometric data and minor malformations in newborns of epileptic mothers. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:299-301.

29. Dansky L, Andermann E, Andermann F, Sherwin AL, Kinch RA. Maternal epilepsy and congenital malformations: correlation with maternal plasma anticonvulsant levels during pregnancy. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:251-258.

30. Hiilesmaa VK, Teramo K, Granström ML, Bardy AH. Fetal growth and antiepileptic drugs: Preliminary results of the prospective Helsinki study. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:203-206.

31. Lindhout D, Meinardi H, Barth PG. Hazards of fetal exposure to drug combinations. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:275-281.

32. Rating D, Nau H, Jäger-Roman E, et al. Teratogenic and pharmacokinetic studies of primidone during pregnancy and in the offspring of epileptic women. Acta Paediatr Scand 1982; 71:301-11.

33. Kelly TE, Edwards-Klein P, Rein M, Miller JQ, Dreifuss FE. Teratogenicity of anticonvulsant drugs. II: A prospective study. Am J Med Genet 1984; 19:435-443.

34. Miyakoshi M, Seino M. Malformations in children born to mothers with epilepsy. In: Antiepileptic drugs and pregnancy. Amsterdam: Excerpta Medica, 1984:125-131.

35. Jäger-Roman E, Deichl A, Jakob S, Hartmann AM, et al . Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. J Pediatr 1986; 108:997-1004.

36. Robert E, Lofkvist E, Mauguiere F, Robert JM. Evaluation of drug therapy and teratogenic risk in a Rhone-Alpes district population of pregnant epileptic women. Eur Neurol 1986; 25:436-443.

37. West R, Sherman GJ, Downey W. A record linkage study of valproate and malformations in Saskatchewan. Can J Public Health 1985; 76:226-228.

38. Bertollini R, Kallen B, Mastroiacovo P, Robert E. Anticonvulsant drugs in monotherapy. Effect on the fetus. Eur J Epidemiol 1987; 3:164-171.

39. Kaneko S, Otani K, Fukushima Y, Ogawa Y, et al . Teratogenicity of antiepileptic drugs: analysis of possible risk factors. Epilepsia 1988; 29:459-467.

40. Janz D, Fuchs U. Are anti-epileptic drugs harmful when given during pregnancy? Germ med Mth 1964; 9:20-22.

41. Jeavons PM. Non-dose-related side effects of valproate. Epilepsia 1984; 25:S50-S55.

42. Friis ML, Hauge M. Congenital heart defects in live-born children of epileptic parents. Arch Neurol 1985; 42:374-376.

43. Elshove J, van Eck JHM. [Congenital abnormalities, cleft lip and cleft palate in particular, in children of epileptic mothers]. Ned Tijdschr Geneeskd 1971; 115:1371-1375.

44. Maroni E, Markoff R. Epilepsie und schwangerschaft. Gynaecologia 1969; 168:418-421.

45. German J, Kowal A, Ehlers KH. Trimethadone and human teratogenesis. Teratology 1970; 3:349-362.

46. South J. Teratogenic effect of anticonvulsants. Lancet 1972; 2:1154.

47. Speidel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and the newborn. Lancet 1972; 2:839-843.

48. Monson RR, Rosenberg L, Hartz SC, Shapiro S, et al . Diphenylhydantoin and selected congenital malformations. N Engl J Med 1973; 289:1049-1052.

49. Kuenssberg EV, Knox JD. Teratogenic effect of anticonvulsants. Lancet 1973; 1:198.

50. Bjerkedal T, Bahna L. The course and outcome of pregnancy in women with epilepsy. Acta Obstet Gynec Scand 1973; 52:245-248.

51. Niswander JD, Wertelecki W. Congenital malformations among offspring of epileptic women. Lancet 1973; 1:1062.

52. Higgins TA, Comerford JB. Epilepsy in pregnancy. J Ir Med Assoc 1974;

67:317-320.

53. Loiseau P, LeGroux M, Henry P. Epilepsies et grossesses. Bord Med 1974; 8:1157-1164.

54. Goujard J, Huel G, Rumeau-Rouquette C. Antiepileptiques et malformations congenitales. J Gyn Obst Biol Repr 1974; 3:831-842.

55. Biale Y, Lewenthal H, Aderet NB. Congenital malformations due to anticonvulsive drugs. Obstet Gynecol 1975; 45:439-442.

56. Knight AH, Rhind EG. Epilepsy and pregnancy: a study of 153 pregnancies in 59 patients. Epilepsia 1975; 16:99-110.

57. Birmingham Research Unit of the Royal College of General Practitioners. . Morbidity and drugs in pregnancy. J R Coll Gen Pract 1975; 25:631-645.

58. Weber M, Schweitzer M, Andre JM, Tridon P, et al . [Epilepsy, anticonvulsants and pregnancy]. Arch Fr Pediatr 1977; 34:374-383.

59. Annegers JF, Hauser WA, Elveback LR, Anderson VE, Kurland LT. Congenital malformations and seizure disorders in the offspring of parents with epilepsy. Int J Epidemiol 1978; 7:241-247.

60. Seino M, Miyokoshi M. Teratogenic risks of antiepileptic drugs in respect to the type of epilepsy. Folia Psychiatr Neurol Jpn 1979; 33:379-385.

61. Beck-Mannagetta G. Drees B, Janz D. Malformations and minor anomalies in the offspring of epileptic parents: A retrospective study. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:317-323.

62. Koch S, Hartmann AM, Jäger-Roman E, Rating D, Helge H. Major malformations in children of epileptic parents--due to epilepsy or its therapy? In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:313-315.

63. Bjerkedal T. Outcome of pregnancy in women with epilepsy, Norway, 1968 to 1978: Congenital malformations. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:289-295.

64. Robert E, Rosa F. Valproate and birth defects [letter]. Lancet 1983; 1142.

65. French Chapter of I.L.A.E. . Teratogenic risk of antiepileptic drugs, with special reference to sodium valproate (valproic acid) therapy. In: Porter RJ, et al , eds. Advances in Epileptology: XVth Epilepsy International Symposium. New York: Raven Press, 1984:299-307.

66. Satish J, Kalyanaraman S. Teratogenic effects of anticonvulsant drugs. In: Porter RJ, et al , eds. Advances in Epileptology: XVth Epilepsy International Symposium. New York: Raven Press, 1984:315-324.

67. Bertollini R, Mastroiacovo P, Segni G. Maternal epilepsy and birth defects: a case-control study in the Italian Multicentric Registry of Birth Defects (IPIMC). Eur J Epidemiol 1985; 1:67-72.

68. Kallen B. A register study of maternal epilepsy and delivery outcome with special reference to drug use. Acta Neurol Scand 1986; 73:253-259.

69. Dansky LV, Andermann E, Rosenblatt D, Sherwin AL, Andermann F. Anticonvulsants, folate levels, and pregnancy outcome: a prospective study. Ann Neurol 1987; 21:176-182.

70. Brugge HG, Huisjes HJ. De gevolgen voor moeder en kind van epilepsie en het gebruik van anti-epileptica in de zwangerschap. Ned Tijdschr Geneeskd 1988; 132:157-159.

71. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer: why we still don't know. JAMA 1988; 259:3571-3578.

72. Jenicek M. Meta-analysis in medicine. Where we are and where we want to go. J Clin Epidemiol 1989; 42:35-44.

73. Walker AM, Martin-Moreno JM, Artalejo FR. Odd man out: a graphical approach to meta-analysis. Am J Public Health 1988; 78:961-966.

74. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA 1988; 260:652-656.

75. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. Epidemiol Rev 1990; 12:87-107.

76. Yerby MS. Problems and management of the pregnant woman with epilepsy. Epilepsia 1987; 28:S29-36.

Appendix 3.2.1

Design characteristics of 37 studies included in meta-analysis

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE*	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
64	Janz & Fuchs	Germany	56-63	R	Epilepsy Outpatient Clinic	Questionnaire filled out by mother (in 1963?)	Questionnaire filled out (in 1963?)	U
71	Eshlove & Van Eck	Netherlands	59-68	R	All hospital births in Groningen	History taken	Birth records	U
71	Watson & Spellacy	USA	60-70	R	1 hospital in Florida	Records from hospital (women with convulsive disorders)	Maternal & neonatal hospital records reviewed	S
72	South	England	69-71	P	1 hospital in south-west London	Rx recorded in maternity booklet	Birth record	A
72	Speidel & Meadow	England	48-72	R	Departments of neurology at 2 general hospitals	Neurologic records, obstetrical case sheets and GP referral letters	Obstetrical case sheets	S
73	Bjerkedal & Bahna	Norway	67-68	R	All births in Norway 1967 and 1968	Medical registration of birth includes mother's health information before and during pregnancy	Detailed medical registration of birth	A
73	Fedrick	England	66-70	R	2 counties	Epileptic mothers selected from detailed computerized birth registry -Rx history from GP	Hospital birth & admissions systematically abstracted for Oxford Record Linkage Project	S
73	Koppe et al	Holland	63-68	R	All deliveries in an obstetrics department in a hospital in Amsterdam	Clinic records	Hospital birth records	S

* Study type: R = Retrospective follow-up; P = Prospective follow-up.

** Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.2.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE*	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
73	Kuenssberg Knox	Scotland	65-67		272 general practioners reporting on 15,000 pregnancies in Scotland	General practioner records	Birth records	A
73	Lowe	England	65-71	R	Mothers domiciled in Cardiff	Computer birth registry Mention of epilepsy; followed with hospital & GP records	Computer birth registry coded anomalies	S
73	Meyer	Germany		R	Epileptics treated in Heildelbury	Parents interviewed & given questionnnaire; mothers asked about type & duration of antiepileptics during pregnancy	Questionnaire asked about specific anomalies & birth & pregnancy complications	U
73	Millar & Nevin	Ireland	69-72	P	Dept. of Neurology	Clinic records	Data on all pregnancies for women attending 1 neurologist	S
73	Niswander & Wertelecki	U.S.A.	65-71	R	Liveborn infants in U.S. Airforce hospitals	Epilepsy ascertained from computeris separation, but no anticonvulsant ascertainment undertaken. 1/5th of expected epileptic livebirths ascertained	Computerised hospital separation record	U
73	Starreveld/ Zimmerman et al	Netherlands		R	Patients referred to epilepsy centres	Survey	Survey	U
74	Barry & Danks	Australia	69-72	R	A Melbourne Hospital	Women coded as epileptic at antenatal clinic contacted & interviewed (40 interviewed, 32 had moved, 51 no reply)	No details given	U

** Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.2.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE*	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
74	Goujard et al	France	–	P	12,000 women who visted antenatal clinics in 13 maternity hospitals in France during 3rd month of pregnancy	Interview at 3 and 6 months of pregnancy	Children examined on 5th or 6th day, 3 months, 6 months and some at 2 years	S
75	Knight & Rhind	England	53–73	R	Attending outpatient clinic for anticonvulsant management or referred by obstetrical department	Clinic records	Birth record	A
76	Shapiro	USA	59–65	P	Data from Collaborative Perinatal Project (12 hospitals across USA)	Collaborative perinatal study Rx at antenatal interview & inspection of hospital & medical records when appropriate	Detailed follow-up of anomalies to age 1 or to age 4 if death; motor & mental testing at 8 months.	S
77	Weber et al	France	–	R	No details given	"A survey". Controls from all births in Nancy region. Second set of controls from a national sample 1972.	No details given	U
78	Annegers	USA	39–72	R	Mayo Clinic	Comprehensive treatment records for each patient with epilepsy available for several decades	Comprehensive records including examination & detailed review at 4 days & medical history while child remains in the area	S
80	Majewski	Germany	–	R	University Hospital Neurologic clinic (11 neuro psychiatric clinics)	Mothers interviewed about drug use	Infants examined and clinical record	A

* Study type: R = Retrospective follow-up; P = Prospective follow-up.

** Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.2.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE*	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
80	Nakane et al	Japan	74-77	P R	9 University Hospitals, 1 NeuroPsychiatry Unit, National Epilepsy Ctr. & National Research Institute For Nervous & Mental Diseases	Demographic & clinical by psychiatrist	Pro - Psychiatrist collected information on delivery and early neonatal period from obstetrician and patient Retro - malformations confirmed during follow-up	S U
82	Beck-Mannagetta et al	Germany	69-72	R	---	Clinical charts	Offspring examined	U
82	Bjerekedal	Norway	67-78	R	All births in Norway	All livebirths of mothers registered to have epilepsy. A matched comparison group of births to women not registered to have epilepsy. Matched on mother's age, parity single/multiple birth sequence, and birth place of 1st child.	Medical birth registrations	S
82	Bossi	Italy	77-80	P	Clinic	Clinic records Blood Plasma monitoring	No details given	U
82	Dansky et al	Canada		R	Seizure clinic & private neurologic & obstetric practice	Blood folate & AED monitoring from time recruited (before or during pregnancy)	Birth record, clinical record and clinical examination	S
82	Dansky et al	Canada	81	P	Montreal seizure clinic, neurologic & obstetrical practices	Detailed history taken during pregnancy, monthly AED intake, review & blood serum monitoring	Review of neonatal exam & later records; exam at birth & during 1st year, followup to age 6	S

* Study type: R = Retrospective follow-up; P = Prospective follow-up.

** Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.2.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE*	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
82	Granstrom & Hillesma	Finland	76-79	P	2 departments of obstetrics in Helsinki	Clinic records?	Newborn examination	A
82	Hill	USA	68-80	P	Private hospitals associated with Baylor Medical College, Houston, Texas	Selected at admission to labour Detailed history taken Obst & GP letters to confirm medication during pregnancy	Detailed physical exam at birth 1,2,3,4,6,9,12,18,36 months. Examiner blinded to Rx	S
82	Koch et al	Germany	76-81	P	5 obstetric clinics in West Berlin + referals from neurologists	Blood samples for anticonvulsant levels through pregnancy	Infants examined at birth, day 4 and 4 further examinations during first year of life	S
82	Lindhout et al	Netherlands	72	P	Epilepsy outpatient clinic	Info about prev preg & anticonvulsant 1st Tri serum levels, fits entered on a standard form at visit after birth (generally available case history too)	In hospital births routinely examined by pediatricians Info registered at 1st visit to epilepsy clinic after birth	S
32	Rating	Germany	76-80	P	5 obstetrical clinics in Berlin	14 women on Primidone (blood sampled regularly)	Examined at birth, 4 days & 4 further exams in FYOL	S
84	Miyakoshi	Japan	75-84	P	National Epilepsy Centre	Interview	Interviewed mother & attending obstetrician or pediatrician for neonatal death or stillbirth. 63 out 123 live births examined in infancy by doctor at clinic in charge of patient	S

* Study design: R = Retrospective; P = Prospective

** Methodological Strength Assessement: U = Uncertain; A = Adequate; S = Sound

(continued)

Appendix 3.2.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE*	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
86	Kallen	Sweden	73-81	R	Swedish Medical Birth Registe.	Diagnoses of epilepsy recorded on summary birth form Hospital charts retrieved for diagnoses confirmation and possible anticonvulsant use *Only 1/3 to 1/4 of expected number of epileptic women found	Pediatric examination of newborns	U
86	Robert	France	76-83	R	Women who had an EEG between 76 & 83 at the hospital of Neurology & Neurosurgery. Wertheimer,Lyon France, & 3 Lyon maternity wards	Questionaire sent to women	Questionaire sent to women	U
88	Kaneko	Japan	78-84	P	2 university hospitals & medical college hospital	Data prospectively collected at monthly intervals including compliance and seizures	Examination by obstetricians & neuropsychiatrists on day 1, day 5, day 13 and at time of	S

* Study type: R = Retrospective follow-up; P = Prospective follow-up.

** Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

META-ANALYSIS OF ANTIEPILEPTIC THERAPY AND CONGENITAL MALFORMATIONS

KENNETH C JOHNSON B.E.S. 1
GREGORY J. SHERMAN Ph.D 1

1. Diseases of Infants and Children Division
Bureau of Chronic Disease Epidemiology
Laboratory Centre for Disease Control
Health Protection Branch

ABSTRACT

A meta-analysis was performed using data from published epidemiologic studies to compare the teratogenic risks associated with specific antiepileptic therapies women with epilepsy were treated with during the first trimester of pregnancy. The analysis demonstrated the inadequacies of many study reports--vague descriptions of methods often restricted assessment of study quality and incomplete reporting of results was largely responsible for restricting the analysis to 31 of the more than 60 published studies. Women with epilepsy on anticonvulsant monotherapy experienced increased risk of congenitally malformed children relative to both women with epilepsy but not treated with anticonvulsants (Mantel-Haenszel study-stratified estimate of relative risk (RR) 1.8, 95% confidence interval (CI) 0.8-4.8), and to women who did not have epilepsy (and no anticonvulsant treatment)(RR=2.5, CI=1.8-4.0). Available published data are insufficient to demonstrate statistically significant differences in risk among commonly-used monotherapies. Among one-drug therapies, phenobarbital and carbamazepine were associated with the lowest risk estimates; risks for phenytoin and valproic acid relative to phenobarbital were, respectively, 1.4 (CI=0.7-2.8) and 2.0 (CI=0.6-6.6). Two-drug therapy was associated with a 20% elevation of risk over monotherapy, but three-drug therapy was associated with more than a doubling of risk in comparison to one-drug therapy (RR=2.2, CI=1.3-3.7). The analysis thus would suggest that three-drug therapy may be associated with a four- to five-fold increase in malformation risk relative to women with no anticonvulsant therapy. Data required to evaluate the role that confounding by severity or type of epilepsy might play in the risk associated with polytherapy were not available from the individual reports. Nevertheless, this analysis when combined with other related research on choice of anticonvulsant therapy suggests that avoiding therapy with three or more anticonvulsants in the first trimester would be prudent.

INTRODUCTION

The results of over 60 analytic epidemiologic studies demonstrate that the offspring of epileptic women exposed to anticonvulsants during the first trimester of pregnancy experience a two- to three- fold increase in risk of congenital anomalies compared to offspring of non-epileptic women.[1-3] Nevertheless, the teratogenic potential of specific anticonvulsant therapies remains poorly understood,[1,2] because of the difficulties inherent in studying the subject,[4]--in particular the potential for confounding by indication and the inadequate statistical power of individual studies.[4] Neither general reviews of the literature,[1,2,5-8] nor reviews of specific anticonvulsants [9-13] have adequately evaluated the differences in risk associated with particular anticonvulsant therapies. Because of the clinical and etiological significance of the issue, we undertook a meta-analysis to quantify the risks, using the published epidemiologic literature.

MATERIALS AND METHODS

National Library of Medicine's English-language databases from January 1966 to March 1990 were searched using MEDLINE, for reports of analytic studies of anticonvulsant use by epileptic women during pregnancy and congenital anomalies in their offspring. The search employed the terms "abnormalities, drug induced", in combination with "anticonvulsants". Bibliographies in located reports and in five recent reviews[1,2,5-8] were also used to identify studies.

Epidemiologic studies examining the risks of serious congenital malformations in the offspring of women with epilepsy were deemed eligible for inclusion in this analysis. Both retrospective and prospective follow-up studies as well as case-control studies were considered for inclusion but case reports were not. "Congenital anomalies", "serious malformations", "serious physical disfigurements", and similar descriptions were accepted. Where major and minor anomalies were clearly distinguished, only the major

anomalies were included in the analysis.

Establishing the quality of a number of the individual studies was difficult. First, the description of the methods and materials was often short and vague. Second, details required to judge the quality of routine birth records and the extent of birth defect ascertainment were frequently lacking. Third, we could not establish that those examining infants had been blinded to epilepsy or anticonvulsant status in the vast majority of retrospective or prospective studies. On the other hand, about 95% of the studies we located were of a follow-up design, a design not generally perceived to be as open to serious bias as the case-referent (case-control) design. Typically the studies involved following up all the women attending a clinic for epilepsy, or the births of an entire population. In consideration of the above factors and the problems of small sample size that plague many of the studies, we decided to evaluate the methodological strength of individual studies on a simple relative ranking of unacceptable, "uncertain" (U), "adequate" (A) or "sound" (S), present the results for all studies not labelled unacceptable, and compare the results obtained from all acceptable studies with those based only on studies labelled "sound".

The following criteria were used to evaluate the quality of follow-up studies:

1) a medical diagnosis of epilepsy;

2) medical record evidence of the anticonvulsant use in the first trimester;

3) anomaly ascertainment (intensity of search) that appeared to be independent of anticonvulsant exposure; and

4) loss to follow-up that appeared independent of anticonvulsant exposure.

The methodological quality of case-control studies was evaluated using criteria one and two above plus the following:

a) for studies involving community controls, choice of controls that would indicate that had they been diagnosed with a major malformation they would have been selected as cases;

b) data collected for cases and controls in a similar manner;

c) the same exclusion criteria applied to cases and controls; and

d) if an interview was involved, the interviewer was blinded to case-control status.

Study methodological quality was evaluated by one of the authors (KCJ) without examining study results and where a decision was unclear a consensus was reached between authors. Follow-up studies were categorized as follows. Studies that clearly met the first four criteria were labelled "sound". Studies that appeared to meet the first four criteria, but where the details were sketchy, or that appeared sound but did not meet criteria one or two, were rated "adequate". Studies that provided too little information to evaluate whether the four criteria were met were labelled "uncertain". Studies clearly not meeting criteria three or four were excluded. Case-control studies not meeting criteria a), b) and c) were excluded. Case-control studies meeting all the criteria set for case-control studies were labelled "sound"; if criteria one or two was not met the study was labelled "adequate"; and if some methodological details were unclear the study was labelled "uncertain".

In addition to the study quality criteria, the presentation of study results had to include the following to be used in the meta-analysis: 1) counts of epileptic women on specific mono- or poly- anticonvulsant therapies during the first trimester; 2) data on all serious congenital anomalies in the resultant offspring. Follow-up studies in which anticonvulsant exposures were reported in the study results for only certain anticonvulsant therapies were not excluded. When a study was reported more than once, the most detailed report and any additional information from the other paper(s) was used. Case-control studies were required to report the specific mono- or poly- therapy for every exposed subject.

As a first exploratory step, crude rates of congenital malformation, congenital heart malformations and cleft lip and/or palate were calculated by the number of types of

anticonvulsants used in the first trimester and for each specific anticonvulsant therapy by pooling data from the included follow-up studies. Crude relative risks (RRs) were calculated using the offspring of the non-exposed epileptic women as the comparison group. Tests for linear trend in proportions over the number of types of anticonvulsants prescribed in the first trimester and anomaly risk were calculated with Armitage's Chi-square test.[14]

Where sufficient data were available, specific therapies were compared within individual studies. Within study estimates of relative risk (RR) and exact 95% CI were calculated using the odds ratio and exact 95% CI routines available in EGRET[15]. With rare outcomes like birth defects, odds ratios provide a close approximation of the RR. Because many of the studies included were small, exact calculations of 95% CI were preferable and were available in EGRET for odds ratios but not for RR's. Using odds ratios also allowed direct inclusion of case-control studies in summary estimates. To present and summarise the results of the individual studies in a succinct form, allow for ready evaluation of inter-study heterogeneity and to examine the impact of study quality on estimated RR's, individual study RR estimates and exact 95% CI's were plotted for each included study,[15] ordered according to CI width and presented on a log scale.[16] The homogeneity of the RR's was evaluated by examining each graph for a common area where all the confidence intervals overlapped, which would indicate study homogeneity.

A study-stratified summary estimate of RR and associated 95% CI were calculated[15] using the Mantel-Haenszel procedure,[17] which weights individual study risks according to their precision. When no congenital anomalies were reported in a study for one of the exposures being compared, the RR for that comparison was either undefined or zero and the study was not plotted, because of its low information value and the visual distraction caused by very wide CI's, although the comparison did contribute to the RR summary estimate.

RESULTS

Reports on 61 analytic follow-up studies of congenital anomalies in the offspring of epileptic women[4,9,11,18,74] and three case-control studies of drug exposure and birth defects[44,75,76] were identified. Only 31 (48%) of the follow-up studies met the inclusion criteria.[4,18,19,22,26,27,29-31,34,35,38,43,44,48-50,53-55,57,58,61,62,65-67,70,71,74] Exclusions were as follows: Two studies[11,65] did not meet the minimum methodological quality criteria. One report did not study all serious anomalies.[69] No anticonvulsant information was captured in three studies.[25,33,52] Twenty-four follow-up studies and two case-control studies failed to present the number of women exposed to particular therapies, often combining mono- and poly-therapy.[9,20,21,23,24,28,32,36,39-42,45-47,51,56,59,60,64,72,73,75-77] Two studies did not present exact exposures for the offspring with malformations.[37,68]

Epilepsy clinics were the source of study subjects in half of the included studies but in only one third of the excluded studies. Over one third of the included studies were carried out prospectively, but only two (8.7%) of the excluded studies were prospective. Sample size among all studies was small--among the included follow-up studies the average was 105 livebirths of anticonvulsant-exposed epileptic women. Design details and methodological quality assessment for included studies are presented in Appendix 3.3.1. Among the 31 included studies 17 (55%) received a methodological quality assessment of "sound".

Specific first trimester anticonvulsant therapies of epileptic women were extracted for 3,670 live born infants. Additionally, malformation rates stratified by number of drugs were presented in one report.[78] Table 3.3.1 presents details of the extraction for each included study and summarizes the extraction by study design. A strong positive gradient was observed between the number of anticonvulsants used in the first trimester and the crude rate of malformed babies (see Table 3.3.2). A test for trend was significant ($b=.039$, $P < .001$). The consistency of this trend was examined by categorizing studies by study base (epilepsy clinic, hospital, population or other), by overall anomaly rate

(<5%, 5-<10%, 10% +), by design (prospective or retrospective) and anomalies studied ("major congenital anomalies" or "congenital anomalies"). The observed trends in risk remained intact among the stratified subsets of data. (see Table 3.3.1) Congenital anomaly rates were consistently markedly higher among women treated with three or more drugs than among those treated with one- or two-drug therapy.

Study-stratified analyses were then undertaken where sufficient data was present. A comparison of the risk associated with monotherapy relative to the risk among epileptic women with no first trimester anticonvulsant exposure was possible in seven studies and yielded a summary RR of 1.8 (95% CI .8-4.8), although only the four studies assessed as "sound" could be plotted. A comparison of epileptics on monotherapy relative to non-epileptics with no anticonvulsant use yielded a summary RR estimate of 2.5 (95% CI 1.8-4.0) and involved only studies assessed as "sound" (see Figure 3.3.1). Two-drug therapy was associated with a slight increase in risk compared to monotherapy (RR 1.2, 95% CI .9 -1.5) based on 25 studies (15 "sound"). Comparison of three-drug therapy to one-drug therapy (Figure 3.3.2), based on 19 studies, resulted in a summary risk estimate of 2.2 (95% CI 1.3-3.7). Three-drug risk was higher than one-drug risk in 10 of the 11 studies plotted. Removal of studies that did not achieve the "sound" methodological quality assessment did not materially change the point estimate for any of the four summary risks above.

Crude pooled rates of congenital malformation associated with specific anticonvulsant therapies are presented in Table 3.3.3. Phenobarbital and phenytoin accounted for three quarters of mono-therapies, and were used in combination in approximately three quarters of the poly-therapies. Carbamazepine, primidone and valproic acid were also often used.

Phenobarbital and carbamazepine monotherapies were associated with the lowest crude malformation rates, respectively, 4.6% (95% CI 3.2-6.4) and 4.5% (95% CI 1.7-9.6). Among two-drug therapies with more than 25 exposures, the combination of primidone

and phenytoin was associated with the highest crude malformation rate (20.3, 95% CI 9.1-33.3). Although based on very small numbers, most three- and four-drug combinations were associated with high risk estimates.

Phenobarbital was chosen as the referent group for within study comparisons because it was the most common therapy in the majority of studies. Thus it tended to have the most stable risk estimates and be available for comparisons to other anticonvulsant therapies. Study-stratified comparison of phenytoin monotherapy relative to phenobarbital monotherapy (Figure 3.3.3) yielded a summary risk estimate of 1.4 (95% CI .7-2.8). Six of seven RR's were above one although three were close to unity. Valproic acid monotherapy could be compared to phenobarbital monotherapy within only seven studies, exposed numbers were small, three of the four studies that were plotted did not receive the "sound" rating and confidence intervals were wide (Figure 3.3.4). Primidone could be compared to phenobarbital monotherapy within seven studies, five studies contributed to the summary risk estimate of 0.3 (95% CI 0.1 - 1.1), but only two studies could be plotted. Similarly carbamazepine could be compared to phenobarbital monotherapy within 11 studies, eight studies contributed to the summary risk estimate of 0.7 (95% CI 0.2-2.6), but only one study could be plotted. When more than a few of the studies involved in the summary estimate include zero cells, the Mantel-Haenszel estimator breaks down and these estimates must be interpreted cautiously. Although other methods may be used in these situations, they were not because data was so sparse that any further analysis seemed of questionable value.

Therapies including both phenytoin and primidone resulted in high risk estimates relative to monotherapy (summary risk 2.8, 95% CI 1.5-6.2) (Figure 3.3.5). Two studies reported risks relative to monotherapy in excess of 15.

Many study-stratified comparisons of risk were not feasible because of sparse data. Epileptic women on three-drug therapy could be compared to epileptic women without first trimester anticonvulsant exposure within only three studies. However combining our

estimate of risk of monotherapy relative to no-drug therapy (RR 1.8), and three-drug exposure relative to monotherapy (RR 2.2), would suggest that three-drug therapy may be associated with a four-fold increase in risk relative to no exposure.

Cleft lip and/or palate and congenital heart defect data demonstrate a similar, though stronger pattern of increasing risk with increasing number of anticonvulsants (See Table 3.3.4) . Chi-squared tests for linear trend were significant for both anomaly groups (cleft lip/palate b=.0076, p <.001); congenital heart disease (b=.0096, P < .001). The small numbers of these defects makes evaluation within specific drug exposure groups or within studies difficult, but the crude patterns of distribution appear similar to those for all anomalies combined (See Table 3.3.5). Of particular note is the high rate of congenital heart defects associated with therapies combining primidone with phenytoin or phenobarbital.

DISCUSSION

For this meta-analysis we considered only published reports as sources of data. Bias occurs where publication depends not only on study quality but also on the statistical significance of the results.[79] However, the major finding of our analysis--that three-drug therapy is associated with a substantially higher congenital anomaly risk than monotherapy--is unlikely to be the result of publication bias. Few reports focused on the risk associated with polytherapy; the focus was generally on the teratogenic potential of individual anticonvulsants. Therefore neither a negative or a positive finding for three-drug therapy would have precluded publication. As well, the small number of women exposed to three-drug therapy in most studies limited the generalizability of individual study observations.

Bias may have resulted from selective reporting of results. A number of studies were excluded because they failed to distinguish exposures to monotherapy from those to

polytherapy. It is possible that specific anticonvulsant combinations might only be identified when associated with elevated risk which could result in a spurious positive association between three-drug therapy and increased risk. Although this bias could increase the risk estimate, it is unlikely to explain the relationship for the following reasons. First, because many of the women were treated with more than one anticonvulsant and the effects of one drug might thus be confused with the effects of another, it would seem logical that the number of women exposed to specific monotherapies and polytherapies would be presented separately. Second, in no excluded study did the authors report combining data from monotherapy and polytherapy exposures because they found no confounding; it appears rather that the possibility of confounding or drug interaction was not given enough consideration. Third, the pattern of increased risk was consistent across included studies. If, in fact, the reports we used comprise a biased sample of the research performed, and increased risk was not associated with three-drug therapy in the excluded studies, it would suggest heterogeneity in the data--that two different phenomena were being observed--not that the observed relationship is spurious.[80]

Bias resulting from selective reporting could affect rates associated with specific drug combinations and specific anomalies. If a particular anticonvulsant therapy was associated with a high malformation rate in a study, there might be a higher probability of presenting that combination separately. However if it were just a chance finding, similar high risk would be unlikely to be observed in other studies.

When meta-analysis is used in epidemiology to estimate the effect size of a specific clinical therapy from randomized controlled trials, tight quality and comparability criteria are essential for answering a very specific question.[81] We chose to limit criteria for several reasons. First, our intent was exploratory--to quantify the existing published literature and examine the risk patterns. Second, strict criteria would have eliminated almost all studies, primarily because of vague reporting of the study methods which does not necessarily imply poor design. Third, for all the potential flaws in individual studies,

the shortcomings in reporting and heterogeneity between studies, the studies are almost all of a follow-up design, a design not thought to be nearly as likely to be seriously distorted by bias as the case-control study. Fourth, with the assessment of quality we used, we did not generally find that the studies assessed as "sound" resulted in materially different risk estimates than those that failed to receive the "sound" rating. Fifth, when all studies meeting basic quality criteria are included, more studies may contribute to the observed patterns of risk, and if results are consistent among a larger number of studies the observed association is strengthened.

When analytic studies are combined, design heterogeneity is inevitable.[80] One must consider carefully whether the existing heterogeneity is small enough relative to other sources of variation to be reasonably ignored.[80] Among the studies, protocols for examination at birth and follow-up after birth varied substantially, and the range of anomalies studied differed. To compensate for study heterogeneity: (1) we analyzed cleft lip and/or palate and congenital heart defects separately; (2) we performed a sensitivity analysis on the risk differences between one-, two-, and three-drug therapy; (3) we adopted a graphic approach to study summarization where feasible, allowing preservation of within-study comparisons; and (4) we used the Mantel-Haenszel procedure to summarize risk across studies, a technique which averages the results of comparisons made within strata and does not implicitly assume that data in one strata (i.e. study) can be directly compared to data in another strata.[82]

The comparability of studies with different follow-up protocols is contingent on the type of anomaly being examined. Congenital heart defects, for example, may be apparent at birth or may not be diagnosed for several years and therefore, longer follow-up is likely to result in substantially higher defect rates.[83] On the other hand, for cleft lip, readily visible at birth, and cleft palate, which often causes medical complications soon after birth, ascertainment rates should not be strongly affected by differences in length of follow-up.

Many anomalies can be expressed in a range of severities; for example a congenital heart defect can be life threatening at birth or it can be totally functional. However, the standardized coding system commonly used for congenital anomalies, the International Classification of Diseases, contains no provision for differentiation of the severity of most birth defects. Anneger et al.[4] suggest that the criteria of Leck[84] have generally been used in this field of study to define congenital anomalies but we found no written evidence of this from the published reports. Reports which specified studying "major anomalies" only had anomaly rates approximately 25 percent lower than those studies reporting on "congenital anomalies", suggesting that generally when the term "congenital anomalies" was used the majority of reported anomalies were major.

Type of epilepsy may confound the relationship between specific drug therapy and malformation rate, if specific types of epilepsy are most often controlled with specific anticonvulsant therapy and specific types of epilepsy result in higher rates of major malformations in the offspring. Although few reports provided information required to evaluate the concern directly,[2] we feel that type of epilepsy is unlikely to seriously confound the results. First, we found large variations among studies in the use of specific anticonvulsants, the rate of polytherapy, and the use of specific anticonvulsant combinations in patient populations where there is no reason to expect marked differences in prevalence of different types of epilepsy. For example, in Bertollini's study of monotherapy which combined information from studies in four European countries, phenytoin was the drug of choice in Sweden and yet virtually unused as monotherapy in the other three countries.[71]

Second, a number of recent thorough reviews of drug treatment of epilepsy[85-87] reach conclusions similar to those of Beghi et al.[88] who suggest that "antiepileptic drug selection is still based on fashion, market pressures and individual experience rather than on sound scientific considerations". If, as the literature seems to indicate, therapy is not particularly specific to type of epilepsy across time and place, then by combining studies from a number of time periods and locations this type of confounding, should it exist,

would be greatly diluted in the pooled data and would be unlikely to seriously bias the results.

There is the potential for confounding of the anticonvulsant-malformation relationship by the severity of the epilepsy if increased severity is related to the therapy with several types of anticonvulsants and increased severity is related to congenital anomaly risk. This type of confounding could not be examined in our analysis because epilepsy severity is difficult to quantify and the reports we used did not use measures of it to stratify anticonvulsant use. We expected to see higher rates of anomalies in clinic-based studies, based on the assumptions that individuals with more severe and/or less well controlled epilepsy would be more likely to be treated at specialty clinics[89] and would more likely be on polytherapy. However, we found that the clinic-based studies reported lower rates of anomalies overall than either the hospital or population-based studies, and that polytherapy was less common in clinic than hospital-based studies. The lower anomaly rates may reflect shorter or less detailed follow-up but this is difficult to assess.

The incidence of epileptic fits during the first trimester could confound the relationship between number of drugs and anomaly risk (i.e. poorly controlled (more severe?) epilepsy increases the likelihood of polytherapy). However, malformation frequency does not appear to be related to the frequency of epileptic fits.[1,2,6]

A plausible biological argument for the increased anomaly risk associated with polytherapy may relate to folate deficiency. Dansky et al.[72] measured folate levels in pregnant epileptic women and found lower folate levels for the women on polytherapy than on monotherapy. Combinations of phenytoin and phenobarbital or primidone, with or without other anticonvulsants were associated with the highest risk of folate deficiency. Anticonvulsants are known to interact with each other, altering plasma levels in inconsistent ways.[90] Through drug interaction, drug combinations may increase the probability of high plasma levels of specific anticonvulsants,[90] and the interaction possibilities increase as the number of anticonvulsants increases. There is evidence from

animal studies that all of the common anticonvulsants have some teratogenic potential.[1]

In summary, this meta-analysis found the following: study reporting has often been inadequate (half the studies located could not be incorporated into this analysis), first trimester anticonvulsant monotherapy is associated with a approximately a doubling of congenital anomaly risk relative to no anticonvulsant exposure; available data are insufficient to demonstrate statistically significant differences in risk among the various monotherapies commonly in use, although phenobarbital and carbamazepine appear to have the lowest risks; and three-drug therapy is associated with more than a two-fold increase in risk relative to monotherapy. The results suggest that women with epilepsy who are considering pregnancy not be treated with anticonvulsant polytherapy, particularly with three or more types of anticonvulsants.

Table 3.3.1 Number of anticonvulsants used and congenital anomaly rates for 31 studies included in meta-analysis

MAJOR*	METHOD	SOURCE	YEAR	REPORT (1ST AUTHOR)	NO ANTI-CONVULSANTS			1 ANTI-CONVULSANT			2 ANTI-CONVULSANTS			3 ANTI-CONVULSANTS			EXPOSED TOTALS**			% OF WOMEN ON POLYTHERAPY
					CA	LB	RATE/ 100 LB	CA	LB	RATE/ 100 LB	CA	LB	RATE/ 100 LB	CA	LB	RATE/ 100 LB	CA	LB	RATE/ 100 LB	
	R	C	64	Janz	0	130	0.0%	3	170	1.8%	1	65	1.5%	2	24	8.3%	6	259	2.3%	34.4%
	P	H	67	Melchior				1	16	6.3%	1	16	6.3%				2	32	6.3%	50.0%
	R	H	71	Watson				0	5	0.0%	3	43	7.0%	0	3	0.0%	3	51	5.9%	90.2%
	R	P	73	Fedrick	2	19	10.5%	7	74	9.5%	11	50	22.0%	3	15	20.0%	21	139	15.1%	46.8%
	R	H	73	Koppe				7	45	15.6%	4	167	2.4%	0	2	0.0%	11	214	5.1%	79.0%
	R	P	73	Lowe	3	111	2.7%	3	66	4.5%	6	68	8.8%				9	134	6.7%	50.7%
	R	O	73	Meyer				17	89	19.1%	14	75	18.7%	6	21	28.6%	37	185	20.0%	51.9%
	P	C	73	Millar				3	20	15.0%	8	69	11.6%	2	20	10.0%	13	109	11.9%	81.7%
	R	C	73	Starfield				3	65	4.6%	9	70	12.9%	5	54	9.3%	17	189	9.0%	65.6%
	R	C	74	Annegers				6	57	10.5%	3	75	4.0%	0	1	0.0%	9	133	6.8%	57.1%
	R	H	74	Barry	0	20	0.0%	3	17	17.6%	10	50	20.0%	0	11	0.0%	13	78	16.7%	78.2%
	P	H	74	Hill				2	13	15.4%	0	6	0.0%	0	1	0.0%	2	20	10.0%	35.0%
M	P	O	76	Hanson				1	15	6.7%							1	15	6.7%	
	P	H	76	HansonCPP				2	41	4.9%	3	63	4.8%	4	17	23.5%	9	121	7.4%	66.1%
M	P	H	76	Shapiro				2	26	7.7%							2	26	7.7%	
	R	C	80	Deitrich				0	6	0.0%	0	18	0.0%				0	24	0.0%	75.0%
	R	C	80	Majewski				2	46	4.3%	0	18	0.0%				2	64	3.1%	28.1%
M	R	C	80	Nakane				1	45	2.2%							1	45	2.2%	
	P	C	82	Bossi				0	30	0.0%	0	14	0.0%	0	1	0.0%	0	45	0.0%	33.3%
	P	O	82	Dansky	3	45	6.7%	4	15	26.7%	2	21	9.5%	3	5	60.0%	9	41	22.0%	63.4%
	R	C	82	Dansky,Anderman				0	6	0.0%	7	52	13.5%	5	17	29.4%	12	75	16.0%	92.0%
M	P	H	82	Hillesma	0	17	0.0%	6	79	7.6%	2	29	6.9%	0	4	0.0%	8	112	7.1%	29.5%
	P	C	82	Lindout				2	51	3.9%	4	61	6.6%	5	16	31.3%	15	135	11.2%	61.9%
	P	C	82	Rating				1	8	12.5%	0	6	0.0%				1	14	7.1%	42.9%
M	P	C	84	Miyakoshi				2	29	6.9%							2	29	6.9%	
	P	C	84	Kelly	3	21	14.3%	1	60	1.7%	2	49	4.1%	0	6	0.0%	3	115	2.6%	47.8%
	P	C	86	Jager-Roman				4	14	28.6%	0	10	0.0%				4	24	16.7%	41.7%
	R	O	86	Robert	0	35	0.0%	4	59	6.8%	2	45	4.4%	1	7	14.3%	7	111	6.3%	46.8%
M	R	P	86	West				0	3	0.0%							0	3	0.0%	
M	R	O	87	Bertollini				19	558	3.4%							19	558	3.4%	
	P	H	88	Kaneko				1	29	3.4%	6	46	13.0%	8	53	15.1%	23	172	13.5%	82.9%

* Column 1: M desginates studies where major anomalies were separated from minor anomalies or where the report specified studying only major anomalies

Column 2: R = retrospective study, P = prospective study

Column 3: source of subjects--C = epilepsy clinics, H = hospitals, P = general population, O = other

Column 4: report publication year

CA = congenital malformations (serious malformations only where specifically separated); LB = live births

** Totals include 4 and 5 drug exposure for two studies: Lindout - 4 malformations in 7 exposures (57.1%);Kaneko - 8 malformations in 44 exposures (18.2%)

(continued)

Table 3.3.1 (continued)

SUBTOTALS	NO ANTI-CONVULSANTS CA	LB	RATE/ 100 LB	1 ANTI-CONVULSANT CA	LB	RATE/ 100 LB	2 ANTI-CONVULSANTS CA	LB	RATE/ 100 LB	3 ANTI-CONVULSANTS CA	LB	RATE/ 100 LB	EXPOSED TOTALS** CA	LB	RATE/ 100 LB	% OF WOMEN ON POLYTHERAPY
THERAPIES STUDIED																
ALL THERAPIES STUDIED				82	1081	7.6%							236	2593	9.1%	
MONOTHERAPY ONLY STUDIED				25	676	3.7%							25	676	3.7%	
METHOD																
RETROSPECTIVE	5	315	1.6%	75	1311	5.7%	70	796	8.8%	22	155	14.2%	167	2262	7.4%	42.6%
PROSPECTIVE	6	83	7.2%	32	446	7.2%	28	390	7.2%	22	123	17.9%	94	1010	9.3%	55.7%
SOURCE																
CLINIC BASED	3	151	2.0%	28	607	4.6%	34	507	6.7%	19	139	13.7%	85	1260	6.8%	51.8%
HOSPITAL BASED	0	37	0.0%	24	271	8.9%	29	420	6.9%	12	91	13.2%	73	826	8.9%	67.1%
POPULATION BASED	5	130	3.8%	10	143	6.9%	17	118	14.4%	3	15	14.3%	30	276	10.8%	48.2%
OTHER BASE	3	80	3.8%	45	736	6.1%	18	141	12.8%	10	33	30.3%	73	910	8.0%	19.1%
OVERALL STUDY MALFORMATION RATE																
LESS THAN 5%	3	151	2.0%	26	918	2.8%	3	164	1.8%	2	31	6.5%	31	1113	2.8%	
5 - 10%	3	163	1.8%	38	511	7.4%	33	582	5.7%	10	88	11.4%	81	1181	6.9%	
>10%	5	84	6.0%	43	328	13.1%	62	440	14.1%	32	159	20.1%	143	978	15.3%	
MAJOR ANOMALIES ONLY																
MAJOR ANOMALIES ONLY	0	17	0.0%	45	889	5.1%	19	279	6.8%	14	56	25.0%	82	1231	6.7%	
NOT SPECIFIED	11	381	2.9%	62	868	7.1%	79	907	8.7%	30	222	13.5%	179	2041	8.8%	
TOTAL	11	398	2.8%	107	1757	6.1%	98	1186	8.3%	44	278	15.8%	261	3272	8.0%	46.3%

Table 3.3.2

Crude pooled rates of congenital malformations in offspring of epileptic mothers stratified by number of anticonvulsants during the first trimester of pregnancy

Number of Anticonvulsants	Live Births	Malformed Children	Rate /100LB	Crude RR
None	587	13	2.2	1.0
1	1,850	110	5.9	2.7
2	1,418	111	7.8	3.5
3	465	65	14.0	6.3
4	109	28	25.7	11.6
5+	60	6	10.0	4.5
Exposed Totals	3,902	320	8.2	3.7

Table 3.3.3

Crude pooled rates of congenital malformations in the offspring of epileptic mothers on specific anticonvulsant therapies during the first trimester of pregnancy

Anticonvulsants	Malformed Children	Live Births	Rate /100LB	Relative Risk
No Anticonvulsants	11	398	2.8	1.0
PHB Monotherapy**	33	716	4.6	1.6
DPH "	41	550	7.5	2.7
PRM "	11	188	5.9	2.1
VPA "	13	137	9.5	3.4
CBZ "	6	133	4.5	1.6
SUX "	2	24		
TRI "	1	5		
CLN "	0	4		
PHB+DPH	67	890	7.5	2.7
" +PRM	3	29	10.3	3.7
" +VPA	3	25	12.0	4.3
" +CBZ	1	34	2.9	1.0
DPH+PRM	14	69	20.3	7.3
" +CBZ	1	30	3.3	1.2
PRM+SUX	5	30	16.7	6.0
Other 2 Drug Combos*	4	79	5.0	1.8
PHB+DPH+PRM	9	41	22.0	7.9
" + " +OTHER(N/S)	24	163	14.7	5.3
PHB+CBZ+VPA	4	8	50.0	17.9
Other 3 Drug Combos*	7	66	10.6	3.8
DPH+PRM+ 2 OTHERS	5	30	16.6	5.9
PHB+DPH+CBZ+VPA	5	8	62.5	22.4
Other 4+5 Drug Combos*	2	13	15.3	5.5
EXPOSED TOTALS	261	3272	8.0	2.9

* less than 25 exposures to any one of these combinations among all the included studies combined

** PHB=phenobarbital; DPH=phenytoin; PRM=primidone; VPA=valproic acid; CBZ=carbamazepine; SUX=ethosuximide; TRI=trimethadione; CLN=clonazepam

*** breakdown of exposures by individual study available from the authors

Table 3.3.4

Crude pooled rates of congenital heart defects and cleft lip and/or palate for offspring of epileptic mothers stratified by the number of 1st trimester anticonvulsants

		Cleft Lip and/or Palate			Congenital Heart Defects		
Number of Anticonvulsants	Live Births*	#	Rate /100LB	Relative Risk	#	Rate /100LB	Relative Risk
None	223	1	0.4	1.0	2	0.9	1.0
1	1,452	9	0.6	1.4	14	1.0	1.1
2	1,082	15	1.4	3.1	16	1.5	1.6
3	248	4	1.6	3.6	9	3.6	4.0
4	40	3	7.5	16.7	3	7.5	8.4
5	11	0	0.0		0	0.0	
Exposed Totals	2,803	32	1.1	2.5	44	1.6	1.8

* live birth totals from studies where information about individual anomalies was reported

Table 3.3.5

Crude pooled rates of cleft lip and/or palate and heart defects in offspring of epileptic mothers on specific anticonvulsant therapy during the first trimester

Anticonvulsants	Live-Births*	Cleft Lip and/or Palate #	Rate /100LB	Crude RR	Congenital Heart Defects #	Rate /100LB	Crude RR
No Anticonvulsants	223	1	0.4	1.0	2	0.9	1.0
PHB Monotherapy**	617	7	1.1	2.5	6	1.0	1.1
DPH "	429	1	0.2	0.5	4	0.9	1.0
PRM "	134	1	0.7	1.7	3	2.2	2.5
VPA "	119	0			1	0.8	0.9
CBZ "	130	0			0		
SUX "	15	0			0		
TRI "	4	0			0		
CLN "	4	0			0		
PHB+DPH	808	9	1.1	2.5	12	1.5	1.6
" +PRM	11	0			1	9.1	10.1
" +VPA	25	1	4.0	8.9	0		
" +CBZ	34	0			0		
DPH+PRM	65	4	6.1	13.6	2	3.1	3.4
" +CBZ	27	0			0		
PRM+SUX	30	1	3.3	7.4	0		
Other 2 drug combos***	79	0			1	1.3	1.4
PHB+DPH+PRM	36	0			2	5.5	6.1
" + " +other(N/S)	139	2	1.4	3.1	6	4.3	4.8
PHB+CBZ+VPA	8	0			0		
Other 3 Drug combos***	66	2	3.0	6.8	1	1.5	1.7
DPH+PRM+ 2 OTHERS	30	0			1	3.3	3.7
PHB+DPH+CBZ+VPA	7	3	42.9	95.7	2	28.6	31.8
Other 4+5 drug combos***	13	0			0		
EXPOSED TOTALS	2803	32	1.1	2.5	44	1.4	1.6

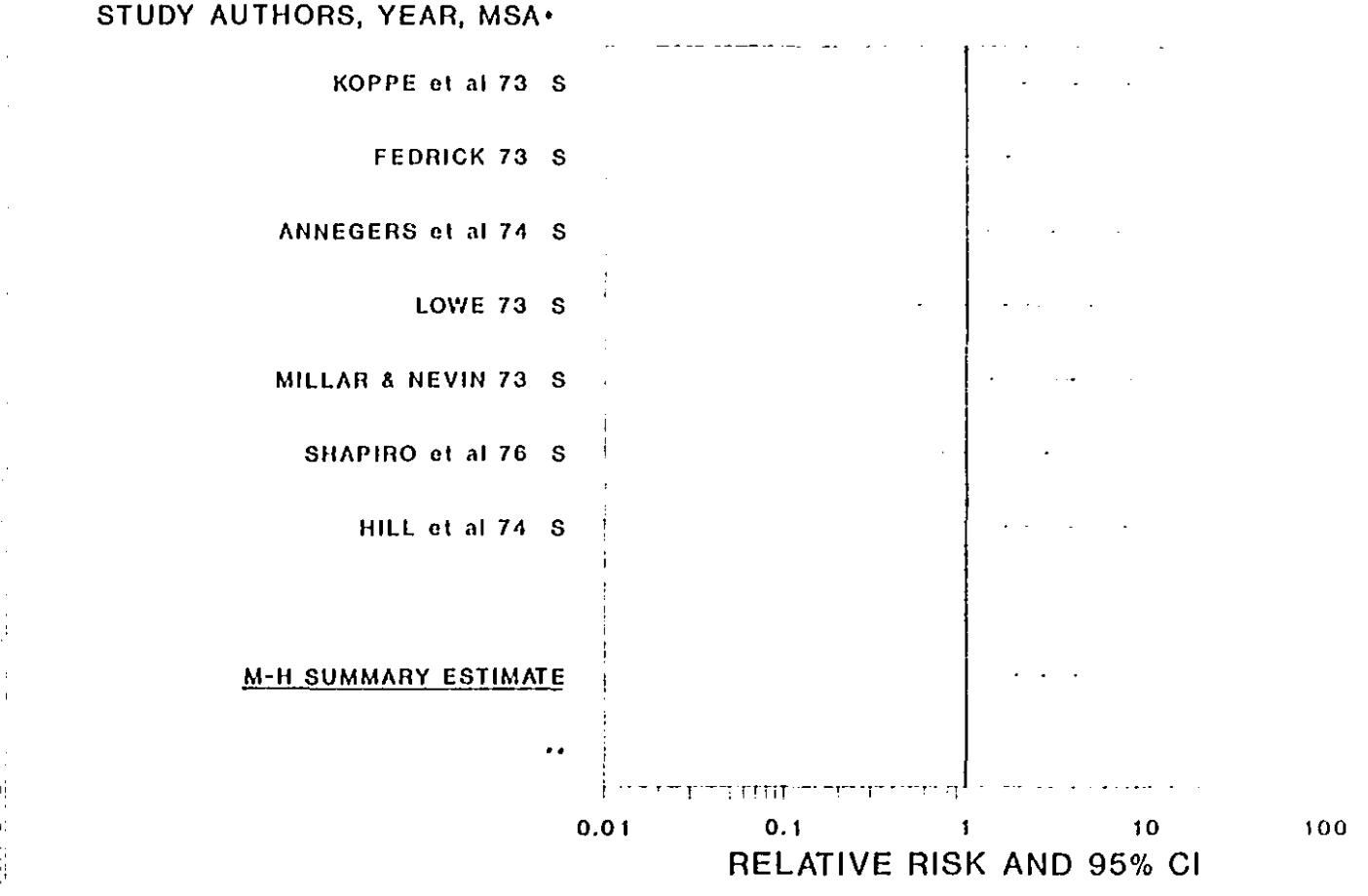
* live births where information about cleft lip and/or palate and conginital heart defects was reported

** PHB=phenobarbital; DPH=phenytoin; PRM=primidone; VPA=valproic acid; CBZ=carbamazepine; SUX=ethosuximide; TRI=trimethadione; CLN=clonazepam

*** less than 25 exposures to any one of these combinations among all the included studies combined

**** breakdown of exposures by individual study available from the authors on request

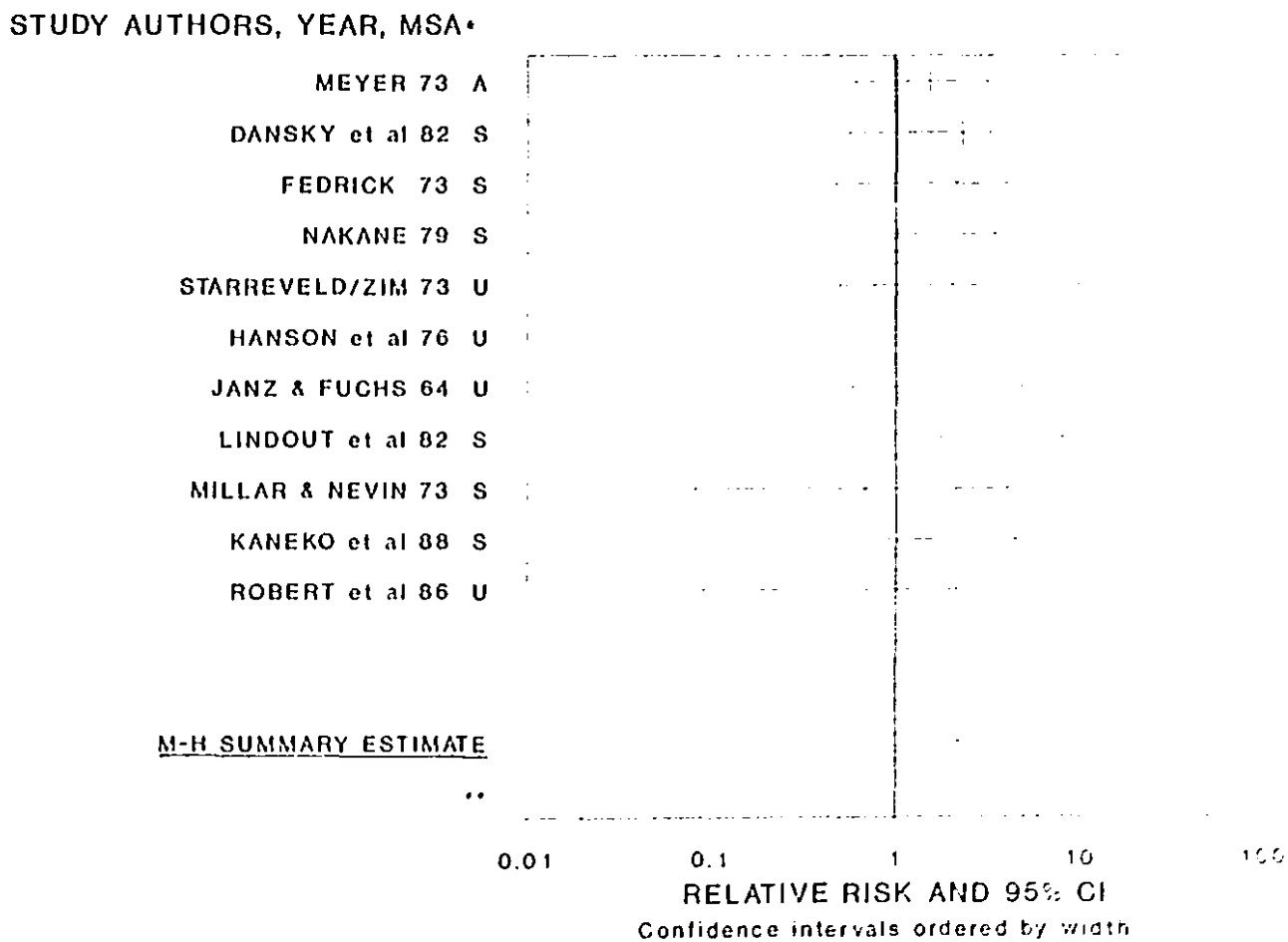
Figure 3.3.1 Congenital anomaly risk among offspring of epileptic women on anticonvulsant monotherapy relative to offspring of non-epileptic women without anticonvulsant therapy



* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

** Mantel-Haenszel summary RR estimate includes data from the 7 plotted studies.
*** Confidence intervals (CI) ordered by width in all graphs.

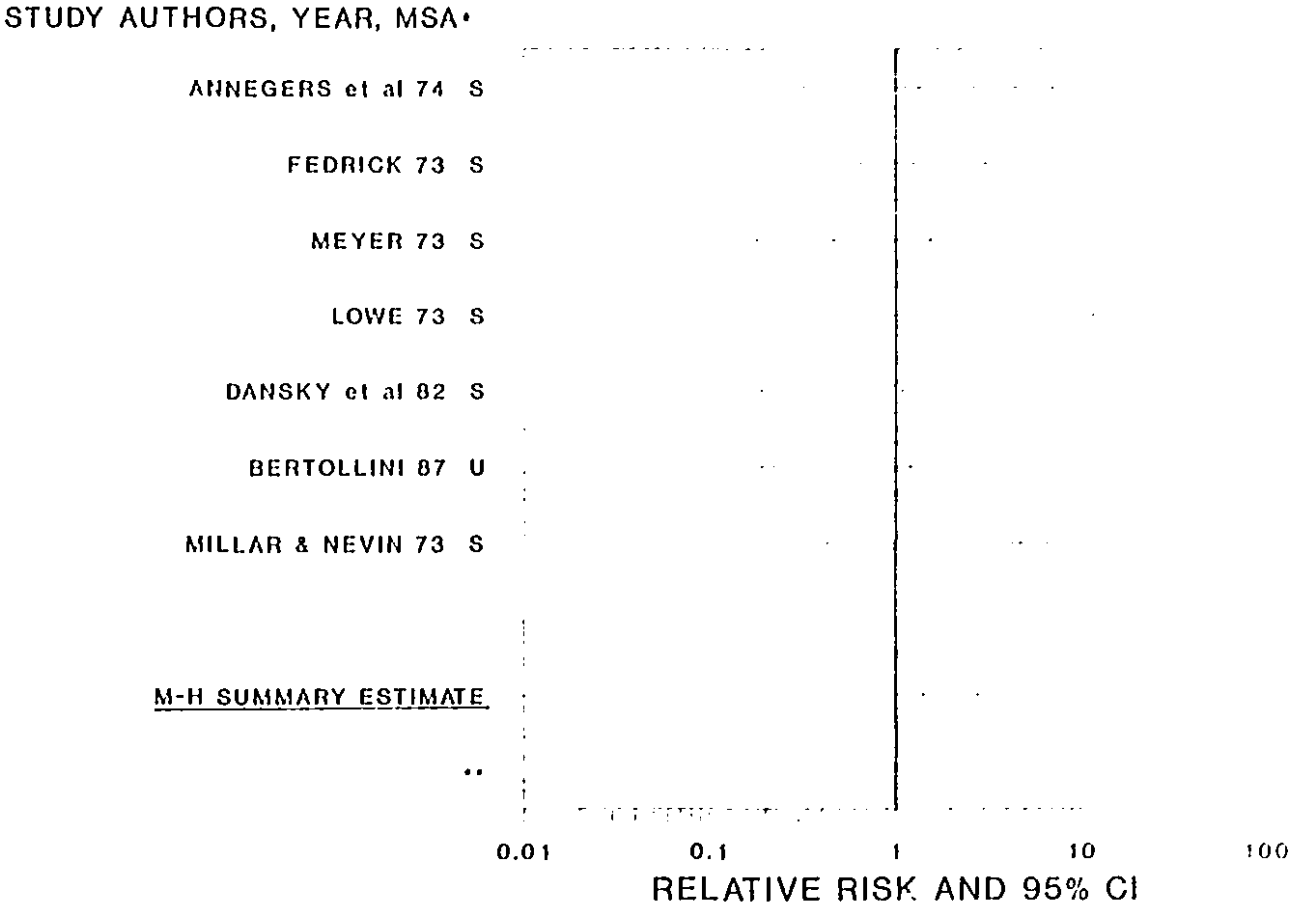
Figure 3.3.2 Congenital anomaly risk for offspring of epileptic women on three anticonvulsants relative to monotherapy



* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

** Mantel-Haenszel summary RR estimate includes data from the 11 plotted studies and 7 studies not plotted because the RR was zero or undefined. Totals (anomalies/livebirths) for un-plotted studies:
three-drug therapy - 0/2,0/1,0/11,0/1,5/17,0/4,0/6;
monotherapy - 7/45,6/57,3/17,2/13,0/6,6/79,1/60.

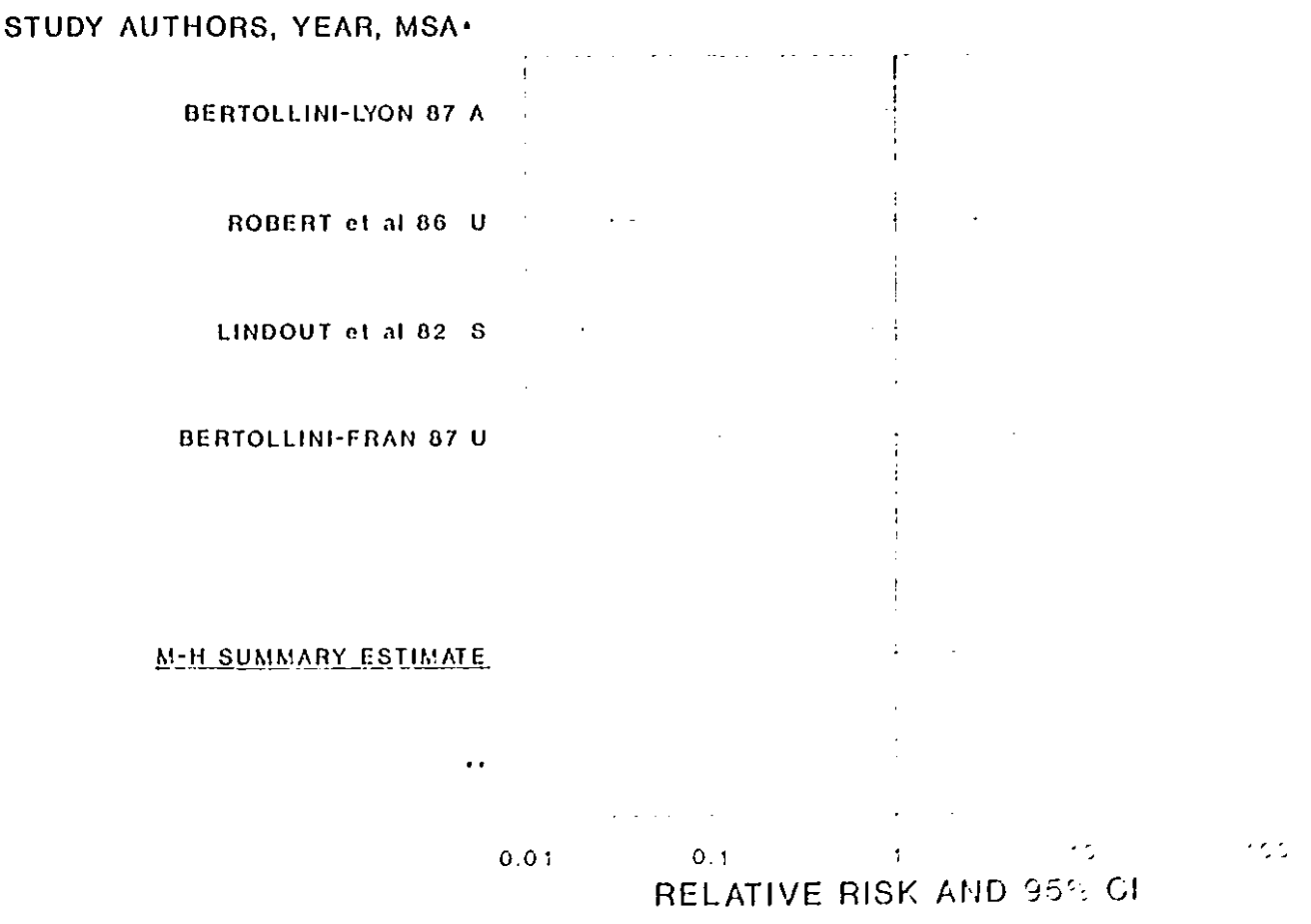
Figure 3.3.3 Congenital anomaly risk for phenytoin monotherapy relative to phenobarbital monotherapy



* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

**(see legend Figure 2) Summary estimate includes 9 un-plotted studies: phenytoin 2/55,0/4,0/3,2/8,2/9,2/24,2/28,3/55,0/6; phenobarbital 0/51,6/36,3/61,0/3,0/3,0/17,0/18,0/4,1/14.

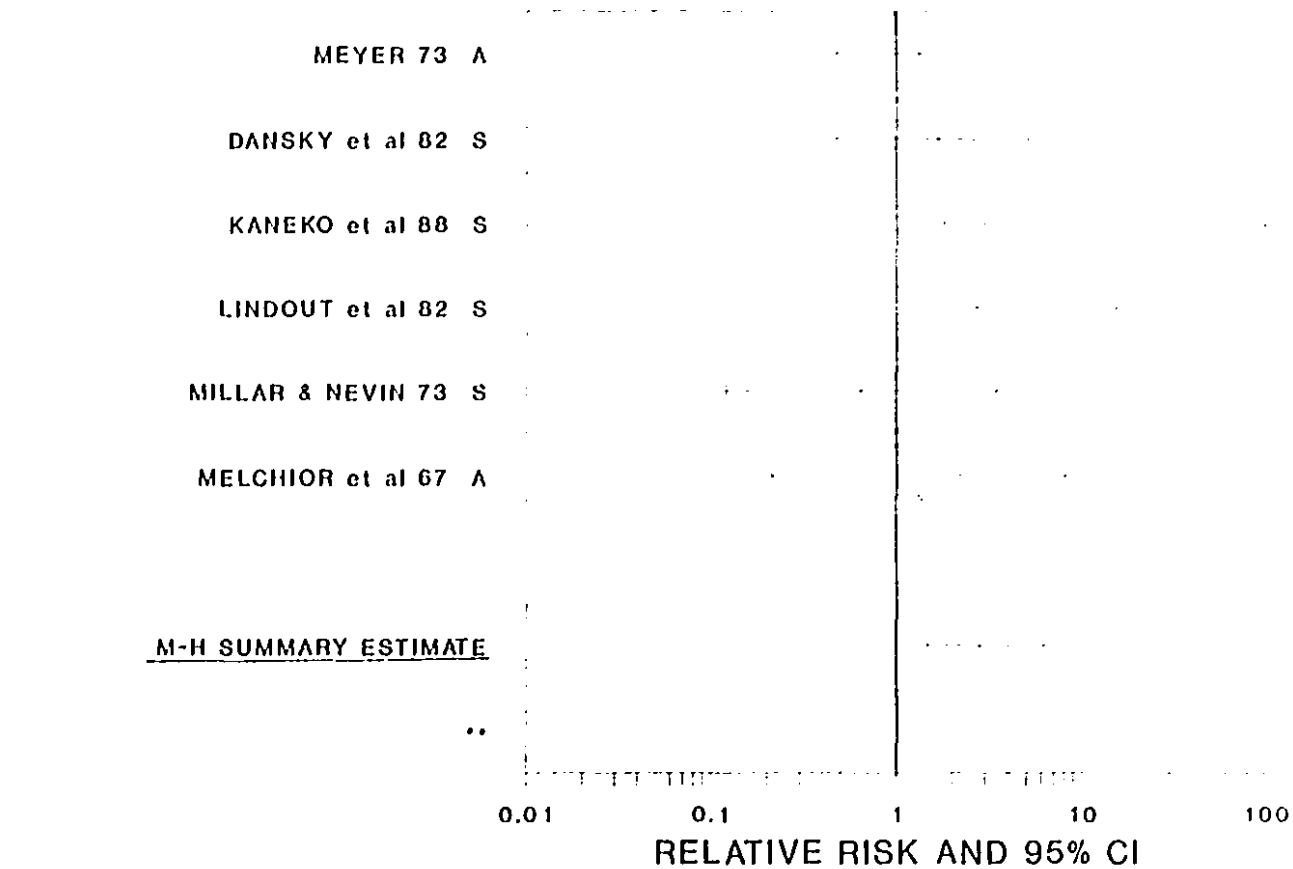
Figure 3.3.4 Congenital anomaly risk for valproic acid monotherapy relative to phenobarbital monotherapy



* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound

**(see legend Figure 2) Summary estimate includes 3 un-plotted studies: valproic acid 2/18,0/40,0/3; phenobarbital 0/7,3/156,1/30.

Figure 3.3.5 Congenital anomaly risk for phenytoin + primidone/+ other anticonvulsants relative to monotherapy



* MSA = Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound.

**(see legend Figure 2) Summary estimate includes 2 un-plotted studies: phenytoin + primidone/+ 0/2,0/2; monotherapy 3/66,1/8.

REFERENCES

1. Bossi L. Fetal effects of anticonvulsants. In: Morselli PL, ed. Antiepileptic Drug Therapy in Pediatrics. New York City: Raven Press, 1983:37-64.

2. Annegers JF, Kurland LT, Hauser WA. Teratogenicity of anticonvulsant drugs. In: Ward AA, Penry JK, Purpura D, eds. Epilepsy. New York City: Raven Press, 1983:239-248.

3. Johnson KC, Sherman GJ. Meta-analysis of congenital malformation risk in the offspring of epileptic women: a graphical presentation. (UnPublished)

4. Annegers JF, Elveback LR, Hauser WA, Kurland LT. Do anticonvulsants have a teratogenic effect? Arch Neurol 1974; 31:364-373.

5. Nakane Y. The teratological problem of antiepileptic drugs. Folia Psychiatrica et Neurologica 1980; 34:277-287.

6. Janz D. On major malformations and minor anomalies in the offspring of parents with epilepsy: review of the literature. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:211-222.

7. Janz D. Antiepileptic drugs and pregnancy: altered utilization patterns and teratogenesis. Epilepsia 1982; 23:S53-S63.

8. Kelly TE. Teratogenicity of anticonvulsant drugs. I: Review of the literature. Am J Med Genet 1984; 19:413-434.

9. German J, Kowal A, Ehlers KH. Trimethadone and human teratogenesis. Teratology 1970; 3:349-362.

10. Albengres E, Tillement JP. Phenytoin in pregnancy: a review of the reported risks. Biol Res Pregnancy 1983; 4:71-74.

11. Jeavons PM. Non-dose-related side effects of valproate. Epilepsia 1984; 25:S50-S55.

12. Rosa FW. Teratogenesis in epilepsy: birth defects with maternal valproic acid exposures. In: Porter RJ et al., ed. Advances in Epileptology: XVth Epilepsy International Symposium. New York: Raven Press, 1984:309-314.

13. Hanson JW. Teratogen update: fetal hydantoin effects. Teratology 1986; 33:349-353.

14. Armitage P. Statistical Methods in Medical Research. New York: Wiley, 1971.

15. Mauritsen R. EGRET. Seattle, Washington: Statistics and Epidemiology Research Corporation 1990.

16. Galbraith RF. A note on graphical presentation of estimated odds ratio from several clinical trials. Stat Med 1988; 7:889-894.

17. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Natl Cancer I 1959; 22:719-748.

18. Janz D, Fuchs U. Are anti-epileptic drugs harmful when given during pregnancy? Germ med Mth 1964; 9:20-22.

19. Melchior JC, Svensmark O, Trolle D. Placental transfer of phenobarbitone in epileptic women, and elimination in newborns. Lancet 1967; 2:860-861.

20. Maroni E, Markoff R. Epilepsie und schwangerschaft. Gynaecologia 1969; 168:418-421.

21. Elshove J, van Eck JHM. [Congenital abnormalities, cleft lip and cleft palate in particular, in children of epileptic mothers]. Ned Tijdschr Geneeskd 1971; 115:1371-1375.

22. Watson ID, Spellacy WN. Neonatal effects of maternal treatment with the anticonvulsant drug diphenylhydantoin. Obstet Gynecol 1971; 37:881-885.

23. South J. Teratogenic effect of anticonvulsants. Lancet 1972; 2:1154.

24. Speidel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and the newborn. Lancet 1972; 2:839-843.

25. Bjerkedal T, Bahna L. The course and outcome of pregnancy in women with epilepsy. Acta Obstet Gynec Scand 1973; 52:245-248.

26. Fedrick J. Epilepsy and pregnancy: a report from the Oxford Record Linkage Study. Brit Med J 1973; 2:442-448.

27. Koppe JG, Bosman W, Oppers VM, Spaans F, Kloosterman GJ. Epilepsie en aangeboren afwijkingen. Ned T Geneesk 1973; 117:220-224.

28. Kuenssberg EV, Knox JD. Teratogenic effect of anticonvulsants. Lancet 1973; 1:198.

29. Lowe CR. Congenital malformations among infants born to epileptic women. Lancet 1973; 1:9-10.

30. Meyer JG. The teratological effects of anticonvulsants and the effects on pregnancy and birth. Eur Neurol 1973; 10:179-190.

31. Millar JH, Nevin NC. Congenital malformations and anticonvulsant drugs. Lancet 1973; 1:328.

32. Monson RR, Rosenberg L, Hartz SC, Shapiro S, et al . Diphenylhydantoin and selected congenital malformations. N Engl J Med 1973; 289:1049-1052.

33. Niswander JD, Wertelecki W. Congenital malformations among offspring of epileptic women. Lancet 1973; 1:1062.

34. Starreveld-Zimmerman AAE, van der Kolk WJ, Meinardi H, Elshove J. Are anticonvulsants teratogenic? Lancet 1973; 2:48-49.

35. Barry JE, Danks DM. Anticonvulsants and congenital abnormalities [letter]. Lancet 1974; 2:48-49.

36. Goujard J, Huel G, Rumeau-Rouquette C. Antiepileptiques et malformations congenitales. J Gyn Obst Biol Repr 1974; 3:831-842.

37. Higgins TA, Comerford JB. Epilepsy in pregnancy. J Ir Med Assoc 1974; 67:317-320.

38. Hill RM, Verniaud WM, Horning MG, McCulley LB, Morgan NF. Infants exposed in utero to antiepileptic drugs. Am J Dis Child 1974; 127:645-653.

39. Loiseau P, LeGroux M, Henry P. Epilepsies et grossesses. Bord Med 1974; 8:1157-1164.

40. Biale Y, Lewenthal H, Aderet NB. Congenital malformations due to anticonvulsive drugs. Obstet Gynecol 1975; 45:439-442.

41. Birmingham Research Unit of the Royal College of General Practitioners. . Morbidity and drugs in pregnancy. J R Coll Gen Pract 1975; 25:631-645.

42. Knight AH, Rhind EG. Epilepsy and pregnancy: a study of 153 pregnancies in 59 patients. Epilepsia 1975; 16:99-110.

43. Hanson JW, Myrianthopoulos NC, Harvey MAS, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the

fetal hydantoin syndrome. J Pediatr 1976; 89:662-668.

44. Shapiro S, Slone D, Hartz SC, Rosenberg L, et al . Anticonvulsants and parental epilepsy in the development of birth defects. Lancet 1976; 2:272-275.

45. Weber M, Schweitzer M, Andre JM, Tridon P, et al . [Epilepsy, anticonvulsants and pregnancy]. Arch Fr Pediatr 1977; 34:374-383.

46. Annegers JF, Hauser WA, Elveback LR, Anderson VE, Kurland LT. Congenital malformations and seizure disorders in the offspring of parents with epilepsy. Int J Epidemiol 1978; 7:241-247.

47. Seino M, Miyokoshi M. Teratogenic risks of antiepileptic drugs in respect to the type of epilepsy. Folia Psychiatr Neurol Jpn 1979; 33:379-385.

48. Dieterich E, Steveling A, Lukas A, Seyfeddinipur N, Spranger J. Congenital anomalies in children of epileptic mothers and fathers. Neuropaediatrie 1980; 11:274-283.

49. Majewski F, Raff W, Fischer P, Huenges R, Petruch F. [Teratogenicity of anticonvulsant drugs (author's transl)]. Dtsch Med Wochenschr 1980; 105:719-723.

50. Nakane Y, Okuma T, Takahashi R, Sato Y, et al . Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: A report of a collaborative study group in Japan. Epilepsia 1980; 21:663-680.

51. Beck-Mannagetta G, Drees B, Janz D. Malformations and minor anomalies in the offspring of epileptic parents: A retrospective study. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:317-323.

52. Bjerkedal T. Outcome of pregnancy in women with epilepsy, Norway, 1968 to 1978: Congenital malformations. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:289-295.

53. Bossi L, Battino D, Boldi B, Caccamo ML, et al . Anthropometric data and minor malformations in newborns of epileptic mothers. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:299-301.

54. Dansky L, Andermann E, Andermann F, Sherwin AL, Kinch RA*. Maternal epilepsy and congenital malformations: correlation with maternal plasma

anticonvulsant levels during pregnancy. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:251-258.

55. Hiilesmaa VK, Teramo K, Granström ML, Bardy AH. Fetal growth and antiepileptic drugs: Preliminary results of the prospective Helsinki study. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:203-206.

56. Koch S, Hartmann AM, Jäger-Roman E, Rating D, Helge H. Major malformations in children of epileptic parents--due to epilepsy or its therapy? In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:313-315.

57. Lindhout D, Meinardi H, Barth PG. Hazards of fetal exposure to drug combinations. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:275-281.

58. Rating D, Nau H, Jäger-Roman E, et al. Teratogenic and pharmacokinetic studies of primidone during pregnancy and in the offspring of epileptic women. Acta Paediatr Scand 1982; 71:301-11.

59. Robert E, Rosa F. Valproate and birth defects [letter]. Lancet 1983; 1142.

60. French Chapter of I.L.A.E. . Teratogenic risk of antiepileptic drugs, with special reference to sodium valproate (valproic acid) therapy. In: Porter RJ, et al , eds. Advances in Epileptology: XVth Epilepsy International Symposium. New York: Raven Press, 1984:299-307.

61. Kelly TE, Edwards-Klein P, Rein M, Miller JQ, Dreifuss FE. Teratogenicity of anticonvulsant drugs. II: A prospective study. Am J Med Genet 1984; 19:435-443.

62. Miyakoshi M, Seino M. Malformations in children born to mothers with epilepsy. In: Antiepileptic drugs and pregnancy. Amsterdam: Excerpta Medica, 1984:125-131.

63. Niermeijer MF. [Use of valproic acid by pregnant women with epilepsy and the risk of congenital abnormalities in the child]. Ned Tijdschr Geneeskd 1984; 128:2460-241.

64. Bertollini R, Mastroiacovo P, Segni G. Maternal epilepsy and birth defects: a case-control study in the Italian Multicentric Registry of Birth Defects (IPIMC). Eur J Epidemiol 1985; 1:67-72.

65. Friis ML, Hauge M. Congenital heart defects in live-born children of epileptic parents. Arch Neurol 1985; 42:374-376.

66. West R, Sherman GJ, Downey W. A record linkage study of valproate and malformations in Saskatchewan. Can J Public Health 1985; 76:226-228.

67. Jäger-Roman E, Deichl A, Jakob S, Hartmann AM, et al . Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. J Pediatr 1986; 108:997-1004.

68. Kallen B. A register study of maternal epilepsy and delivery outcome with special reference to drug use. Acta Neurol Scand 1986; 73:253-259.

69. Lindhout D, Schmidt D. In-utero exposure to valproate and neural tube defects [letter]. Lancet 1986; 1392-1393.

70. Robert E, Lofkvist E, Mauguiere F, Robert JM. Evaluation of drug therapy and teratogenic risk in a Rhone-Alpes district population of pregnant epileptic women. Eur Neurol 1986; 25:436-443.

71. Bertollini R, Kallen B, Mastroiacovo P, Robert E. Anticonvulsant drugs in monotherapy. Effect on the fetus. Eur J Epidemiol 1987; 3:164-171.

72. Dansky LV, Andermann E, Rosenblatt D, Sherwin AL, Andermann F. Anticonvulsants, folate levels, and pregnancy outcome: a prospective study. Ann Neurol 1987; 21:176-182.

73. Brugge HG, Huisjes HJ. De gevolgen voor moeder en kind van epilepsie en het gebruik van anti-epileptica in de zwangerschap. Ned Tijdschr Geneeskd 1988; 132:157-159.

74. Kaneko S, Otani K, Fukushima Y, Ogawa Y, et al . Teratogenicity of antiepileptic drugs: analysis of possible risk factors. Epilepsia 1988; 29:459-467.

75. Greenberg G, Inman WHW, Wheatherall JAC, Adelstein AM, Haskey JC. Maternal drug histories and congenital abnormalities. Br Med J 1977; 2:853-856.

76. Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979; 109:4:433-439.

77. Satish J, Kalyanaraman S. Teratogenic effects of anticonvulsant drugs. In: Porter RJ, et al , eds. Advances in Epileptology: XVth Epilepsy International Symposium. New York: Raven Press, 1984:315-324.

78. Nakane Y. Congenital malformation among infants of epileptic mothers treated during pregnancy--the report of a collaborative study group in Japan. Folia Psychiatr Neurol Jpn 1979; 33:363-369.

79. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA 1988; 260:652-656.

80. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9:1-30.

81. Jenicek M. Meta-analysis in medicine. Where we are and where we want to go. J Clin Epidemiol 1989; 42:35-44.

82. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarctions: An overview of randomized trials. Prog Cardiovasc Dis 1985; XXVI:335-371.

83. Annegers JF, Hauser WA. Teratogenicity of anticonvulsant drugs. Res Publ Assoc Res Nerv Ment Dis 1983; 61:239-48.

84. Leck I, Record RG, McKeown T, et al . The incidence of malformations in Birmingham, England, 1950 - 1959. Teratology 1968; 1:263-280.

85. Gram L, Drachmann-Bentsen K, Parnas J, Flachs H. Controlled trials in epilepsy: a review. Epilepsia 1982; 23:491-519.

86. Smith DB, Delgado Escueta AV, Cramer JA, Mattson RH. Historical perspective on the choice of antiepileptic drugs for the treatment of seizures in adults. Neurology 1983; 33:2-7.

87. Coatsworth JJ. Studies on the clincal efficacy of marketed antiepileptic drugs. NINDS Monograph No. 12, 1971: 1-35.

88. Beghi E, Di Mascio R. Antiepileptic drug toxicity: definition and mechanism of action. Ital J Neurol Sci 1986; 7:209-222.

89. Starreveld-Zimmerman AA, van der Kolk WJ, Elshove J, Meinardi H. Teratogenicity of antiepileptic drugs. Clin Neurol Neurosurg 1975; 77:81-95.

90. Kutt H. Interactions of antiepileptic drugs. Epilepsia 1975; 16:393-402.

Appendix 3.3.1

Design characteristics of 31 studies included in meta-analysis

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
64	Janz & Fuchs	Germany	56-63	R	Epilepsy Outpatient Clinic	Questionnaire filled out by mother (in 1963?)	Questionnaire filled out (in 1963?)	U
67	Melchior et al	Denmark	62-65	P	Mothers delivering at a university hospital	Blood sample - umbilical cord	Examination shortly after birth	A
71	Watson & Spellacy	USA	60-70	R	Florida Hospital	Records from Hospital (women with convulsive disorders)	Maternal & neonatal hospital records reviewed	S
73	Bjerkedal & Bahna	Norway	67-68	R	All births in Norway 1967 and 1968	Medical registration of birth includes mother's health information during pregnancy	Detailed medical registration of birth	A
73	Fedrick	England	66-70	R	2 counties	Epileptic mothers selected from detailed computerized birth registry -Rx History from GP	Hospital birth & admissions systematically abstracted for Oxford Record Linkage Project	S
73	Koppe et al	Holland	63-68	R	Hospital	Clinic records	Hospital records	S
73	Lowe	England	65-71	R	Mothers domiciled in Cardiff	Computer birth registry Mention of epilepsy; followed with hospital & GP records	Computer birth registry coded anomalies	S
73	Meyer	Germany		R	Epileptics treated in Heildelbury	Parents interviewed & given questionaire;	Parents questionaire	U
73	Millar & Nevin	Ireland	69-72	P	Dept. of Neurology	Clinic records	Data on all pregnancies for women attending 1 neurologist	S
73	Starreveld/ Zimmerman et al	Netherlands		R	Patients referred to epilepsy centres	Survey	Survey	U

* Study Type: R= retrospective follow-up; P = Prospective follow-up.

**Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.3.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
74	Annegers	USA	39-72	R	Mayo Clinic	Comprehensive treatment records for each patient with epilepsy available for several decades	Comprehensive records including examination & detailed review at 4 days & medical history while child remains in the area	S
74	Barry & Danks	Australia	69-72	R	A Melbourne Hospital	Women coded as epileptic at antenatal clinic contacted & inverviewed (40 interviewed, 32 had moved, 51 no reply)	No details given	U
74	Hill	USA	69-72	P	Private hospitals associated with Baylor College OFM	Selected at admission to labour Detailed history taken Obst & GP letters to confirm medication during preg	Detailed physical exam at birth 1,2,3,4,6,9,12,18,36 months. Examiner blinded to Rx	S
76	Hanson	USA		P	Seattle Clinic?	Clinic in Seattle?	Physical exam of 35 children	U
76	Shapiro	USA	59-65	P	Data from Collaborative Perinatal Project (12 hospitals across USA)	Collaborative perinatal study Rx at antenatal interview & inspection of hospital & medical records when appropriate	Detailed follow-up of anomalies to age 1 or to age 4 if death; motor & mental testing at 8 months.	S
79	Nakane	Japan	74-77	P R	9 University Hospitals, 1 NeuroPsychiatry Unit, National Epilepsy Ctr. & National Research Institute For Nervous & Mental Diseases	Demographic & clinical by psychiatrist	Pro - Psychiatrist collected information on delivery and early neonatal period from obstetrician and patient Retro - malformations confirmed during follow-up	S S
80	Deitrich	Germany	79	R	Clinic	Clinic records?	Physical exam of children (aged 0.5 - 16 years) (cross-sectional)	U

* Study Type: R= retrospective follow-up; P = Prospective follow-up.

**Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.3.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
80	Majewski	Germany			University Hospital Neurologic clinic (11 neuro psychiatric clinics)	Mothers interviewed about drug use	Children examined	A
82	Bossi	Italy	77–80	P	Clinic	Clinic records Blood Plasma monitoring		U
82	Dansky et al	Canada			Seizure clinic & private neurologic & obstetric practice	Blood folate & AED monitoring from time recruited (before or during pregnancy)	Birth record, clinical record, clinical exam	S
82	Dansky et al	Canada	81	P	Montreal seizure clinic, neurologic & obstetrical practices	Detailed history taken during pregnancy, monthly AED intake, review & blood serum monitoring	Review of neonatal exam & later records; exam at birth & during 1st year, followup to age 6	S
82	Hiilesmaa	Finland	76–79	P	Epilepsy clinic?	Clinic records	Examination	U
82	Lindhout et al	Netherlands	72	P	Epilepsy outpatient clinic	Info about prev preg & anticonvulsant 1st Tri serum levels, fits entered on a standard form at visit after birth (generally available case history too)	In hospital births routinely examined by pediatricians Info registered at 1st visit to epilepsy clinic after birth	S
82	Rating		76–80	P	5 obstetrical clinics in Berlin	14 women on Primidone (blood sampled regularly)	examined at birth, 4 days & 4 further exams in FYOL	S
84	Kelly et al	USA	77–80	P	Epilepsy outpatient clinics	Standardized data on epileptic women of child-bearing age. Regular update of information Blood serum regularly monitored	Neonatal exam by investigators + 6 – 12 weeks & 10 – 14 mths, for other hospitals newborn records requested. (Home visit for followup if necessary)	S

* Study Type: R= retrospective follow-up; P = Prospective follow-up.

** Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

(continued)

Appendix 3.3.1 (continued)

PUBLICATION YEAR	AUTHORS	STUDY PLACE	STUDY YEARS	STUDY TYPE	SAMPLING BASE	EXPOSURE ASCERTAINMENT	OUTCOME ASCERTAINMENT	MSA**
84	Miyakoshi	Japan	75-83	P	National Epilepsy Centre	Data prospectively collected	Interviewed mother & attending obstetrician or pediatrician for neonatal death or stillbirth. 63 out 123 live births examined in infancy by doctor at clinic in charge of patient	A
86	Jager Roman et al	Germany	76	P	Neurological clinic	Regular interviews during pregnancy & review of obstetric medical record. Serum blood levels in 1st trimester.	Neonatal nurses & Pediatricians blinded to exposure status	S
86	Robert	France	76-83		Women who had an EEG between 76 & 83 at the hospital of Neurology & Neurosurgery P. Wertheimer,Lyon France, & 3 Lyon maternity wards	Questionaire sent to women	Questionnaire sent to women	U
86	West et al	Canada	80	R	95% of Saskatchewan population served by provincial drug plan	Saskatchewan provincial drug plan computer files	Saskatchewan admission-separatio hospital abstract data	A
87	Bertollinii	France	73-83	R	Epilepsy league data	Physician' records	Physician's records	U
		Lyon	76-84	R	Clinic & hospital	Maternity health records	Malformation registry	A
		Italy	83-85	P	Multicentre registry	Details not given	Details not given	U
		Sweden	73-81	R	Birth defects registry & population data	Hospital records	Computerized birth files	U
88	Kaneko	Japan	78-84	P	2 university hospitals & medical college hospital	Data prospectively collected at monthly intervals including compliance and seizures	examination by obstetricians & neuropsychiatrists on day 1, day 5, day 13 and at time of developmental milestones.	S

* Study Type: R= retrospective follow-up; P = Prospective follow-up.

**Methodological Strength Assessment: U = Uncertain; A = Adequate; S = Sound. (See Text)

CHAPTER 4. SASKATCHEWAN RECORD LINKAGE STUDY

MATERIALS AND METHODS

This historical follow-up study examines anticonvulsant drug therapy during pregnancy and selected reproductive outcomes occurring between January 1, 1977 and March 31, 1984 among the approximately 95% of women in Saskatchewan covered by the provincial prescription drug and hospitalization plans. The names used and the protocols described in this thesis reflect the setup at the time the study was initiated (1984). (The setup and protocols for the prescription drug plan changed twice in the late 1980's.)

4.1 Sources of data

Demographic information

Saskatchewan Health maintains a Health Insurance Registration File which contains demographic data on each of the approximately 950,000 individuals registered in the Health Plan. A unique eight digit number, the Registration Beneficiary Number (RBN), is assigned to each individual when he or she enters the Plan. The first six digits identify the family; the last two digits identify family members. At age eighteen individuals receive their own family number. A woman's RBN generally changes to her husband's family number when she marries and if she becomes divorced she may receive her own family number.

Drug exposure data

Between September 1, 1975 and June 30, 1987 the SPDP directly paid pharmacies the actual drug material cost and a portion of the dispensing fee for prescriptions for

formulary drugs issued out of hospital to eligible residents of Saskatchewan. The SPDP covered over 95% of the province's approximately one million inhabitants, excluding only those covered by other government plans. The reimbursement rules and mechanisms were changed on July 1, 1987, to a family rather than individual-oriented reimbursement scheme which diminished the usefulness of the data for pharmacoepidemiology. However, the plan was altered again in early 1989 to a system more like the original scheme and renamed the Saskatchewan Prescription Drug Services Branch.

The SPDP covered some 1500 drug related products contained in the Saskatchewan Formulary. The participating pharmacies (351 in 1983) submitted claims to the SPDP on multi-line claim forms or through direct computer links. Claims received by SPDP on claim forms were scanned for completeness, keyed onto disk and microfilmed. Once machine readable, each claim was checked for an eligible RBN, the drug name, manufacturer, pharmacy, dosage form, quantity dispensed, and prescribing physician. Claims passing the data checks were automatically paid. The SPDP maintained cumulative computer files of these individual claims data.

Reproductive outcome data

All permanent residents of Saskatchewan are entitled to hospital services without payment of a premium. They are required to register and participate in SHSP (now named Saskatchewan Hospital Services Branch) unless covered under other provincial or federal programs. A hospital discharge abstract form is required by SHSP for every discharge from one of the 153 public hospitals in the province (1983). Automated hospital Inpatient Statistics records are created by SHSP from these forms and include routine demographic data, the patient's RBN, the discharge date, separation type, days stay, operations performed and provision for a primary diagnosis on discharge and secondary diagnosis or complication codes. SHSP staff code the primary and secondary diagnostic

codes to 4 digits using the Ninth Revision of the International Classification of Diseases (ICD-9). Prior to September 1, 1979 coding was done using the Eighth Revision of the ICD, but these codes had been retrospectively updated to ICD-9 codes in the files accessed for the study.

4.2 Methods - Record linkage

The record linkage strategy for this study is presented in two flowcharts. Figure 4.2.1 describes the linkage of reproductive outcome data from the hospitalization database. Figure 4.2.2 describes the extraction of drug data, the creation of the linked maternal prescription drug-reproductive outcome database and initiation of the anticonvulsant-birth defect study.

Hospital data extraction

SHSP's computerized files of hospital discharge abstract data for the period April 1, 1977 through March 31, 1984 were scanned to locate records with the following discharge diagnosis codes (primary or secondary) or other identifiers: pregnancy complications (ICD-9 codes 640-648); pregnancy outcomes not resulting in a livebirth (including ectopic pregnancy, spontaneous abortion, therapeutic abortion, and stillbirth (ICD-9 630-639. 656.4)); delivery (ICD-9 650-669); births (identified by a newborn age code); childhood hospital separations up to age 5; and childhood deaths up to age 5.

For each category above, a computer file was created and all data items on the computerized individual admission-separation records meeting the criteria were copied into the appropriate file. The selected files were extensively checked through cross tabulations to ensure that appropriate selection criteria had been used, that the selection algorithm was working correctly and that the counts of selected records were consistent

with data from SHSP's annual reports and internally consistent across years.

The individual files were then sorted by the RBN and discharge date to facilitate internal and cross-file linking of records of a mother's individual pregnancy and delivery and of the infant's records. Through a series of linkage steps, maternal, newborn and childhood records were consolidated by matching on the RBN and the time of discharge to create one summary record per pregnancy. The summary pregnancy records were matched to the Health Insurance Registration File to flag, date and cross-reference all instances where the mother's RBN changed during the year preceding the pregnancy outcome. When more than one pregnancy outcome was reported for a woman during the study period, each was flagged as such and all were kept in the database, allowing for the possibility of within mother comparisons and the ability to restrict the analysis to first reported outcomes.

Drug data extraction

SPDP prescription claims files for January 1, 1976 through December 31, 1983 were scanned and the individual record for every prescription dispensed to a reproductive age woman (15-49 years) was copied to a new file. In the same scan, the individual record for every prescription dispensed for an anticonvulsant drug to anyone in the drug plan was extracted and copied into a second file.

The data on anticonvulsant prescriptions were sorted by RBN and dispensing date and then consolidated by RBN to establish a file with data on all individuals who had received any anticonvulsant prescriptions during the eight-year period, each with an individual anticonvulsant prescription history spanning the eight-year period. (See Table 4.2.1.) Anticonvulsants other than phenobarbital are used almost exclusively for epilepsy control (Krogh et al., 1987) and thus prescriptions dispensed for these anticonvulsants can be used to flag individuals likely to have epilepsy. Phenobarbital is often used as an

anticonvulsant but it is also prescribed as a sedative or anxiolytic agent for the relief of tension and apprehension, and as a hypnotic for the short term management of insomnia.(Krogh et al., 1987)

Linking drug and hospital data

The consolidated pregnancy outcome file was merged with the file containing data on all prescriptions for reproductive-age women to complete the prescription drug-reproductive outcomes database. Data on all prescriptions dispensed to the mother in the year preceding the outcome under her RBN at the time of delivery were appended to the pregnancy record. A one-year cutoff was selected in order that all prescriptions used during the first trimester, the primary focus for drug use and birth defects research, would be linked to the mother. Data assembled in this maternal prescription drug use-reproductive outcomes database is presented in Table 4.2.2.

This database was then linked to the consolidated anticonvulsant users file to flag pregnancies where a parent may have been epileptic and to append the anticonvulsant prescription history to the pregnancy record. Where both the mother and the father had been dispensed anticonvulsants, a separate group was formed. Because the group was small, for analysis they were added to the group of pregnancies where the mother had a history of anticonvulsant exposure.

If a woman's RBN changed during the year before a pregnancy outcome, the prescriptions issued to the woman before the change in her RBN could not be linked to the pregnancy. Similarly, separate anticonvulsant histories would be created for each RBN. It is possible to resolve changes in RBN's so that complete linkage can be made, but this process would have required an involved process to update the RBN's for all prescriptions for reproductive-age women and for all records selected from SHSP to the most recent RBN. The cost of such a procedure was prohibitive (at least as expensive

as the rest of the study) and not done. Instead, women whose number changed during the year preceding a pregnancy outcome were simply flagged and the date of the change, as recorded in the Master Registration File, added to the individual pregnancy record. This allowed the researcher to be aware of the pregnancies and the time window where there might be missing prescriptions.

Because those women who might be missing data on prescriptions could be flagged and less than 10 percent of individual RBN's change in the course of a year, the shortcoming in prescription ascertainment was not perceived as a problem that would jeopardize analysis. The likely effect of the missing data would be non-differential misclassification of some of these women's drug exposure status during early pregnancy to unexposed when they actually had been dispensed prescriptions. The effect would be to diminish estimates of risk based on exposed/not exposed analysis towards the null. Furthermore, by adding the RBN change flag, analysis could be done with and without the flagged data allowing evaluation of an unforseen bias. However, if dose-risk analysis was performed, missing prescriptions would tend to reduce the dose thus increasing the risk associated with a specific dose.

Table 4.2.1

Information consolidated for each individual in Saskatchewan dispensed any anticonvulsants through the SPDP between 1976 and 1983.

A) All anticonvulsant prescriptions filled between January 1, 1976 and December 31, 1983 through SPDP. For each prescription dispensed, the following information is recorded:

-date prescription filled
-drug identification number (D.I.N.)
-quantity prescribed (number of tablets)
-active ingredient number (AIN)
-strength
-form
-class
-repeat (yes/no)

B) An eight year summary history of each anticonvulsant used, including for each anticonvulsant:

-date first dispensed
-date last dispensed
-total number of prescriptions dispensed
-date person entered drug plan
-date person left drug plan

Table 4.2.2

Information assembled for each pregnancy outcome in the linked SPDP-SHSP maternal drug use-reproductive outcome database.

From the Master Registration File:

-flag indicating a change of RBN in the one year period preceding a pregnancy outcome
-date of RBN changes
-old RBN(s)

From the SHSP Admission-Separation Summary Record Files:

A) From the mother's hospitalization for delivery

-date of birth
-5-year age group
-residence code
- diagnosis - primary (ICD-9 4-digit)
-diagnosis - secondary (ICD-9 4-digit)
-discharge date
-operation code
-responsibility for payment
-separation type

B) From the infant's separation after birth

-last 2 digits of child's RBN (used to establish mother's parity)
-date of birth
-sex
-diagnosis - primary (ICD-9 4-digit)
-diagnosis - secondary (ICD-9 4-digit)
-discharge date
-separation type

C) From infant and early childhood separations (age 0-5 years) for late anomaly diagnosis

-diagnosis - primary (ICD-9 4-digit)
-diagnosis - secondary (ICD-9 4-digit)
-discharge date

(continued)

Table 4.2.2 (continued)

D) From separations for infant death (age 0-5 years, all causes)

-diagnosis - primary (ICD-9 4-digit)
-diagnosis - secondary (ICD-9 4-digit)
-discharge date
-separation type

From The SPDP Prescription Files:

A) All prescriptions filled for a woman in the year preceding any inpatient hospital-recorded reproductive outcome for that women. For each prescription dispensed, the following information is recorded:

-date prescription filled
-drug identification number (D.I.N.)
-quantity prescribed (number of tablets)
-active ingredient number (AIN)
-strength
-form
-class
-repeat (yes/no)

Figure 4.2.1 Mother - Infant SHSP Record Linkage Flowchart

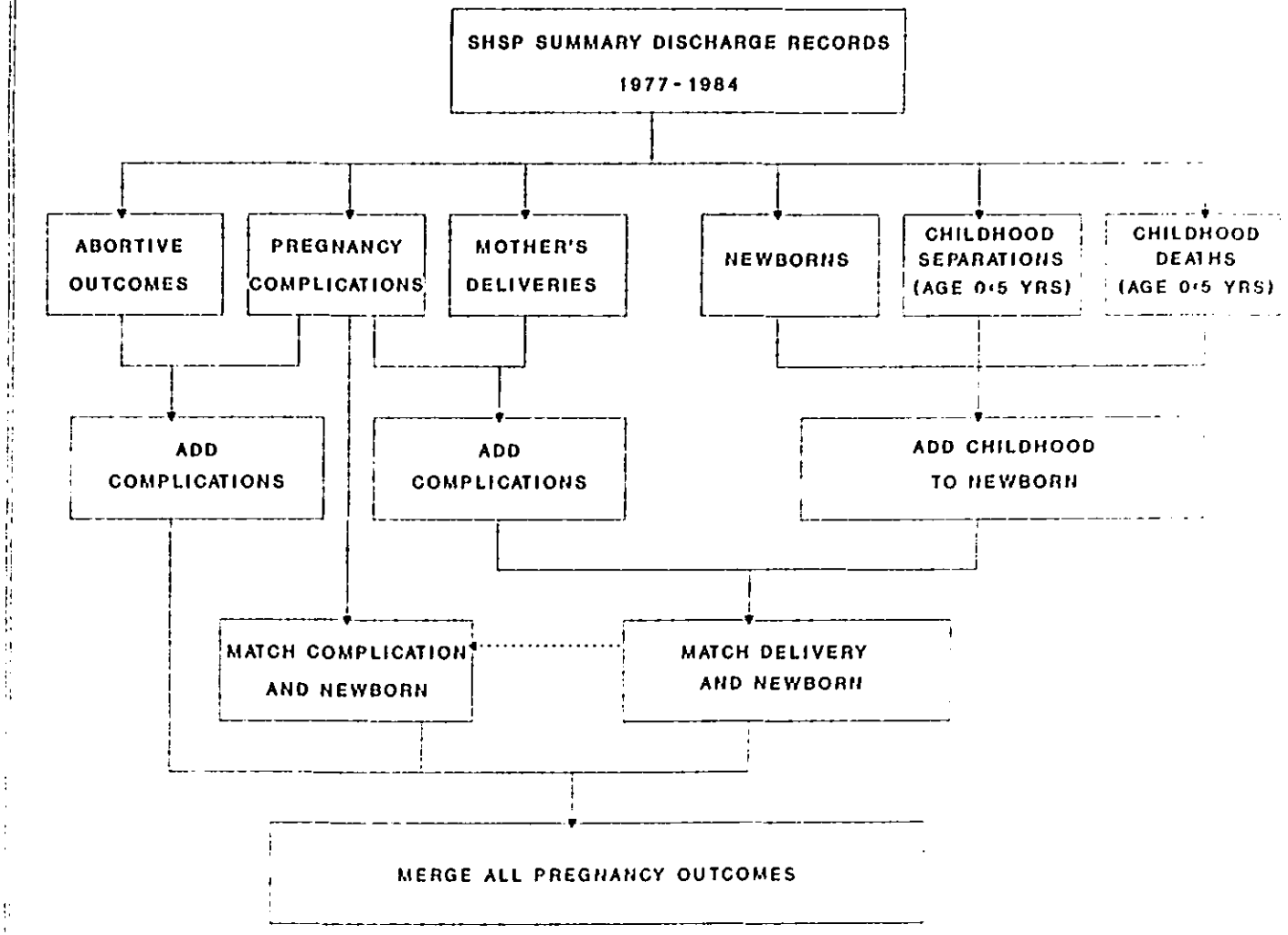
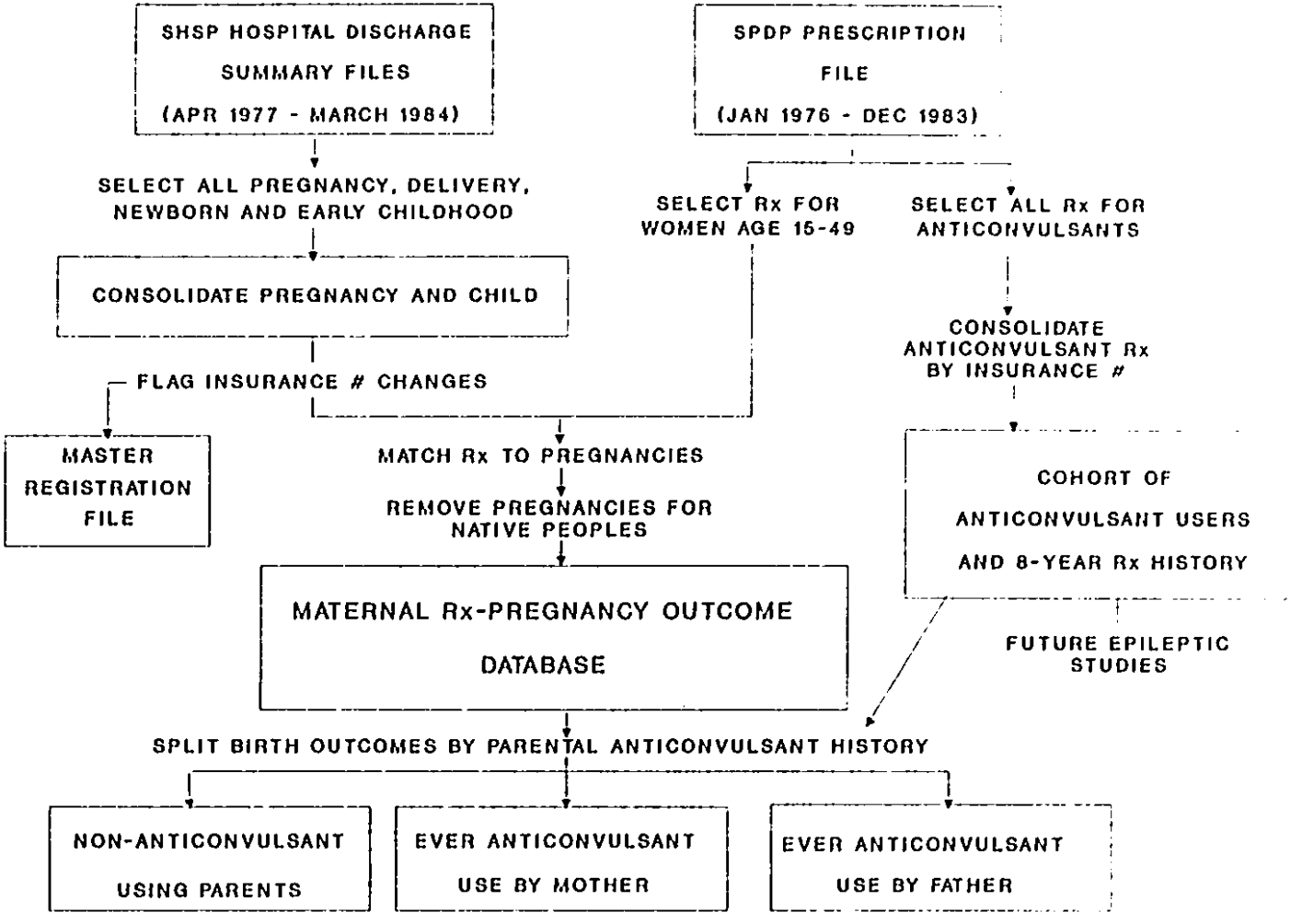


Figure 4.2.2 Saskatchewan Maternal Drug Use - Reproductive Outcome Database Creation and Anticonvulsant Study Initiation Flowchart



4.3 Evaluating the level of birth defects ascertainment in the database

The interest in this thesis is primarily focused on "major congenital malformations" (i.e. serious congenital anomalies, serious birth defects). In the literature review and meta-analyses the original study authors' interpretations of what constituted an important anomaly had to be adopted, although they were rarely explicitly stated. Most of the studies used written descriptions of the anomalies reported in the hospital chart or an actual examination of each child to decide whether an eligible anomaly was present.

However, in the Saskatchewan record linkage study we were dependent on 4-digit International Classification of Disease codes (sometimes aided by two or three word written diagnoses available from the validation study copies of hospital-separation abstracts). Differentiations between major and minor anomalies can be complicated by the fact that some anomalies can be expressed in a range of severities from totally functional to life threatening. This can be problematic because the standardized coding system commonly used for congenital anomalies, the International Classification of Diseases, contains no provision for differentiation of the severity of most birth defects.

Birth defect cases were defined for the Saskatchewan study on the basis of the ICD-9 rubrics. Classifications 740.0-759.9 were included with some specific diagnoses excluded. Tongue ties (750.0), undescended testicle (752.5), and the code including skin tags and birth marks (757.3) were not included, since in general they can be considered normal variants (Sever et al., 1988). These conditions are common and generally medically unimportant. High variability in reporting of these conditions can mask important variation in less common but more important conditions. Patent ductus arteriosus (747.0) has also been removed because it often occurs as a consequence of prematurity in which case it is not a defect. (Gestational age is unavailable in SHSP admission-separation summary dataset, so premature infants are difficult to identify to distinguish which patent ductus cases should be considered birth defects.)

The level of birth defect ascertainment was examined by comparing the Saskatchewan prevalence at birth of birth defects (as ascertained in the first year of life using the SHSP admission-separation summary records) with other birth defect databases. The birth prevalences of the 20 three-digit ICD categories (740-759) in the congenital anomalies chapter were compared with data from nearby provinces as assembled by the Canadian Congenital Anomalies Surveillance System (CCASS) operated by Health and Welfare Canada.

Saskatchewan does not have its own registry of congenital anomalies and thus does not participate in CCASS. During the early 1980's an increasing number of hospitals in Saskatchewan began using the services of the Hospital Medical Records Institute (HMRI) and by 1984 about 80 percent of inpatient admissions in the province were being reported to HMRI. However, unlike in Ontario and British Columbia in particular, the HMRI data for Saskatchewan is not useful for monitoring because identifying information required to bring together multiple admissions is sparse. In Appendix A data are presented on the frequency with which the hospital insurance number, the geographic code and the postal code were recorded among HMRI records for Saskatchewan which included a diagnosis for a congenital anomaly in the first two years of life. (There are no names or addresses on the HMRI dataset to facilitate linkage.) As a result no attempt was made to compare the SHSP anomaly data with the HMRI data for Saskatchewan.

Data from multi-source registries in British Columbia and Alberta, a hospitalization-based registry in Manitoba, and HMRI-based monitoring in Ontario for similar time periods (generally 1978-1984) were chosen for comparison to the Saskatchewan dataset. Each of these registries includes birth defects reported in the first year of life. In Canada the experience has been that monitoring restricted to hospitalizations will generally pick up about 90% of the cases that multi-source monitoring yields. (Johnson, 1990) All chosen data had been recorded or recoded ICD-9. As in Saskatchewan, other provinces adopted the Ninth Revision of the ICD around 1979.

Analysis was done at the three-digit ICD category level because detailed code resolution schemes not available at SHSP are required to correctly chose appropriate four-digit ICD-9 codes for congenital anomalies when, as often occurs, a child is hospitalized more than once and the discharge summaries contain differing four-digit codes within the three-digit categories. The number of cases, as opposed to the number of anomalies, and birth prevalences at the three-digit ICD level were calculated for each province. In all provinces, minor anomalies were excluded as discussed above.

4.4 Estimating anticonvulsant exposure during pregnancy

In developing a plan to estimate periods of exposure and dose estimates for women dispensed anticonvulsant around the time of pregnancy, the following needed to be considered:

1) SPDP had not developed an algorithm for translating prescription dispensing information into probable drug use patterns.

2) Information about gestation length was not present on the SHSP file.

3) Anticonvulsant prescription patterns varied markedly. Prescriptions for anticonvulsants can be dispensed in 30 day or 100 day supplies, although which time period is not indicated on the SPDP data file. In many instances repeat prescriptions were dispensed on dates not near either 30 or 100 days from the last prescription for the same anticonvulsant (see below).

4) The appropriate therapeutic dose for individual anticonvulsants can vary considerably among persons with epilepsy and can be established only through a trial and error process to find the minimum dose that keeps a patient seizure-free over an extended period of time.

5) Epileptic convulsion frequency has been observed to remain unchanged in about half of the pregnant women with epilepsy, to decrease in about 25 percent of women, and increase in the other 25 percent (Schmidt, 1982). Therapy may be

altered in response to convulsions.

6) Some women may individually decide to reduce or even to stop their intake of anticonvulsants once they suspect they are pregnant because of their fear of teratogenicity (Schmidt, 1982). This probably contributes to the changes in convulsion frequency observed.

7) Because Saskatchewan Health did not allow the researcher access to individual records, it was not possible to examine individual dispensing patterns. Close visual inspection of these might have offered added understanding of specific individuals' dispensing patterns and better estimates of exposure.

To deal with these constraints the following strategy was devised: "Short", "average" and "long" windows of probable gestation length and of likely dates of the first trimester in relation to the date the pregnancy ended were developed for livebirths, stillbirths, induced abortions and ectopic pregnancies. (see Table 4.4.1.) An algorithm was developed to translate the data on each anticonvulsant prescription dispensed to an individual into a probable anticonvulsant exposure and dose status during a certain number of days following the dispensing date. The time between prescriptions, the strength, the amount of drug prescribed, whether the prescription was a repeat and the consistency of the pattern of prescriptions were used to evaluate probable exposure time (elapsed days) and make an estimate of daily dose.

Frequency tabulations of the number of days between dispensing dates in the year before a pregnancy outcome were performed for each anticonvulsant. Although in many cases the times between prescriptions were reasonably close to 30 or 100 days, a surprising number were not and therefore most difficult to evaluate. Table 4.4.2 summarises the distributions for the most commonly used anticonvulsants - phenobarbital, phenytoin and carbamazepine. Histograms of the number of days between prescriptions for the most commonly used anticonvulsants, phenobarbital and phenytoin, are presented in Figures 4.4.1 and 4.4.2.

Table 4.4.3 summarises the assumptions made about the elapsed number of days over which an anticonvulsant prescription was assumed to have been completely used. With some patterns of anticonvulsant dispensing it was more difficult to establish exposure estimates. Therefore, an exposure assessment reliability scale was developed to quantify confidence in the exposure period and dose estimates. Each different type of anticonvulsant was dealt with independently. Once the elapsed days for all prescriptions for a specific anticonvulsant had been established for an individual, the average daily dose for each prescription was calculated as follows:

$$\text{Rx Average Daily Dose} = \frac{\text{Rx strength} \times \text{Rx quantity}}{\text{Rx elapsed days}}$$

The total exposure of an individual to a specific anticonvulsant in a window was calculated as:

$$\text{Total exposure in window} = \sum_{\#\text{ of Rx in window}} \text{Number of days exposed during window} \times \text{Rx average daily dose}$$

An examination of the exposure and dose classifications for each anticonvulsant based on the different gestation length assumptions yielded very similar numbers of "exposed in the first trimester" and "any exposure during pregnancy". The exposure estimates based on the mean pregnancy length were chosen for the cross tabulations sent to the Laboratory Centre for Disease Control for the analysis of congenital malformation risk.

Table 4.4.1

Windows for anticonvulsant exposure during pregnancy

Outcome	Gestation	First Day of Window: 1st Trimester or Whole Pregnancy	Last Day of Window: 1st Trimester Exposure	Last Day of Window: Whole Pregnancy Exposure
Live birth	Mean	273*	182	0
	Short	259	168	0
	Long	293	202	0
Stillbirth	Mean	266	175	0
	Short	140	49	0
	Long	293	202	0
Induced abortion	Mean	110	19	0
	Short	70	0	0
	Long	140	49	0
Ectopic pregnancy	Mean	42	0	0
	Short	14	0	0
	Long	70	0	0

* Days before outcome date

Table 4.4.2

Elapsed days between prescriptions for women on phenobarbital, phenytoin or carbamazepine in Saskatchewan 1976-1983

	Phenobarbital		Phenytoin		Carbamazepine	
	#	(%)	#	(%)	#	(%)
Single prescription	908	(25.9%)	80	(4.9%)	52	(8.0%)
Last prescription	539	(15.4%)	268	(16.4%)	97	(15.0%)
Days between prescriptions	2,060	(58.7%)	1,289	(78.7%)	499	(77.0%)
<25 days	280	(8.0%)	110	(6.7%)	55	(8.5%)
25-39 days	588	(16.8%)	358	(21.9%)	184	(28.4%)
40-89 days	721	(20.6%)	473	(28.9%)	168	(25.9%)
90-99 days	116	(3.3%)	93	(5.7%)	27	(4.2%)
101-130 days	197	(5.6%)	167	(10.2%)	49	(7.6%)
>130 days	158	(4.5%)	88	(5.4%)	16	(2.5%)
Total	3,507	(100.%)	1,637	(100.%)	648	(100.%)

Table 4.4.3

Anticonvulsant prescription patterns, assumed days of exposure and reliability assessment

Total Rx for a Specific Anticonvulsant	Last Rx	Elapsed Days Between Rx Dispensing Dates	Assumed Elapsed Days of Rx Exposure	Exposure Reliability Assessment Flag	Reliability Assessment
1	---		30	2	Probable
2 or more	N	<100	Elapsed days between Rx	1	Very probable
2 or more	N	100–130	100	1	Very probable
2 or more	N	>131	100	4	Possibly
2 or more	Y		Elapsed days between previous 2 Rx	3	Possibly

Figure 4.4.1 Elapsed days between prescriptions for phenobarbital among Saskatchewan women 1976-1983

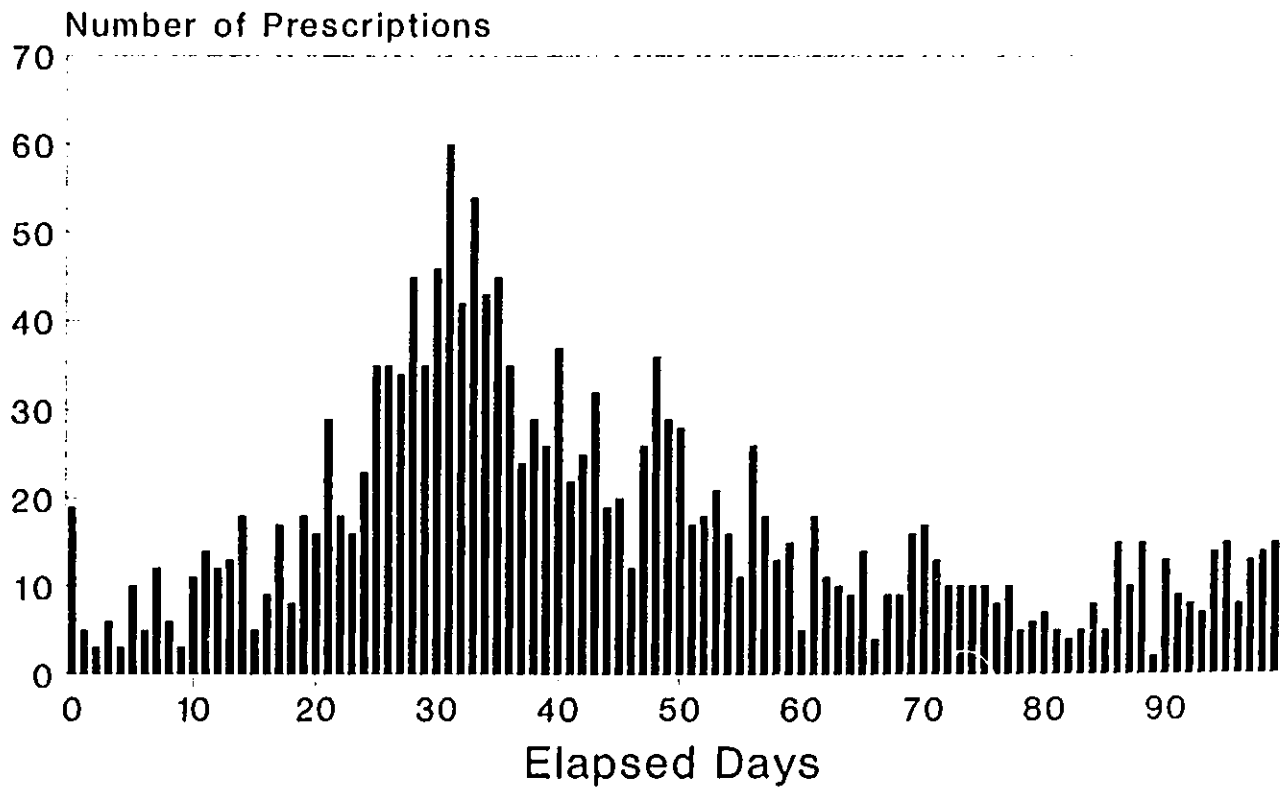
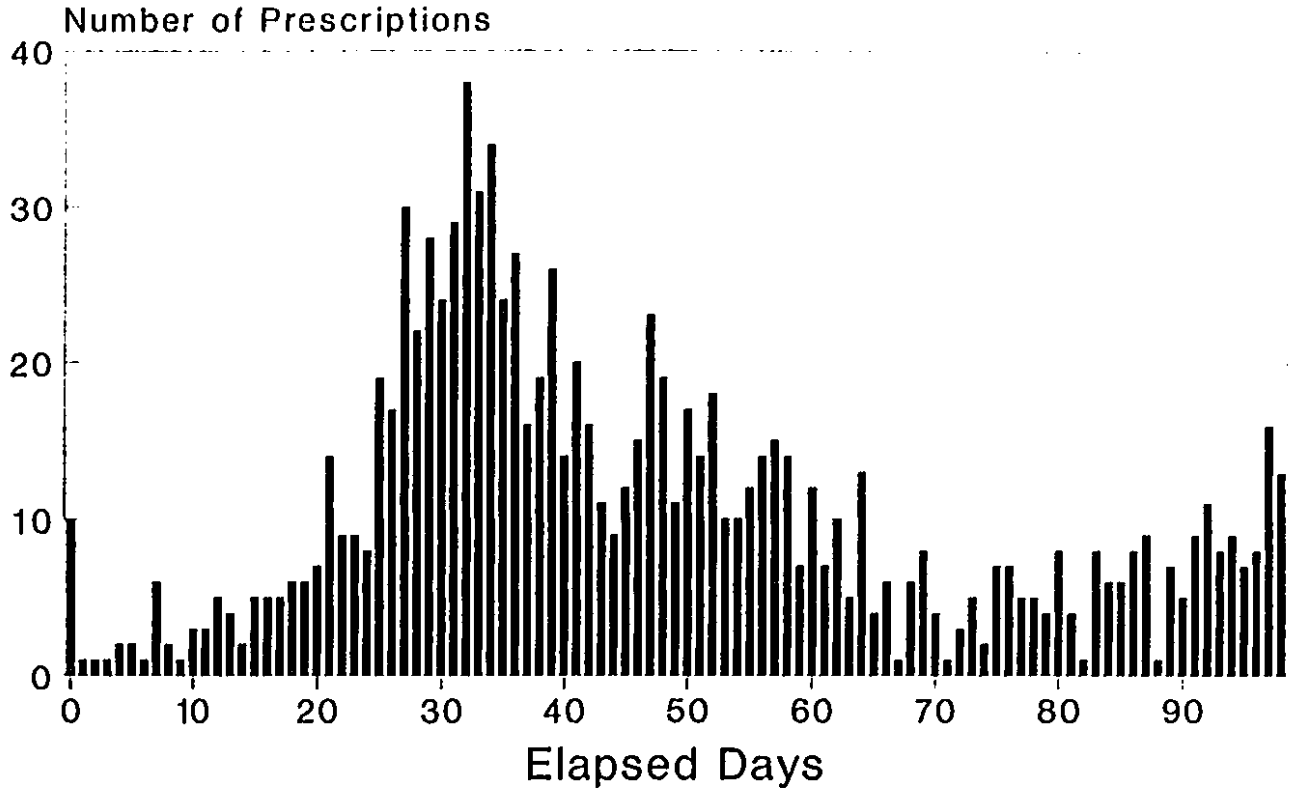


Figure 4.4.2 Elapsed days between prescriptions for phenytoin among Saskatchewan women 1976-1983



4.5 Validating the ICD coding of congenital anomalies from written descriptions on admission-separation summary records

Admission-separation abstract forms are submitted to SHSP for every discharge from a public hospital in Saskatchewan. These forms include a short written primary and secondary diagnosis on discharge which are coded to 4 digits using the ICD by trained SHSP staff. Data from these forms are then made machine readable and used for SHSP's accounting file. Copies of the original forms are kept on microfiche at SHSP. A validation study was undertaken to assess how accurately the one-line written descriptions of anomalies had been coded into the ICD and entered into the database, and to confirm the anomalies reported among the offspring of women and men treated with anticonvulsants at any time during the eight-year study period.

A sample of 234 admission-separation summaries for 182 infants with anomalies reported were chosen from the maternal drug-reproductive outcome database. The sample included all discharges for infants who had an anomaly and whose mother or father had received any anticonvulsants during the eight-year study period. The one exception to this rule was that only a sample of the records (about half) was taken of the women with an anticonvulsant prescription history including only phenobarbital and who had not taken it during the first trimester. As well, a sample of 50 records (every fiftieth record with an anomaly) was chosen of infants with anomalies whose mother and father had not been treated with anticonvulsants during the eight-year study period.

This list was referred to SHSP staff who found the copy of the admission-separation summary record on microfiche, photocopied it, and removed individual identifying information. A clerk at CCASS with extensive anomaly coding experience and blinded to SHSP's coded diagnoses and the anticonvulsant exposure status, recoded the primary and secondary written diagnoses from the photocopied admission-separation records. The original and recoded values were then compared.

4.6 Statistical analysis

To explore the dataset and describe the number and distribution of pregnancies where the parents were likely to be epileptic based on their anticonvulsant prescription histories, a series of cross-tabulations was performed. Both the number of types of anticonvulsant prescription and the total number of prescriptions dispensed under the present RBN were examined to group parents as to probable epilepsy status.

The risk of birth defects and of selected non-livebirth outcomes ascertained through hospitalizations was then examined in relationship to differences in maternal anticonvulsant use during the estimated first trimester of pregnancy or paternal anticonvulsant use during the estimated spermatogenesis period. Pregnancy outcomes were first categorised by whether the mother or father had ever been dispensed an anticonvulsant under their current RBN during the period 1976 to 1983. Because phenobarbital is often prescribed for indications other than epilepsy, the anticonvulsant exposure status was also stratified by whether the anticonvulsant exposure had been restricted to phenobarbital.

Pregnancies where neither the mother nor the father had been dispensed an anticonvulsant between 1976 and 1983 through the drug plan under their current benefit number were used as the referent group throughout the analysis. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated with standard statistical methods (Rothman, 1986) using the statistical analysis package Epi Info (Version 5.01)(Dean et al., 1990). Where expected cell values of less than five were encountered exact binomial confidence intervals were calculated using the program Exactbin (Guess et al., 1987) because the asymptotic methods for estimating intervals are not accurate with such sparse data. The 95 percent confidence level was chosen to conform to standard practice.

First trimester anticonvulsant exposure was then categorized by the number of types of

anticonvulsants dispensed to a woman in the estimated time of the first trimester or to the father during the approximate time of spermatogenesis. The analysis then examined the risks of specific groups of congenital anomalies, in particular heart defects and cleft lip and/or palate, because increased risk of these defects have often been associated with anticonvulsant use in other studies.

(Similar analyses were done for women with first trimester anticonvulsant exposure and for fathers with exposure during spermatogenesis, for both congenital anomalies and selected non-livebirth outcomes. For simplicity, the analysis methods are described here for first trimester exposure and congenital anomaly risk only.)

The association between defect risk and the number of types of anticonvulsants dispensed in the first trimester was assessed for linear trend in proportions using the chi-square test for trend (Mantel extension) available in Epi Info (Dean et al., 1990). A chi-square statistic, on one degree of freedom, tested the hypothesis of constant relative risks against the alternative hypothesis of a linear increase across the five categories of number of types of anticonvulsants (i.e. none during the first trimester, one type during the first trimester, two, three, and four). Births where neither parent had a history of anticonvulsant use between 1976 and 1983 were used to create the referent category. (This test will be referred to as the "linear trend test".) This linear trend test assumed a constant interval between adjacent anticonvulsant-use categories; thus each successive anticonvulsant category was represented by an integer from one to five. Results must be interpreted cautiously when there are few observed cases and if the distribution by number of types of anticonvulsants is skewed.

Anticonvulsant exposure was then examined more closely by calculating RR's and 95% CI's associated with individual anticonvulsants and specific anticonvulsant combinations. The problems inherent in evaluating a small number of exposed pregnancies and rare outcomes limited the statistical analysis of these more finely categorized data.

Regression analysis

A more refined analysis was carried out using logistic regression (Rothman, 1986) to simultaneously control for the potential confounders age and parity and to evaluate potential risk factors such as number and type of anticonvulsants used. The modelling was done using the logistic regression module in EGRET (Mauritsen, 1988). The logistic model was built with the occurrence of a congenital malformation case as a dichotomous dependent variable.

Variables describing the total number of anticonvulsant prescriptions received between 1977 and 1983, the total number of types of anticonvulsants a woman had ever been dispensed and a phenobarbital only flag were entered as categorical variables as proxies for epilepsy. A term was entered for each anticonvulsant indicating whether there was probable first trimester exposure. A term was also entered indicating the number of types of anticonvulsants a woman was exposed to in the first trimester.

The potential confounders and potential risk factors were evaluated in the model and those not associated with risk of congenital malformation were eliminated. The final model allowed estimation of the odds ratio associated with specific anticonvulsants while simultaneously taking into account other factors affecting risk. Interaction terms were added to the model to evaluate interactions between terms.

4.7 Confidentiality and data analysis restrictions

To insure confidentiality the SPDP insisted on maintaining all original individual data within the Saskatchewan Health computer facilities. Only multi-way cross-tabulated data were available for analysis. These detailed cross-tabulations were received in machine readable form from Saskatchewan and many cells could be reconstructed into individual records with all categorical variables for analysis. (Data on diagnosis from the individual

records in the validation study were used to assist in specifying and validating the anomalies reported among anticonvulsant users, but this was only a fortuitous offshoot of the validation study.) Although this made an analysis possible, it did not allow detailed examination of individual data before categorization. For example, once a satisfactory dose algorithm had been developed one could not go back and explore the possible effects on outcome of changing the algorithm without going back to Saskatchewan Health and requesting a whole new cross-tabulation and then totally reprocessing the resulting data back into a dataset.

CHAPTER 5. RESULTS OF THE SASKATCHEWAN STUDY

5.1 Creation of the reproductive outcomes-prescription drug database

Figures 5.1.1 and 5.1.2 summarise the results at each step of the record linkage process used to create the reproductive outcomes-prescription drug database and to initiate the anticonvulsant study.

From the 1.4 million SHSP hospital discharge abstracts scanned, the following records were selected: 16,210 non-livebirth pregnancy outcomes; 42,208 admissions for pregnancy complications; 119,080 deliveries; 119,984 births; 33,890 childhood separations under age five; and 590 deaths under age five.

Table 5.1.1 compares livebirth and stillbirth counts reported in Statistics Canada's annual reports on births and deaths (1977-1984) with those extracted from the SHSP files. Livebirth counts are comparable between the two sources but before 1981 there is a shortfall of stillbirths in the SHSP dataset.

Figure 5.1.2 details the consolidation of the selected hospital records. A match was found with a newborn record for 19,927 of the childhood separations (59%), and 398 of the deaths to age five (67%). Matching rates in this range were expected because many of the deaths and separations between 1977 and 1980 were from the birth cohort of April 1, 1973 - March 31, 1977 for which no newborn record was extracted.

Newborn records could be matched to a mother's record with a delivery code for 110,621 newborns (92.2%), and to a mother's record with a pregnancy complication code in a further 3,844 newborns (3.2%). Thus, newborns were successfully matched to mothers for 114,465 of 119,984 newborns (95.4%). Analysis of the still unmatched newborns, by hospital location, sex, primary ICD-9 and secondary ICD-9 code showed no substantial variations by year of birth. Approximately 75 newborns each year (<

0.5% of livebirths) were not expected to match because of adoption shortly after birth in which case SHSP changes the infant's RBN to prevent the child and natural mother from being linkable. Officials at SHSP were unable to provide an explanation for the remaining unmatched births. They may have resulted from a variety of uncommon occurrences such as incorrect specification of the mother's or infant's insurance number or the miscoding of or failure to include a delivery code on the mother's admission-separation summary.

Table 5.1.2 presents pregnancy outcomes among the women covered by the drug plan as well as 3,328 congenital malformations in their offspring ascertained from newborn and/or childhood hospital separations to age one.

The scan of the Health Insurance Registration File indicated that the RBN's of 12,034 of the mothers (9.3%) had changed during the one-year period prior to the date of the pregnancy outcome. More than one pregnancy outcome was recorded for the same RBN during the study period for 42,589 women (32.6% of the outcomes and 48.3% of the women). Flags were set to indicate a change in RBN and to indicate a repeat pregnancy.

From a scan of data on over 32 million prescriptions filled between January of 1976 and December of 1983, records for 7.1 million prescriptions dispensed to reproductive age women were selected.

When the SHSP and SPDP data were merged, 299,153 prescriptions were located which had been dispensed to women in the one-year window prior to the delivery date or end of pregnancy. At this point, 9,931 births and 1,512 non-livebirth outcomes of native women, identified by a RBN starting with "R," were removed from the merged file as these women are not covered by the SPDP. Twin and triplet pregnancies resulted in 1,251 births and these births were also removed as they present special problems in statistical analysis which are not justified given their small numbers in this population.

No prescriptions were located in the year preceding the pregnancy outcome for 32,199 (29.1%) of the women covered by the drug plan, 21.0 percent had been dispensed one prescription, 15.4 percent two, 10.7 percent three, and 23.8 percent four or more prescriptions (see Table 5.1.3). On average, every woman was dispensed 2.5 prescriptions in the one-year period prior to delivery. Among those women receiving prescriptions, the average was 3.4.

Table 5.1.1

Comparison of Saskatchewan vital statistics livebirth and stillbirth counts with Saskatchewan Hospital Services Plan (SHSP) records extracted and matched

Calendar or Fiscal Year*	LIVEBIRTHS				STILLBIRTHS		
	Vital Statistics	SHSP Records Extracted	Delivery–Newborn Matches**	(%)	Vital Statistics 20+ weeks	Vital Statistics 28+ weeks	SHSP Records Extracted
77	16,547	16,871	13,628		163	126	0
78	16,550	16,339	16,376	100.2%	139	104	1
79	16,944	16,470	16,166	98.2%	142	110	52
80	17,057	16,979	16,025	94.4%	133	95	95
81	17,209	17,682	16,119	91.2%	136	103	136
82	17,722	17,887	16,835	94.1%	139	103	130
83	17,847	17,756	16,869	95.0%	126	98	139
84***	18,014		2,447		128	87	16
Total	137,890	119,984	114,465	95.4%	1,106	826	569

* SHSP Records Extracted counts are by fiscal years (e.g., 77 = April 1, 1977 to March 31, 1978); other counts by calendar year

** number of newborn records where a mother's delivery record could be matched to a newborn record using the first six digits of SHSP number and birth date

*** SHSP counts for 1984 include data for the time period January 1–March 31

Table 5.1.2

Pregnancy outcomes in the Saskatchewan Hospital Services Plan linked dataset 1977–1984 among women covered by the Saskatchewan Prescription Drug Plan

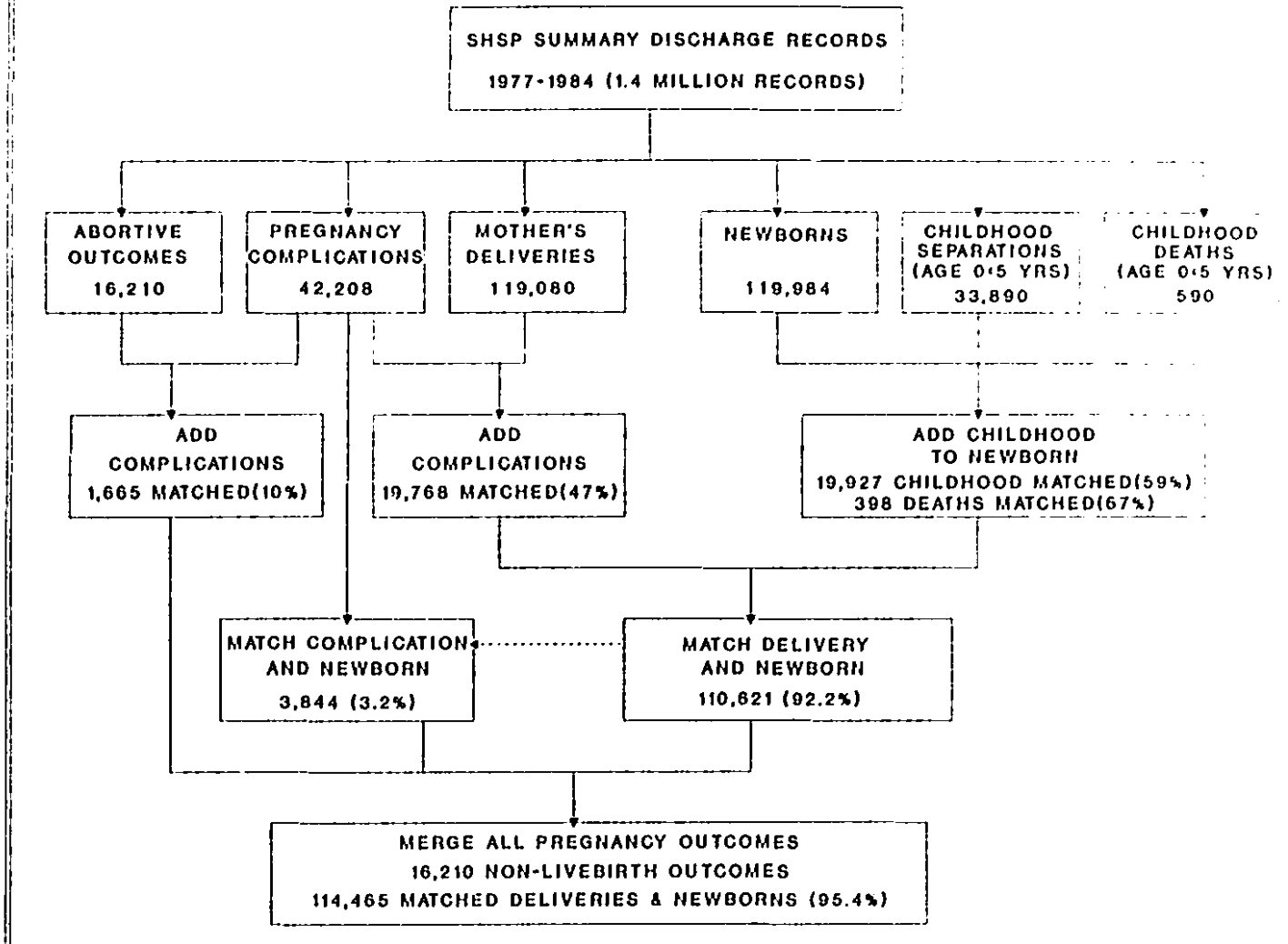
Outcome	ICD–9 Code	Number	Rate per 10,000 Livebirths
Total Singleton Livebirths		103,283	
Multiple Births		1,251	
Stillbirths	656.4	527	51.0
Ectopic Pregnancy	633	1,176	113.9
Induced Abortion	635	10,154	983.1
Spontaneous Abortion	634	2,841	275.1
CONGENITAL ANOMALIES			
Anencephalus and similar anomalies	740	11	1.1
Spina bifida	741	58	5.6
Other congenital anomalies of nervous system	742	96	9.3
Congenital anomalies of eye	743	49	4.7
Congenital anomalies of ear, face, and neck	744	66	6.4
Bulbus cordis & cardiac septal closure anomalies	745	223	21.6
Other congenital anomalies of heart	746	284	27.5
Other congenital anomalies of circulatory system	747	173	16.8
Congenital anomalies of respiratory system	748	105	10.2
Cleft palate and cleft lip	749	190	18.4
Other congenital anomalies of upper alimentary tract	750	237	22.9
Other congenital anomalies of digestive system	751	158	15.3
Congenital anomalies of genital organs	752	373	36.1
Congenital anomalies of urinary system	753	66	6.4
Certain congenital musculoskeletal deformities	754	503	48.7
Other congenital anomalies of limbs	755	266	25.8
Other congenital musculoskeletal anomalies	756	157	15.2
Congenital anomalies of the integument	757	77	7.5
Chromosomal anomalies	758	114	11.0
Other and unspecified congenital anomalies	759	122	11.8
Total Congenital Anomalies	740–759	3,328	322.2

Table 5.1.3

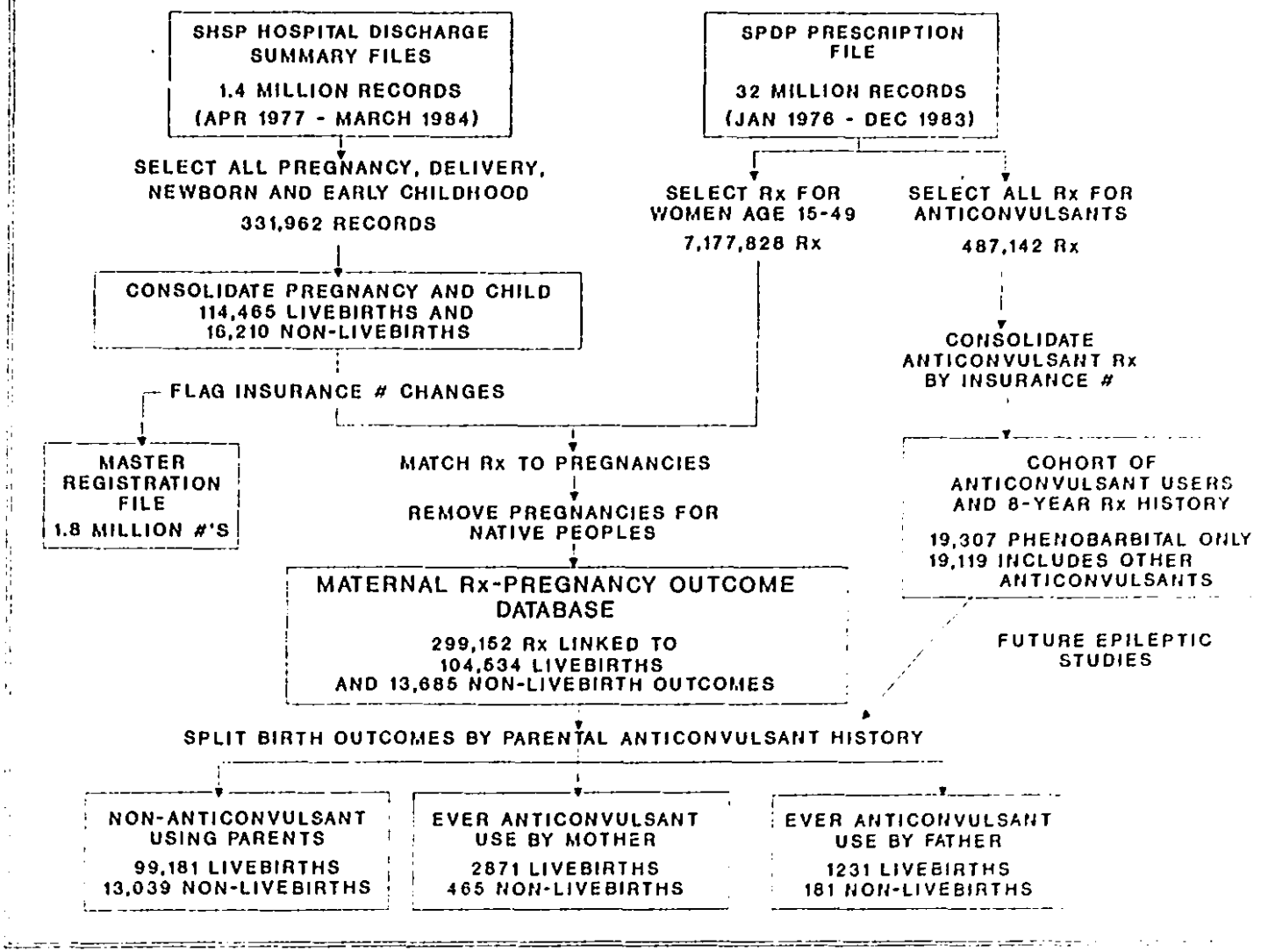
Number of prescriptions dispensed to women covered by the Saskatchewan Prescription Drug Plan 1977–1984 in the year preceding the pregnancy outcome, by year

Pregnancy outcome year	Number of prescriptions per woman					
	0	1	2	3	4+	All
1977	24.4%	20.1%	15.3%	11.4%	28.8%	100%
1978	27.4%	20.8%	15.2%	11.2%	25.4%	100%
1979	28.6%	20.7%	15.3%	11.2%	24.1%	100%
1980	29.9%	21.0%	15.7%	10.9%	22.5%	100%
1981	30.3%	21.1%	15.4%	10.3%	22.8%	100%
1982	31.1%	21.7%	15.3%	9.8%	22.0%	100%
1983	30.0%	21.6%	15.8%	10.3%	22.3%	100%
1984	34.0%	20.1%	15.3%	9.9%	20.7%	100%
Total	29.1%	21.0%	15.4%	10.7%	23.8%	100%

Figure 5.1.1 SHSP Mother - Infant Hospital Record Linkage - Results



5.1.2 SPDP-SHSP database creation and anticonvulsant study initiation flowchart - results



5.2 Evaluation of reproductive outcome ascertainment and coding

Birth defect birth prevalences for the 20 three-digit categories in the congenital anomalies chapter of the ICD-9 are presented in Table 5.2.1 for Saskatchewan, British Columbia, Alberta, Manitoba and Ontario. In Table 5.2.2, percentage differences in birth defect birth prevalences between Saskatchewan and each of the other provinces are presented. Substantial deficits in the Saskatchewan birth prevalence in many 3-digit categories are apparent in comparison to BC, Manitoba and Ontario. In Alberta the picture is more mixed.

Manitoba and Ontario data should provide the most appropriate comparison group for Saskatchewan as they are both based on similar data sources, i.e. an automated search of hospitalization admission/discharge records during infancy. Alberta's system depends on hospitals notifying the central registry of defects observed. When hospitals were required to notify a central registry in Ontario between 1973 and 1977, much lower birth prevalences were recorded there (see Appendix B). The one immediately apparent difference between Saskatchewan and the provinces of Ontario and Manitoba is that the SHSP admission-separation summary record provides for the coding of only two diagnostic codes, while the HMRI form used in Ontario provides space for up to 15 diagnostic codes and the Manitoba form has provision for 16.

The results of the validation study to determine the quality of ICD coding and data entry of congenital anomalies from written descriptions on SHSP admission-separation summary abstracts are summarized in Appendix C. In 210 of the 234 records examined (90.5%), the anomalies recorded were identical between the SHSP computer file and the blinded recode performed from the microfiche copy of admission-separation record. In 22 records (9%) the anomalies were recoded differently. In 14 of these records the difference was only at the fourth digit of the code, in eight of the records the codes did not agree at the three-digit level. As well, 17 additional defect codes were observed on the microfiche which had not made it to the machine readable summary, including 12

that were different at the three-digit level from the reported code(s).

Table 5.2.1

Birth defect birth prevalences * (1 year follow-up) in Saskatchewan Hospital Services Plan linked dataset and other provincial monitoring systems

Outcome	ICD-9 Code	Number	Rate per 10,000 Live Births				
			Saskatchewan 77-84	British Columbia 78-84	Alberta 80-84	Manitoba 78-84	Ontario 78-84
Total Live Births		103,283	103,283	269,277	217,083	116,739	877,317
CONGENITAL MALFORMATIONS (case counts)							
Anencephalus and similar anomalies	740	11	1.1	4.7	3.2	4.4	5.0
Spina bifida	741	58	5.6	7.3	4.6	8.0	9.6
Other congenital anomalies of nervous system	742	96	9.3	20.2	12.9	17.0	24.0
Congenital anomalies of eye	743	49	4.7	9.5	4.4	10.1	7.3
Congenital anomalies of ear, face, and neck	744	66	6.4	15.8	21.4	15.6	13.1
Bulbus cordis & cardiac septal closure anomalies	745	223	21.6	49.4	35.0	35.8	38.2
Other congenital anomalies of heart	746	284	27.5	51.7	19.0	32.4	30.7
Other congenital anomalies of circulatory system	747	173	16.8	29.0	20.7	20.6	29.2
Congenital anomalies of respiratory system	748	105	10.2	12.1	7.2	10.3	11.4
Cleft palate and cleft lip	749	190	18.4	21.8	16.4	20.1	17.9
Other congenital anomalies of upper alimentary tract	750	237	22.9	34.6	12.0	28.5	42.3
Other congenital anomalies of digestive system	751	158	15.3	20.2	10.1	19.6	16.0
Congenital anomalies of genital organs	752	373	36.1	48.3	24.0	36.9	37.1
Congenital anomalies of urinary system	753	66	6.4	18.5	10.6	15.8	13.6
Certain congenital musculoskeletal deformities	754	503	48.7	144.5	72.2	157.1	94.3
Other congenital anomalies of limbs	755	266	25.8	62.8	36.3	66.2	47.2
Other congenital musculoskeletal anomalies	756	157	15.2	32.9	17.7	27.5	32.1
Congenital anomalies of the integument	757	77	7.5	10.7	7.9	8.4	4.5
Chromosomal anomalies	758	114	11.0	17.2	12.8	13.0	17.6
Other and unspecified congenital anomalies	759	122	11.8	18.6	7.6	17.5	16.6
Total Congenital Malformations	740-759	3,328	322	630	356	565	508

* trivial anomalies such as skin tags and tongue tie removed

Table 5.2.2

Percentage differences in birth defect birth prevalences* (1 year follow-up) in the Saskatchewan Prescription Drug-Hospital Services Plan linked dataset compared to other provincial monitoring systems

Outcome	ICD-9 Code	Number	Saskatchewan rates relative to other provinces			
			British Columbia 78-84	Alberta 80-84	Manitoba 78-84	Ontario 78-84
Total Live Births		103,283	269,277	217,083	116,739	877,317
CONGENITAL MALFORMATIONS (case counts)						
Anencephalus and similar anomalies	740	11	-77%	-66%	-76%	-79%
Spina bifida	741	58	-23%	22%	-30%	-41%
Other congenital anomalies of nervous system	742	96	-54%	-28%	-45%	-61%
Congenital anomalies of eye	743	49	-50%	8%	-53%	-35%
Congenital anomalies of ear, face, and neck	744	66	-60%	-70%	-59%	-51%
Bulbus cordis & cardiac septal closure anomalies	745	223	-56%	-38%	-40%	-44%
Other congenital anomalies of heart	746	284	-47%	45%	-15%	-10%
Other congenital anomalies of circulatory system	747	173	-42%	-19%	-19%	-43%
Congenital anomalies of respiratory system	748	105	-16%	41%	-1%	-11%
Cleft palate and cleft lip	749	190	-15%	12%	-9%	3%
Other congenital anomalies of upper alimentary tract	750	237	-34%	92%	-20%	-46%
Other congenital anomalies of digestive system	751	158	-24%	52%	-22%	-4%
Congenital anomalies of genital organs	752	373	-25%	50%	-2%	-3%
Congenital anomalies of urinary system	753	66	-65%	-40%	-60%	-53%
Certain congenital musculoskeletal deformities	754	503	-66%	-33%	-69%	-48%
Other congenital anomalies of limbs	755	266	-59%	-29%	-61%	-45%
Other congenital musculoskeletal anomalies	756	157	-54%	-14%	-45%	-53%
Congenital anomalies of the integument	757	77	-30%	-5%	-11%	66%
Chromosomal anomalies	758	114	-36%	-13%	-15%	-37%
Other and unspecified congenital anomalies	759	122	-36%	55%	-32%	-29%
Total Congenital Malformations	740-759	3,328	-49%	-9%	-43%	-37%

* e.g. reported anencephaly birth prevalence 77% lower in Saskatchewan than in British Columbia

5.3 Initiation of epilepsy-birth defects study

In the scan of the SPDP files, data on all 487,142 prescriptions for anticonvulsant drugs (dispensed to women, men or children) were also extracted. When these anticonvulsant prescriptions were consolidated by RBN, 38,426 individual RBN's were identified. For 19,307 of these RBN's (50.2%), the only anticonvulsant dispensed had been phenobarbital. Using these data, 3,336 pregnancies were identified where the mother had received a prescription for an anticonvulsant at some time during the eight-year study period (see Table 5.3.1).

In 973 of these pregnancies the history included exposure to an anticonvulsant other than phenobarbital. A further 1,412 pregnancies were flagged where the father had been dispensed at least one anticonvulsant during the study period. The anticonvulsant history was not restricted to phenobarbital in 970 of these pregnancies. In 58 of the pregnancies both the mother and the father had a history of anticonvulsant exposure. These pregnancies are reported throughout the analysis with the mothers only. The small numbers make it impractical to evaluate this group separately and the literature suggests that the mother's anticonvulsant therapy is more likely to alter risk than that of the father (Janz, 1982).

Table 5.3.1

Hospital recorded pregnancy outcomes 1977–1984 for parents with any exposure to anticonvulsants 1976–1983

	Prescription history includes anticonvulsants other than phenobarbital*	Anticonvulsant history includes phenobarbital only	Total
Mothers			
Not Livebirth	166	299	465
Livebirth	807	2,064	2,871
Total	973	2,363	3,336
Fathers			
Not Livebirth	119	62	181
Livebirth	851	380	1,231
Total	970	442	1,412

* phenobarbital may or may not also be present

5.4 Estimated anticonvulsant exposure during pregnancy

Tables 5.4.1 through 5.4.5 further characterize the pregnancy outcomes of parents who had at least one prescription filled for an anticonvulsant between 1976 and 1983. As noted in the methods section, several sets of criteria were developed to assess a woman's use of an anticonvulsant during the first trimester. The different criteria yielded quite similar counts. The final criteria chosen yielded 359+276=635 pregnancies (522 livebirths, 106 non-livebirth pregnancy outcomes) where the woman was categorized as likely to have been taking an anticonvulsant during the first trimester of pregnancy. (See Table 5.4.1.) Among those women whose 1976-1983 anticonvulsant history had been restricted to phenobarbital, less than 12 percent of the pregnancies met the criteria to be considered exposed during the first trimester, while among those with anticonvulsant histories not restricted to phenobarbital, 37% were labelled as exposed during the first trimester.

For 269+52=321 pregnancies, the father was likely to have been taking an anticonvulsant during the estimated period of spermatogenesis. For those fathers with a history limited to phenobarbital, there were 52 pregnancies recorded (11.8%) where it was likely that an anticonvulsant had been taken during the period of spermatogenesis; for fathers with a history of other anticonvulsants dispensed, in 269 (27.7%) of the recorded pregnancies anticonvulsant use was probable during spermatogenesis.

In Table 5.4.2 the anticonvulsant exposure history is further categorized by the total number of recorded anticonvulsant prescriptions dispensed between 1976 and 1983 and the number of types of anticonvulsants an individual had received. In this table pregnancies are categorized as exposed if it was likely that anticonvulsant exposure occurred during any part of pregnancy for women or during spermatogenesis for men. Women with more anticonvulsant prescriptions and with non-phenobarbital anticonvulsant prescriptions were more likely to be exposed during pregnancy. More than two-thirds of the pregnancies among women with more than 10 prescriptions were labelled as

exposed during pregnancy. For those women with two or more types of anticonvulsant prescription, 254 (78%) were labelled as exposed during pregnancy; with one type other than phenobarbital 40 (66%); and for phenobarbital only 54 (72%). Among women with four to ten anticonvulsant prescriptions, 69 (26%) were labelled as exposed during pregnancy, while for those with three or fewer prescriptions, 11% or less were categorized as exposed. The pattern for exposed fathers was similar. Among women, the most common anticonvulsant history was one prescription for phenobarbital. Although only 8.4 percent were exposed during pregnancy, this accounted for 148 exposures during pregnancy.

Table 5.4.3 presents number of pregnancies where there is a high probability that the parent is epileptic based on the anticonvulsant history. Where the mother's history is not restricted to phenobarbital, there are 328 (91%) of the exposed pregnancies where there is a high probability that the mother is epileptic. Where phenobarbital is the only anticonvulsant, more than 10 prescriptions were dispensed for 85 (30%) of the women assessed as exposed in pregnancy. The pattern is again similar for fathers.

All hospital recorded pregnancies between January 1977 and March 31, 1984 in Saskatchewan were eligible for the study and therefore one woman could have more than one recorded pregnancy outcome in the study. Table 5.4.4 categorises the pregnancies among the parents with an anticonvulsant history during the study. About two-thirds of the pregnancies outcomes in this group are the first to be recorded for the mother (under her current RBN) during the study period.

Table 5.4.5 describes the age and parity distributions in the linked dataset. There are no substantial differences in age or parity distribution between the women without a history of anticonvulsant use between 1976 and 1983, those with a history but no first trimester exposure and those assessed to be exposed to anticonvulsants during the first trimester.

To summarise this series of tables:

1) Women were assessed to be likely to be taking (i.e. likely to be "exposed to") anticonvulsants in the first trimester of pregnancy (based on the dispensing pattern) in 359 (37%) of the pregnancies where the women had a history of anticonvulsant use which included anticonvulsants other than phenobarbital and in 276 (12%) of pregnancies where only a phenobarbital history existed.

2) 70% of the women exposed during any part of pregnancy received more than 10 anticonvulsant prescriptions between 1976 and 1983.

3) the prescription histories suggested epilepsy in 91% of the women exposed during the first trimester and with a history including anticonvulsants other than phenobarbital.

4) two-thirds of the pregnancies among the exposed women were the first to be recorded through hospitalization in the study period.

5) the distribution of mother's age and parity was similar for the exposed women, those with a history of anticonvulsant but not exposed, and those women with no anticonvulsant prescriptions recorded.

It also became apparent that the large number of women with some anticonvulsant prescription history between 1976 and 1983 but no first trimester exposure formed an extremely heterogeneous group regarding anticonvulsant history and that it would be difficult to predict epilepsy status from this history alone. The unexposed women were put in a separate group for analysis but no further attempt was made to separate out which were epileptic.

Table 5.4.1

Hospital recorded pregnancy outcomes in Saskatchewan 1977-1984 by exposure to anticonvulsants in 1st trimester or spermatogenesis period for parents with any anticonvulsant exposure 1976-1983

	Prescription history includes anticonvulsants other than phenobarbital*		Anticonvulsant history includes phenobarbital only		
	Exposed (%)**	Unexposed	Exposed (%)	Unexposed	Total
Mothers					
Not Livebirth	77 (46.4%)	89	36 (12.0%)	263	465
Livebirth	282 (34.9%)	525	240 (11.6%)	1824	2871
Total	359 (36.9%)	614	276 (11.7%)	2087	3336
Fathers					
Not Livebirth	33 (27.7%)	86	11 (17.7%)	51	181
Livebirth	236 (27.7%)	615	41 (10.8%)	339	1231
Total	269 (27.7%)	701	52 (11.8%)	390	1412

* phenobarbital may or may not also be present

** percents indicate percent exposed for an outcome, within a phenobarbital category

Table 5.4.2

Anticonvulsant exposure history and exposure during pregnancy in Saskatchewan 1976–1983

Anticonvulsant prescription history 1976–1983		Mother's anticonvulsant exposure during any part of pregnancy				Father's exposure during spermatogenesis window			
Total Rx	Types	Exposed	(%)	Not Exposed	Total	Exposed	(%)	Not Exposed	Total
11+ Rx	2 or more	254	(77.7%)	73	327	190	(77.2%)	56	246
11+ Rx	1 Anticonvulsant	40	(65.6%)	21	61	34	(55.7%)	27	61
11+ Rx	Phenobarbital only	54	(72.0%)	21	75	24	(64.9%)	13	37
4–10 Rx	2 or more	18	(21.2%)	67	85	9	(12.9%)	61	70
4–10 Rx	1 Anticonvulsant	19	(27.5%)	50	69	14	(16.5%)	71	85
4–10 Rx	Phenobarbital only	32	(28.3%)	81	113	6	(20.7%)	23	29
2–3 Rx	2 or more	7	(10.1%)	62	69	2	(2.7%)	72	74
2–3 Rx	1 Anticonvulsant	9	(11.4%)	70	79	6	(5.9%)	96	102
2–3 Rx	Phenobarbital only	43	(11.1%)	346	389	5	(8.6%)	53	58
1 Rx	1 Anticonvulsant	15	(5.4%)	264	279	14	(4.1%)	327	341
1 Rx	Phenobarbital only	148	(8.4%)	1605	1753	17	(5.3%)	301	318
Totals		639	(19.4%)	2660	3299	321	(22.6%)	1100	1421

Table 5.4.3

Hospital recorded pregnancy outcomes 1977–1984 by exposure to anticonvulsants in 1st trimester or spermatogenesis period for parents with a high probability of having epilepsy based on anticonvulsant exposure 1976–1983

Parents with any anticonvulsant history 1976–1983	Prescription history includes anticonvulsants other than phenobarbital*				Anticonvulsant history includes phenobarbital only				
	First trimester				First trimester				
	Exposed		Unexposed		Exposed		Unexposed		Total	
Pregnancies where prescription history suggests mother is likely to be epileptic										
Not Livebirth	63	(17.5%)	25	(4.1%)	14	(5.1%)	11	(0.5%)	113	(3.4%)
Livebirth	265	(73.8%)	186	(30.3%)	71	(25.7%)	89	(4.3%)	611	(18.3%)
Total where epilepsy is likely	328	(91.4%) **	211	(34.4%) **	85	(30.8%) **	100	(4.8%) **	724	(21.7%) **
Total Pregnancies	359	(100.0%)	614	(100.0%)	276	(100.0%)	2087	(100.0%)	3336	(100.0%)
Pregnancies where prescription history suggests father is likely to be epileptic										
Not Livebirth	31	(11.5%)	25	(3.6%)	6	(11.5%)	5	(1.3%)	67	(4.7%)
Livebirth	216	(80.3%)	190	(27.1%)	24	(46.2%)	31	(7.9%)	461	(32.6%)
Total where epilepsy is likely	247	(91.8%) **	215	(30.7%) **	30	(57.7%) **	36	(9.2%) **	528	(37.4%) **
Total Pregnancies	269	(100.0%)	701	(100.0%)	52	(100.0%)	390	(100.0%)	1412	(100.0%)

* phenobarbital may or may not also be present

** percent of total pregnancies in exposure category

Table 5.4.4

Pregnancy outcome number in study period by exposure to anticonvulsants in the 1st trimester or spermatogenesis period for pregnancies of parents with anticonvulsant prescriptions 1976–1983 including anticonvulsants other than phenobarbital

Livebirths	Exposed*		Unexposed		Total	
Mothers						
1st pregnancy in study period**	188	(66.6%)	387	(73.7%)	575	(71.3%)
Not 1st pregnancy in study period	94	(33.3%)	138	(26.3%)	232	(28.7%)
Total	282	(100.0%)	525	(100.0%)	807	(100.0%)
Fathers						
1st pregnancy in study period**	147	(62.3%)	432	(70.2%)	579	(68.0%)
Not 1st pregnancy in study period	89	(37.7%)	183	(29.8%)	272	(32.0%)
Total	236	(100.0%)	615	(100.0%)	851	(100.0%)

* phenobarbital may or may not also be present

** the pregnancy is the first to be recorded during the study period for a man or woman under this Registered Benefit Number

Table 5.4.5

Age and parity distributions in the linked Saskatchewan Health Services Plan dataset by anticonvulsant history and first trimester exposure

	No anticonvulsant history 1976–1983		Mother has some anticonvulsant prescription history 1976–1983			
			1st trimester anticonvulsant exposure		No 1st trimester anticonvulsant exposure	
	Number	(%)	Number	(%)	Number	(%)
Age						
<20	13,359	(11.9%)	56	(8.8%)	240	(8.9%)
20–24	38,557	(34.4%)	233	(36.7%)	1,059	(39.2%)
25–29	38,805	(34.6%)	226	(35.6%)	898	(33.2%)
30–34	16,236	(14.5%)	91	(14.3%)	346	(12.8%)
35+	5,264	(4.7%)	29	(4.6%)	158	(5.8%)
Total Pregnancies	112,220	(100.0%)	635	(100.0%)	2,701	(100.0%)
Parity						
0	41,876	(41.2%)	202	(38.7%)	762	(32.4%)
1	30,496	(30.7%)	167	(32.0%)	817	(34.7%)
2	15,879	(16.0%)	86	(16.5%)	445	(18.9%)
3+	10 930	(12.0%)	68	(12.8%)	325	(13.9%)
Total livebirths	99,181	(100.0%)	523	(100.0%)	2,349	(100.0%)

5.5 Anticonvulsant exposure and congenital anomaly risk

In Table 5.5.1, the risks of congenital anomalies are presented for mothers and fathers with any history of anticonvulsant use according to whether they had been categorised as exposed or not exposed during the first trimester for mothers or spermatogenesis period for fathers. Throughout the analysis, pregnancies of parents with no record of an anticonvulsant prescription being dispensed between 1976 and 1983 (under the RBN at the time of the pregnancy outcome) are used as the referent group. Offspring of fathers exposed to anticonvulsants during the spermatogenesis period showed no significant difference in risk from offspring of parents who had no recorded history of anticonvulsant exposure (RR 0.86, 95% CI 0.35-1.78). Women not exposed to anticonvulsants during the first trimester but with some recorded anticonvulsant exposure had a risk close to one (RR 1.09, 95% CI 0.86-1.37). Offspring of mothers exposed to anticonvulsants during the first trimester experienced a slightly elevated but not statistically significant increase in risk (RR 1.24, 95% CI 0.75-1.94).

In Table 5.5.2, the risk of congenital anomalies is categorized by the number of types of anticonvulsants the parent was using during the window of interest. The anticonvulsants were prescribed in monotherapy among 378 (72%) of pregnancies ending in livebirth, as two-drug therapy in 118 livebirths, as three-drug therapy for 23 livebirths and as four-drug therapy for two livebirths. Among exposed women the congenital anomaly risk with one anticonvulsant was 1.18, with two types of anticonvulsants 0.87, and with three 4.10, although the last estimate is based on only 3 anomaly cases among 25 livebirths. A test for linear trend in proportions for the gradient of RR over the number of types of anticonvulsants used during the first trimester was not significant (Chi-square .909, P =.34). Among exposed fathers there were only 7 exposed cases, resulting in very wide confidence intervals and no strong pattern of risk was evident.

Table 5.5.2 also presents the risks of heart anomalies and cleft lip and/or cleft palate. The small number of cases, due to the low prevalence of these conditions and the size

of the exposed population, limits interpretation. Five infants with heart anomalies were observed among the women treated with one anticonvulsant during the first trimester (RR 2.70, 95% CI 0.87-6.34). A heart anomaly and a facial cleft in different infants were observed among the 25 livebirths where the woman had been exposed to three anticonvulsants in the first trimester, resulting in high unstable risk estimates for both conditions. No heart anomalies or facial clefts were seen among the livebirths of fathers exposed to anticonvulsants.

The specific anticonvulsants to which women were exposed during the first trimester of pregnancies that ended in livebirths are presented in Table 5.5.3. More than half of the anticonvulsant exposures (394 of 695) were to phenobarbital, one-quarter (178) were to phenytoin, while the other six prescribed anticonvulsants accounted together for less than a fifth of exposures. Among exposed men, phenytoin was the anticonvulsant used most often accounting for 191 (45%) of the 429 exposures, followed by phenobarbital which accounted for 156 (36%) of the exposures (see Table 5.5.4). Other anticonvulsants accounted for only 82 exposures and, as was the case for the women, accounted for less than 20% of the total exposures.

Four of the anticonvulsants were associated with increased anomaly risk among exposed women. The risk associated with phenytoin was 1.92 (95% CI 0.92-3.54). Primidone had an elevated RR of 4.46 (95% CI, 0.92-13.05). Other anticonvulsants had elevated risks but the outcomes were based on only one case. Phenytoin and primidone were associated with high heart anomaly risks and high facial cleft risks, but only the phenytoin heart anomaly risk was based on more than one case. Among the offspring of men with exposure to anticonvulsants during the spermatogenesis period, none of the anticonvulsants were associated with significantly elevated risks, and no heart anomalies or cleft lip and/or palates were observed. (See Table 5.5.4.)

Because the anticonvulsants were often used in combination and the risk was related to the number of anticonvulsants used, the risks for each anticonvulsant are further

categorized in Table 5.5.5 by whether the anticonvulsant was used alone or in combination with one or more other anticonvulsants. Phenobarbital was used alone in 269 exposed women, phenobarbital plus phenytoin was the most common two-drug therapy, and the combination of phenobarbital, phenytoin and carbamazepine accounted for the majority of three-drug therapies.

In Table 5.5.6, a complete list of combinations of anticonvulsants and livebirth, non-livebirth and congenital malformation counts is presented for women on anticonvulsants during the first trimester. Most specific combinations were used so rarely that little evaluation of risk is possible and therefore confidence intervals are not presented. If an anomaly is observed the risk is very high, otherwise the estimated risk is zero. The most striking risk is that for the combination of phenobarbital, phenytoin and primidone. Among the four livebirths whose mothers were exposed to this combination, two of the offspring had congenital anomalies - one heart anomaly and one facial cleft. Table 5.5.7 lists the specific anomalies reported and the specific first trimester anticonvulsant therapies.

Table 5.5.1

Congenital anomaly risk in Saskatchewan 1977–1984 by anticonvulsant exposure during the 1st trimester of pregnancy or spermatogenesis period

Parent's anticonvulsant prescription history 1976–1983	1st trimester or spermatogenic exposure	Number of livebirths	Congenital anomaly cases			
			Number of cases	Rate per 1,000 livebirths	Relative risk	(95% CI)
None		99,181	2,900	29.2	1.00	
Mothers						
	No	2,349	75	31.9	1.09	(0.86–1.37)
	Yes	523	19	36.3	1.24	(0.75–1.94)
Fathers						
	No	954	29	30.4	1.04	(0.70–1.50)
	Yes	277	7	25.3	0.86	(0.35–1.78)

Table 5.5.2

Selected congenital anomalies risks in Saskatchewan 1977–1984 by the number of types of anticonvulsants used in the 1st trimester or spermatogenesis period

Parent's anticonvulsant prescription history 1976-1983	Number of types of anticonvulsants-1st trimester or spermatogenesis	Livebirths (LB)	Congenital Anomaly Cases				Congenital heart defect cases				Cleft lip/palate cases			
				Rate				Rate				Rate		
		No.	No.	/1000 LB	RR	95 % CI	No.	/1000 LB	RR	95 % CI	No.	/1000 LB	RR	95 % CI
None	0	99,181	2,900	29.2	1.00	(0.96-1.04)	486	4.9	1.00	(0.91-1.09)	182	1.8	1.00	(0.86-1.16)
Mother	0	2,349	75	31.9	1.09	(0.86-1.37)	15	6.4	1.30	(0.72-2.17)	6	2.6	1.39	(0.50-3.09)
	1	378	13	34.4	1.18	(0.63-2.01)	5	13.2	2.70	(0.87-6.34)	0	0.0	0.00	(0.00-5.37)
	2	118	3	25.4	0.87	(0.17-2.49)	0	0.0	0.00	(0.00-6.40)	0	0.0	0.00	(0.00-17.21)
	3	25	3	120.0	4.10	(0.85-12.01)	1	40.0	8.16	(0.21-45.70)	1	40.0	21.80	(0.55-122.99)
	4	2	0	0.0	0.00	---	0	0.0	0.00	---	0	0.0	0.00	---
					*				**				***	
Father	0	954	29	30.4	1.04	(0.70-1.49)	3	3.1	0.64	(0.13-1.89)	1	1.0	0.57	(0.01-3.22)
	1	144	4	27.8	0.95	(0.26-2.44)	0	0.0	0.00	(0.00-5.25)	0	0.0	0.00	(0.00-14.10)
	2	112	2	17.9	0.61	(0.07-2.21)	0	0.0	0.00	(0.00-6.75)	0	0.0	0.00	(0.00-18.13)
	3	21	1	47.6	1.63	(0.04-9.08)	0	0.0	0.00	(0.00-35.98)	0	0.0	0.00	(0.00-96.70)

* Test for linear trend in proportions across number of types of anticonvulsants for mothers. Chi-square = 1.994, P = 0.153.

** Test for linear trend in proportions across number of types of anticonvulsants for mothers. Chi-square = 4.896, P = 0.027.

*** Test for linear trend in proportions across number of types of anticonvulsants for mothers. Chi-square = 1.185, P = 0.276.

Table 5.5.3

Selected congenital anomalies risks in Saskatchewan 1977–1984 by mother's first trimester anticonvulsant exposures

1st Trimester anticonvulsants	Livebirths	Congenital anomaly cases				Heart anomaly cases				Cleft lip/palate cases			
	No.	No.	Rate /1000 LB**	RR	95 % CI	No.	Rate /1000 LB	RR	95 % CI	No.	Rate /1000 LB	RR	95 % CI
No anticonvulsant history 1976–1983*	99,181	2,900	29.2	1.00	(0.97–1.03)	486	4.9	1.00	(0.91–1.09)	182	1.7	1.00	(0.86–1.16)
PHB***	394	13	33.0	1.13	(0.60–1.93)	3	7.6	1.55	(0.32–4.57)	1	2.5	1.54	(0.03–7.81)
DPH	178	10	56.2	1.92	(0.92–3.54)	4	22.5	4.59	(1.24–11.82)	1	5.6	3.40	(0.09–16.72)
CBZ	66	0	0.0	0.00	(0.00–1.99)	0	0.0	0.00	(0.00–11.45)	0	0.0	0.00	(0.00–30.77)
PRM	23	3	130.4	4.46	(0.92–13.05)	1	43.5	8.87	(0.22–49.67)	1	43.5	26.35	(0.60–133.68)
SUX	18	0	0.0	0.00	(0.00–7.01)	0	0.0	0.00	(0.00–41.98)	0	0.0	0.00	(0.00–112.82)
VPA	12	1	83.3	2.85	(0.07–15.89)	0	0.0	0.00	(0.00–62.97)	0	0.0	0.00	(0.00–169.23)
TRM	3	1	333.3	11.40	---	0	0.0	0.00	---	0	0.0	0.00	---
CLN	1	0	0.0	0.00	---	0	0.0	0.00	---	0	0.0	0.00	---

* Referent group for all relative risks is livebirths where parent's prescription history 1976–1983 includes no anticonvulsants.

** LB – livebirths

*** PHB – Phenobarbital; DPH – Phenytoin; PRM – Primidone; VPA – Valproic acid;
CBZ – Carbamazepine; TRI – Trimethadione; SUX – Ethosuximide

Table 5.5.4

Congenital anomalies risk in Saskatchewan 1977–1984 by father's exposure to anticonvulsants during the spermatogenesis period

1st Trimester anticonvulsants	Livebirths	Total anomaly cases				Heart anomalies				Cleft lip/palate			
	No.	No.	Rate /1000 LB**	RR	95 % CI	No.	Rate /1000 LB	RR	95 % CI	No.	Rate /1000 LB	RR	95 % CI
No anticonvulsant history 1976-1983*	99,181	2,900	29.2	1.00	(0.97–1.03)	486	4.4	1.00	(0.91–1.09)	182	1.7	1.00	(0.86–1.16)
PHB	156	4	25.6	0.88	(0.30–1.97)	0	0.0	0.00	(0.00–4.84)	0	0.0	0.00	(0.00–13.02)
DPH	191	6	31.4	1.07	(0.42–2.15)	0	0.0	0.00	(0.00–3.96)	0	0.0	0.00	(0.00–10.63)
CBZ	39	0	0.0	0.00	(0.00–3.24)	0	0.0	0.00	(0.00–19.38)	0	0.0	0.00	(0.00–52.07)
PRM	34	1	29.4	1.15	(0.03–5.61)	0	0.0	0.00	(0.00–22.23)	0	0.0	0.00	(0.00–59.73)
SUX	2	0	0.0	0.00	(0.00–52.38)	0	0.0	0.00	---	0	0.0	0.00	---
VPA	5	0	0.0	0.00	(0.00–20.45)	0	0.0	0.00	---	0	0.0	0.00	---
CLN	2	0	0.0	0.00	(0.00–52.38)	0	0.0	0.00	---	0	0.0	0.00	---

* Referent group for all relative risks is livebirths where parent's prescription history 1976–1983 includes no anticonvulsants.

** LB = livebirths

Table 5.5.5

Congenital anomalies risk in Saskatchewan 1977–1984 by mother's number of types of 1st trimester anticonvulsant exposure

1st Trimester anticonvulsant exposure	Monotherapy (specified anticonvulsant alone)					Two anticonvulsants (specified anticonvulsant & 1 other)					Three anticonvulsants (specified anticonvulsant & 2 others)				
	LB**	CA***	Rate /1000 LB	RR	95 % CI	LB	CA	Rate /1000 LB	RR	95 % CI	LB	CA	Rate /1000 LB	RR	95 % CI
No anticonvulsant history 1976-1983*	99,181	2,900	29.2	1.00											
PHB****	269	7	26.0	0.89	(0.36–1.84)	100	3	30.0	1.03	(0.21–3.00)	23	3	130.4	4.47	(0.92–13.05)
DPH	61	5	82.0	2.81	(0.91–6.55)	93	2	21.5	0.74	(0.99–2.66)	22	3	136.4	4.67	(0.96–13.64)
CBZ	30	0	0.0	0.00	(0.00–4.21)	17	0	0.0	0.00	(0.00–7.43)	19	0	0.0	0.00	(0.00–6.64)
PRM	12	1	83.3	2.85	(0.07–15.89)	7	0	0.0	0.00	---	4	2	500.0	17.12	(2.07–61.83)
SUX	2	0	0.0	0.00	---	13	0	0.0	0.00	(0.00–9.71)	3	0	0.0	0.00	---
VPA	4	0	0.0	0.00	---	5	0	0.0	0.00	---	1	1	1000.0	0.00	---
TRI	0	0	0.0	0.00	---	1	1	1000.0	0.00	---	2	0	0.0	0.00	---
CLN	0	0	0.0	0.00	---	0	0	0.0	0.00	---	1	0	0.0	0.00	---

* Referent group for all relative risks is livebirths where parent's prescription history 1976–1983 includes no anticonvulsants.

** LB = livebirths

*** CA = Congenital anomaly cases

**** PHB – Phenobarbital; DPH – Phenytoin; CBZ – Carbamazepine; PRM – Primidone; SUX – Ethosuximide; VPA – Valproic acid; TRI – Trimethadione; CLN –Clonazepam

Table 5.5.6

Mother's specific 1st trimester anticonvulsant exposure and selected malformation risks

Mother's anticonvulsants during 1st trimester	Livebirths	Non livebirth outcomes	RR*	Congenital anomaly cases	RR	Congenital heart defect cases	RR	Cleft lip/palate cases	RR
No anticonvulsant history 1976–1983	99,181	13,039	1.0	2,900	1.0	486	1.0	182	1.0
Anticonvulsant history but no anticonvulsant exposure during 1st trimester	2,349	352	1.1	75	1.1	15	1.3	6	1.4
PHB **	269	41	1.1	7	0.9	2	1.5	0	0.0
DPH	61	13	1.5	5	2.8	3	10.0	0	0.0
CBZ	30	6	1.4	0	0.0	0	0.0	0	0.0
PRM	12	5	2.5	1	2.9	0	0.0	0	0.0
VPA	4	0	0.0	0	0.0	0	0.0	0	0.0
SUX	2	3	5.2	0	0.0	0	0.0	0	0.0
CLN	0	2	8.6	0	0.0	0	0.0	0	0.0
PHB+DPH	80	23	1.9	2	0.9	0	0.0	0	0.0
PHB+SUX	10	4	2.5	0	0.0	0	0.0	0	0.0
PHB+CBZ	8	2	1.7	0	0.0	0	0.0	0	0.0
PHB+PRM	1	0	0.0	0	0.0	0	0.0	0	0.0
PHB+VPA	1	0	0.0	0	0.0	0	0.0	0	0.0
DPH+PRM	6	3	2.9	0	0.0	0	0.0	0	0.0
DPH+CBZ	4	3	3.7	0	0.0	0	0.0	0	0.0
DPH+VPA	1	1	4.3	0	0.0	0	0.0	0	0.0
DPH+TRI	1	0	0.0	1	34.2	0	0.0	0	0.0
DPH+SUX	1	0	0.0	0	0.0	0	0.0	0	0.0
CBZ+VPA	3	0	0.0	0	0.0	0	0.0	0	0.0
CBZ+PRM	0	2	8.6	0	0.0	0	0.0	0	0.0
CBZ+SUX	2	0	0.0	0	0.0	0	0.0	0	0.0
CBZ+CLN	0	2	8.6	0	0.0	0	0.0	0	0.0
PHB+DPH+CBZ	14	0	0.0	0	0.0	0	0.0	0	0.0
PHB+DPH+PRM	4	1	1.7	2	17.1	1	51.0	1	136.2
PHB+DPH+TRM	2	0	0.0	0	0.0	0	0.0	0	0.0
PHB+DPH+VPA	1	1	4.3	1	34.2	0	0.0	0	0.0
SUX+PHB+VPA	1	0	0.0	0	0.0	0	0.0	0	0.0
CBZ+DPH+PRM	2	0	0.0	0	0.0	0	0.0	0	0.0
CBZ+CLN+SUX	1	0	0.0	0	0.0	0	0.0	0	0.0
CBZ+PHB+PRM	0	1	8.6	0		0	0.0	0	0.0
PHB+DPH+PRM+CBZ	1	0	0.0	0	0.0	0	0.0	0	0.0
PHB+DPH+CBZ+SUX	1	0	0.0	0	0.0	0	0.0	0	0.0
Exposed Totals	523	113	1.5	19	1.2	6	2.3	1	1.0

* RR – Relative risk

** PHB – Phenobarbital; DPH – Phenytoin; PRM – Primidone; VPA – Valproic acid; CLN – Clonazepam; CBZ – Carbamazepine; TRI – Trimethadione; SUX – Ethosuximide

Table 5.5.7

Congenital malformation cases among the offspring of women exposed to anticonvulsants during pregnancy or with recorded anticonvulsant exposure other than to phenobarbital between 1976 and 1983 in Saskatchewan

Year	Sex	1st trimester anticonvulsant exposure **	ICD-9 Codes	Congenital anomaly descriptions
77	F	None	7454,7492	Ventricular septal defect, cleft lip and palate
77	M	None	7505	Pyloric stenosis
77	M	None	7505	Pyloric stenosis
79	M	None	7547,Death	Other feet deformities
80	M	None	7543,7505	Congenital hip dislocation, pyloric stenosis
82	M	None	7468,7566	Other heart anomalies, anomalies of the diaphragm
77	M	PHB	7556	Other anomalies of the lower limb
77	M	PHB	7555	Other anomalies of the upper limb
78	F	PHB	7546	Valgus deformities of feet
79	M	PHB	7515	Other anomalies of the intestine
81	F	PHB	7421	Microcephalus
81	F	PHB	7451	Transposition of great vessels
82	F	PHB	7410	Spina bifida with hydrocephalus
79	M	DPH	7468	Other specified heart anomalies
81	F	DPH	7469,7470,7471,Death	Coarctation of aorta, patent ductus arteriosus
82	M	DPH	7454	Ventricular septal defect
83	M	DPH	7423	Congenital hydrocephalus
83	M	DPH	7505	Pyloric stenosis
81	F	PRM	7597	Multiple congenital malformations
78	M	PHB+TRI	7526	Hypospadias or epispadias
80	M	PHB+DPH	7505	Pyloric stenosis
80	M	PHB+DPH	7512,7558,7569,7597	Atresia and stenosis of rectum, unspecified musculo-skeletal, other specified anomalies of unspecified limb, multiple congenital anomalies
78	F	PHB+DPH+PRM	7454	Ventricular septal defect, gastroenteritis
80	F	PHB+DPH+PRM	7491	Cleft lip
83	M	PHB+DPH+VPA	7550	Polydactly

* M=Male; F=Female

** PHB – Phenobarbital; DPH – Phenytoin; PRM – Primidone; VPA – Valproic acid; CLN – Clonazepam; CBZ – Carbamazepine; TRI – Trimethadione; SUX – Ethosuximide

5.6 Logistic regression analysis

The variables listed in Table 5.6.1. were used to build a logistic model with the occurrence of a congenital malformation as the dependent variable. Variables were entered describing the women's anticonvulsant histories as a proxy for epilepsy but none of these demonstrated explanatory value when first trimester drug exposure variables were in the model. When the individual drugs were entered, trimethadione, primidone and phenytoin each improved the precision of the model. However, a model including only the number of types of anticonvulsants provided a model of almost the same precision. When the three drugs and the number of types of anticonvulsants term were entered into the model, collinearity between the variables reduced the predictive power of each term. When interaction terms were added, the model fitting procedure failed to converge.

Table 5.6.1

Variables used in the logistic regression analysis of 1st trimester anticonvulsant therapy and congenital anomalies in Saskatchewan 1977–1984

LOGISTIC REGRESSION

DEPENDENT VARIABLE: Congenital Malformation Case (Y/N)

INDEPENDENT VARIABLES:

- 1976–1983 anticonvulsant history:
  - phenobarbital only (Y/N)
  - # of types of anticonvulsant
  - # of anticonvulsant Rx total
- first trimester exposure:
  - phenobarbital
  - phenytoin
  - carbamazepine
  - trimethadione
  - primidone
  - valproate
  - number of types of anticonvulsants

5.7 Non-livebirth pregnancy outcomes

The distribution of non-livebirth pregnancy outcomes in Saskatchewan that involved hospital admission (data on outpatients was not available) is presented in Table 5.7.1, stratified by the anticonvulsant use history and first trimester or spermatogenesis period anticonvulsant exposure status. Non-livebirth pregnancy outcomes accounted for 465 (13%) of the 3,336 pregnancy outcomes reported for women with any history of anticonvulsant use in the eight-year study period. Induced abortion accounted for about 10 percent of the total pregnancy outcomes, spontaneous abortion three percent, ectopic pregnancies one percent and stillbirths under one percent. Induced abortions were slightly more common among anticonvulsant exposed than non-exposed women. The data are generally unremarkable except for the number of ectopic pregnancies among the women exposed to anticonvulsants other than phenobarbital. Although only based on 11 cases the estimated risk is three-fold higher than that in each of the other exposure groups.

Tables 5.7.2 through 5.7.7 present counts and risk estimates for the non-livebirth outcomes combined and then each separately, stratified by mothers' and fathers' history of anticonvulsant exposure 1976-1983 and by the number of types of anticonvulsants dispensed in the first trimester or spermatogenesis period. Non-livebirth pregnancy outcomes as a group were more common in exposed mothers than those with no history of anticonvulsant use. There was a gradient of risk for the number of types of anticonvulsants to which a mother was exposed. Treatment with two anticonvulsants during the first trimester was associated with a more than doubling of the risk of a non-livebirth pregnancy outcome compared to women without a history of anticonvulsant exposure (RR 2.18, 95% CI 1.67-2.86). The test for linear trend in proportions across the number of types of anticonvulsants during the first trimester was highly significant (chi-square = 27, P=0.000).

Spontaneous abortions were reported about 30% more often among women with a history

of anticonvulsant exposure but there was no difference in risk between those with and without first trimester exposure. Spontaneous abortions were not more common where the father had a history of anticonvulsant exposure than among women where neither parent had a history of anticonvulsant use. Induced abortions were performed more commonly on a hospital inpatient basis among women treated with anticonvulsants during the first trimester. Women taking two anticonvulsants during the first trimester had a statistically significant elevated RR of 2.20 (95% CI 1.56-3.10). Interpretation of spontaneous abortion and induced abortion data is difficult because induced abortion is often done on an outpatient basis and most spontaneous abortions occur outside of hospital. Differences in the management of epileptic women would seem a reasonable explanation for the observed associations but data unavailable in this study would be required to evaluate this explanation.

Stillbirths were seriously under-reported before 1980 because of ICD-8 to ICD-9 equivalencing problems and this accounts for the low overall observed rate. Stillbirth risk was not elevated among women with first trimester anticonvulsant treatment, but the risk was double (RR 1.94, 95% CI 1.23-2.91) among women not treated during pregnancy but who had been dispensed anticonvulsants between 1976 and 1983. Stillbirth was more common among pregnancies where the father was on anticonvulsant therapy during the spermatogenesis period but the elevated risks were based on only 4 cases.

Ectopic pregnancy risk was not elevated among women with a history of anticonvulsant use but with no anticonvulsant therapy in early pregnancy, nor among women on one anticonvulsant in early pregnancy. However, two-drug therapy was associated with a five-fold, statistically significant elevation in risk (RR 5.74, 95% CI 2.63-10.12.7), although it was based on only nine cases with two-drug treatment. Table 5.7.7 examines ectopic pregnancy risk by the type and number of anticonvulsants with which a woman was treated during the 42-day period that an average ectopic pregnancy lasts. When used in combination with another anticonvulsant, most of the anticonvulsants were associated

with elevated risk, although none of these were associated with substantially increased risk in monotherapy.

Table 5.7.1

Specific hospital recorded pregnancy outcomes in Saskatchewan 1977–1984 by exposure to anticonvulsants in 1st trimester for parents with any anticonvulsant exposure 1976–1983

	Prescription history includes anticonvulsants other than phenobarbital*				Anticonvulsant history includes phenobarbital only					
	Exposed		Unexposed		Exposed		Unexposed		Total	
	Number	(%)**	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Induced Abortion	52	(14.5%)	62	(10.1%)	26	(9.4%)	155	(7.4%)	295	(8.8%)
Spontaneous Abortion	13	(3.6%)	17	(2.8%)	6	(2.2%)	68	(3.3%)	104	(3.1%)
Ectopic Pregnancy	11	(3.1%)	6	(1.0%)	3	(1.1%)	21	(1.0%)	41	(1.2%)
Stillbirth	1	(0.3%)	4	(0.7%)	1	(0.4%)	19	(0.9%)	25	(0.7%)
Total Pregnancy Outcomes	359	(100.0%)	614	(100.0%)	276	(100.0%)	2,087	(100.0%)	3,336	(100.0%)

* phenobarbital may or may not also be present

** percent of total pregnancy outcomes within phenobarbital and 1st trimester exposure category

Table 5.7.2

Risk of non-livebirths outcomes in Saskatchewan 1977-1984 by exposure to anticonvulsants in the 1st trimester or spermatogenesis period

Parent's anticonvulsant Rx history 1976-1983	Number of types of anticonvulsants-1st trimester or spermatogenesis		Non-livebirths			
		NLB+LB*	No.	Rate/1000 NLB+LB	RR	95 % CI
None	0	112,220	13,039	116.2	1.00	
Mother	0	2,701	352	130.3	1.12	(1.02-1.24)
	1	448	70	156.3	1.34	(1.08-1.67)
	2	158	40	253.2	2.18	(1.67-2.86)
	3	28	3	107.1	0.92	(0.18-3.00)
	4	2	0	---	---	(0.00-40.58)
				**		
Father	0	1,091	137	125.6	1.08	(0.92-1.26)
	1	174	30	172.4	1.48	(1.07-2.06)
	2	128	14	111.1	0.96	(0.58-1.57)
	3	21	0	0.0	0.0	(0.00-1.46)

* LB=livebirths, NLB = non-livebirth pregnancy outcomes reported through hospital admission-discharge summaries

** Test for linear trend across number of types of anticonvulsants for mothers: Chi-square = 27.792, P = 0.000.

Table 5.7.3

Risk of spontaneous abortion in Saskatchewan 1977–1984 by exposure to anticonvulsants in the 1st trimester or spermatogenesis period

Parent's anticonvulsant Rx history 1976–1983	Number of types of anticonvulsants–1st trimester or spermatogenesis		Spontaneous abortion			
		NLB+LB*	No.	Rate/1000 NLB+LB	RR	95 % CI
None	0	112,220	2,704	24.1	1.00	
Mother	0	2,701	85	31.5	1.31	(1.06–1.62)
	1	448	15	33.5	1.39	(0.84–2.29)
	2	158	4	25.3	1.05	(0.28–2.79)
	3	28	0	0.0	0.0	(0.00–5.77)
	4	2	0	0.0	0.0	(0.00–>100)
					**	
Father	0	1,091	27	24.7	1.03	(0.71–1.49)
	1	174	5	28.7	1.19	(0.50–2.83)
	2	128	1	7.9	0.33	(0.01–1.86)
	3	21	0	0.0	0.0	(0.00–7.86)

* LB=livebirths, NLB = non-livebirth pregnancy outcomes reported through hospital admission-discharge summaries

** Test for linear trend across number of types of anticonvulsants for mothers: Chi-square = 4.251, P = 0.039.

Table 5.7.4

Risk of induced abortion in Saskatchewan 1977–1984 by exposure to anticonvulsants in the 1st trimester or spermatogenesis period

Parent's anticonvulsant Rx history 1976–1983	Number of types of anticonvulsants–1st trimester or spermatogenesis		Induced abortions			
		NLB+LB*	No.	Rate/1000 NLB+LB	RR	95 % CI
None	0	112,220	8,729	77.8	1.00	
Mother	0	2,701	217	80.3	1.03	(0.91–1.18)
	1	448	48	107.1	1.38	(1.05–1.80)
	2	158	27	170.9	2.20	(1.56–3.10)
	3	28	3	107.1	1.38	(0.27–4.67)
	4	2	0	0.0	0.0	(0.00–63.0)
					**	
Father	0	1,091	86	78.8	1.01	(0.83–1.24)
	1	174	22	126.4	1.63	(1.10–2.41)
	2	128	10	79.4	1.02	(0.56–1.85)
	3	21	0	0.0	0.0	(0.00–2.28)
					***	

* LB=livebirths, NLB = non-livebirth pregnancy outcomes reported through hospital admission-discharge summaries

** Test for linear trend across number of types of anticonvulsants for mothers: Chi-square = 13.703, P = 0.0002.

*** Test for linear trend across number of types of anticonvulsants for fathers: Chi-square = .638, P = 0.424.

Table 5.7.5

Risk of stillbirth in Saskatchewan 1977–1984 by exposure to anticonvulsants in the 1st trimester or spermatogenesis period

Parent's anticonvulsant Rx history 1976–1983	Number of types of anticonvulsants–1st trimester or spermatogenesis		Stillbirths			
		NLB+LB*	No.	Rate/1000 NLB+LB	RR	95 % CI
None	0	112,220	493	4.4	1.00	
Mother	0	2,701	23	8.5	1.94	(1.28–2.94)
	1	448	2	4.5	1.02	(0.12–3.91)
	2	158	0	0.0	0.0	(0.00–5.59)
	3	28	0	0.0	0.0	(0.00–33.23)
	4	2	0	0.0	0.0	(0.00–>100)
Father	0	1,091	5	4.6	1.04	(0.33–2.62)
	1	174	3	17.2	3.92	(0.79–12.57)
	2	128	1	7.9	1.81	(0.04–10.82)
	3	21	0	0.0	0.0	(0.00–45.22)
					**	

* LB=livebirths, NLB = non-livebirth pregnancy outcomes reported through hospital admission-discharge summaries

** Test for linear trend across number of types of anticonvulsants for fathers: Chi-square = 2.212, P = 0.137.

Table 5.7.6

Risk of ectopic pregnancy in Saskatchewan 1977–1984 by exposure to anticonvulsants in the 1st trimester or spermatogenesis period

Parent's anticonvulsant Rx history 1976–1983	Number of types of anticonvulsants–1st trimester or spermatogenesis	NLB+LB*	Ectopics No.	Rate/1000 NLB+LB	RR	95 % CI
None	0	112,220	1,114	9.9	1.00	
Mother	0	2,701	27	10.0	1.01	(0.63–1.55)
	1	448	5	11.2	1.12	(0.33–2.73)
	2	158	9	57.0	5.74	(2.63–12.17)
	3	28	0	0.0	0.0	(0.00–14.27)
	4	2	0	0.0	0.0	(0.00–>100)
					**	
Father	0	1,091	19	17.4	1.75	(1.02–2.91)
	1	174	0	0.0	0.00	(0.00–2.17)
	2	128	2	15.9	1.60	(0.19–6.08)
	3	21	0	0.0	0.0	(0.00–19.44)

* LB=livebirths, NLB = non-livebirth pregnancy outcomes reported through hospital admission-discharge summaries

** Test for linear trend across number of types of anticonvulsants for mothers: Chi-square = 7.879, P = 0.005.

Table 5.7.7

Ectopic pregnancy risk in Saskatchewan 1977–1984 by mother's type of first trimester anticonvulsant exposure

1st Trimester Anticonvulsant exposure	Monotherapy (specified anticonvulsant alone)					Two anticonvulsants (specified anticonvulsant & 1 other)					Three anticonvulsants (specified anticonvulsant & 2 others)				
	LB**	Ectopic pregnancy	Rate /1000 LB+E	RR	95 % CI	LB	Ectopic pregnancy	Rate /1000 LB+E	RR	95 % CI	LB	Ectopic pregnancy	Rate /1000 LB+E	RR	95 % CI
No anticonvulsant history 1976-1983*	99,181	1,114	11.1												
PHB	269	4	14.7	1.32	(0.36–3.40)	125	5	38.5	3.46	(1.12–8.10)	23	0	0.0	0.00	(0.00–14.46)
DPH	61	1	16.1	1.45	(0.04–8.11)	95	6	59.4	5.35	(1.96–11.68)	22	0	0.0	0.00	(0.00–16.73)
PRM	14	0	0.0	0.00	(0.00–23.7)	7	2	222.2	20.01	(2.42–72.44)	4	0	0.0	0.00	(0.00–>100)
CBZ	30	0	0.0	0.00	(0.00–11.1)	17	2	105.3	9.48	(1.15–34.31)	19	0	0.0	0.00	(0.00–17.52)
CLN	0	0	–	–	–	0	1	1000.0	90.03	(2.28–>100)	1	0	0.0	0.00	(0.00–>100)
TRI	0	0	–	–	–	1	0	0.0	0.00	(0.00–>100)	2	0	0.0	0.00	(0.00–>100)
SUX	2	0	0.0	0.00	(0.00–>100)	13	2	133.3	12.00	(1.45–43.47)	3	0	0.0	0.00	(0.00–>100)
VPA	5	0	0.0	0.00	(0.00–66.5)	6	0	0.0	0.00	(0.00–55.4)	1	0	0.0	0.00	(0.00–>100)

* Referent group for all relative risks is livebirths plus ectopic pregnancies where parent's prescription history 1976–1983 includes no anticonvulsants.

** LB = livebirths; E = Ectopics

5.8 Summary of Study Results

An essentially population-based database of maternal drug use and reproductive outcomes was created which included 104,534 livebirths and 13,685 non-livebirth outcomes occurring between April 1977 and March 1984 linked to 299,152 prescriptions dispensed to the mothers in the year preceding the pregnancy outcome. When the congenital anomaly birth prevalences in the dataset were compared with prevalences ascertained by generally similar methods through four birth defect monitoring systems in nearby provinces, deficits in overall prevalence of 9 to 49% were observed for the Saskatchewan dataset.

In the Saskatchewan database, women were assessed to be treated with (i.e. "exposed to") anticonvulsants in the first trimester of pregnancy of 522 livebirths and 106 non-livebirth pregnancy outcomes. Fathers in 321 pregnancies were assessed to be exposed during the spermatogenesis period. Offspring of mothers exposed to anticonvulsants during the first trimester experienced a slightly elevated but not statistically significant increase in risk compared to the standard referent group throughout this study--the offspring of parents with no anticonvulsant prescription history between 1976 and 1983 (RR 1.24, 95% CI 0.75-1.94). Among exposed women the congenital anomaly risk with one anticonvulsant was 1.18 (95% CI 0.63-2.01) (13 cases/378 exposed livebirths), with two types of anticonvulsants 0.87 (95% CI 0.17-2.49) (3/118), and with three types 4.10 (95% CI 0.85-12.01) (3/25).

Five infants with heart anomalies were observed among the women treated with one anticonvulsant during the first trimester (RR 2.70, 95% CI 0.87-6.34). A heart anomaly and a facial cleft in different infants were observed among the 25 livebirths where the women had been exposed to three anticonvulsants in the first trimester, resulting in high but unstable risk estimates for both conditions. No heart anomalies or facial clefts were seen among the livebirths of fathers exposed to anticonvulsants.

More than half of the anticonvulsant exposures (394 of 695) were to phenobarbital, one-quarter (178) were to phenytoin, while the other six prescribed anticonvulsants accounted together for less than a fifth of exposures. Elevated risks were associated with phenobarbital, phenytoin and primidone when used in three-anticonvulsant therapies. The risk of congenital anomalies associated with phenytoin overall was 1.92 (95% CI 0.92-3.54) and with primidone the RR was 4.46 (95% CI, 0.92-13.05). Thus the study yielded results with respect to congenital anomaly risk reasonably consistent with the conclusions of the meta-analyses.

An association, not previously reported in the literature, between anticonvulsant polytherapy and ectopic pregnancy was revealed in the dataset (RR 5.74, 95% CI 2.63-12.17 for therapy with two types of anticonvulsants early in pregnancy).

CHAPTER 6. DISCUSSION OF THE SASKATCHEWAN STUDY

6.1 Summary

This project provided the first detailed evaluation of the utility of Saskatchewan Health's drug and hospital databases for undertaking pharmacoepidemiology research into reproductive outcomes. A database of maternal drug use and reproductive outcomes including more than 100,000 livebirths, 16,000 non-livebirth outcomes, and almost 300,000 prescriptions dispensed in the year before the pregnancy outcomes was created. One of the largest studies to date of anticonvulsant use during pregnancy and selected reproductive outcomes was completed. The database of maternal drug use and reproductive outcomes and the epilepsy study were completed for approximately $60,000. However, two important limitations for using the databases for epidemiologic analysis became apparent. First, birth defect birth prevalences in the Saskatchewan dataset were substantially below those found in other provincial monitoring systems employing similar ascertainment strategies. Second, confidentiality policies which denied the researcher access to anonymized individual data records created a number of obstacles to doing proper epidemiologic research.

This discussion is divided into three parts:

1) The first section discusses technical strengths and limitations of using the Saskatchewan databases for reproductive outcome research in general, and the potential research implications for the present and future studies.

2) The second section addresses study limitations specific to the anticonvulsant study and examines how the present study findings compare with those of the meta-analyses.

3) The final section addresses the restrictive data access policies employed by

Saskatchewan Health and their implications for epidemiologic research.

6.2 Evaluation of the Saskatchewan Health databases for reproductive-outcome pharmacoepidemiology

Several advantages and limitations of using the Saskatchewan Health databases for pharmacoepidemiologic studies of reproductive outcomes came to light through this study. These factors are important for assessing the quality of the present study and would be applicable to other studies using the database of maternal drug use and reproductive outcomes.

Livebirth and non-livebirth outcome ascertainment

SHSP counts for various pregnancy outcomes reported in SHSP's annual reports were virtually identical to the counts of records extracted through the search of the hospital database. Vital statistics livebirth counts were very similar to the hospital counts we extracted. Stillbirth counts however exhibited a heavily time-dependent shortfall. The discrepancy with regards to stillbirths prior to September 1979 arose because the ICD-8 coding at 4 digits cannot be fully equivalenced to the ICD-9 code. Other pregnancy and birth outcome codes were examined but no other problems became apparent. Despite the fact that coding using ICD-9 began in September 1979, there continued to be less than the expected number of stillbirths until 1981.

Birth defect ascertainment

As Saskatchewan has not maintained a birth defects registry, there were no data available for direct comparison to the birth defect data assembled in this study. However, data

used for surveillance of birth defects in Ontario and Manitoba was collected through automated scanning of hospital admission/discharge abstracts using a process quite similar to that employed to create the reproductive outcome database in Saskatchewan. Data from these two provinces should provide for valid comparisons. Birth defect monitoring in both Alberta and British Columbia utilized multiple sources of ascertainment including hospitalizations. Alberta's hospital ascertainment is not done in an automated, systematic way, however, but depends on hospitals reporting defects to a central registry when they are observed. This type of notification system which is dependent on voluntary form completion has been shown to result in serious underreporting of defects in some systems (Johnson, 1990).

Vital statistics data were not used in the study because for the study period the vital statistics data were neither available in machine-readable form nor was the RBN a required individual identifier. However, not having birth defect data from birth certificates was not seen as a serious limitation for the study for reasons including the following: 1) hospitalization is a source of ascertainment in approximately 65-90% of the congenital anomalies that are reported when multiple sources are involved (Johnson, 1990; Pica, 1987); 2) the level of birth defect reporting on birth certificates is often extremely low (Thunem et al., 1988); and 3) reporting deficiencies resulting from reliance on routine hospital data tend to be most marked for the less obvious or less clinically serious congenital anomalies (Pica, 1987) which are not likely to be picked up on birth certificates.

The study found that the birth defect birth prevalences were substantially lower in the Saskatchewan database compared to two provincial monitoring systems which are each based on an automated, systematic search of computerized hospital admission/discharge abstracts. Overall, the Saskatchewan rates were 37% lower than in Ontario and 43% lower than in Manitoba. Saskatchewan rates were 49% lower than in British Columbia,

which at the time had multiple data sources. This could be a serious limitation of the Saskatchewan database for congenital anomalies research.

First, there would be no way to improve the database short of returning to the hospital charts to discover whether anomaly code(s) had been left out. This was considered for offspring of the women treated with anticonvulsants but deemed too expensive. (Locating over 500 charts in hospitals throughout the province at an extraction cost of $75 per chart would cost about $40,000.) Second, congenital anomalies studies almost always suffer from small numbers of outcomes and the resultant lack of statistical power in the analysis. It is unfortunate to have that problem further aggravated through underreporting.

Third, and most importantly, when outcomes are underreported the potential for bias is increased. If there is only non-differential misclassification of outcome (i.e. anomalies are reported to the same extent in exposed and non-exposed births), the risk estimates will not be altered. However, it is quite conceivable that anomalies might be more likely to be reported as a discharge diagnosis when there was concern (e.g. documented in the medical literature) that the anomaly might have occurred because of a maternal drug exposure. For example, if a women with epilepsy on anticonvulsant therapy during pregnancy gave birth to an infant with a cleft lip, the individual filling out the hospital admission-separation summary might be more likely to report the anomaly. If this occurred, confounding would be introduced into the analysis of anticonvulsants and congenital anomalies, artificially elevating and thus producing a biased risk estimate of the effect of anticonvulsants. Because both anticonvulsant use and birth defects are rare, even a small number of occurrences of this altered coding pattern could result in substantial bias.

One conceivable explanation is that only the more important anomalies were reported in the Saskatchewan database. However, we found trivial anomalies such as tongue ties and skin tags (that were removed before any comparison or analysis) in proportions similar

to those in other provinces. Furthermore, three-digit anomaly groups dominated by relatively less important anomalies were on average proportionally no lower in comparison to other provinces than categories dominated by relatively more serious anomalies.

There is recent evidence that many anomalies can be missed in hospital discharge abstracts. In a study by Calle and Khoury (1991), the authors compared the rates of birth defects reported through routine discharge abstracts with the rates found through a thorough search of the hospital birth records. In a sample of 3,421 infants born between 1966 and 1986 across the United States, 237 birth defects cases (6.9 cases/100 livebirths) were documented in hospital birth records, and 49% of those cases (3.4 cases/100 livebirths) had been missed in the discharge diagnosis (28% of major defects and 66% of minor defect cases).

SHSP diagnosis validation through admission-separation summary recoding

Two conclusions can be drawn from the validation study. First, in general, the transcription from a short written description of the discharge abstract to a 4-digit ICD code in the SHSP database seems to be done carefully and reasonably accurately. Error rates of 9% at the four-digit level and 3.5% at the three-digit level are in line with the error rates that have been discovered in other studies of diagnostic coding accuracy of hospital admission/discharge summaries.(Hierholzer, 1991) Second, because the admission-separation summary record has space for only two discharge diagnoses, multiple birth defects will be underreported. If there is more than one hospitalization for an infant more anomalies may be incorporated in the database. Of greater potential concern for congenital anomaly research using the databases is the possibility that a child with anomalies could be missed altogether. For every newborn, one discharge diagnosis code is a birth code (e.g. "V30 - single birth"). If other perinatal problems exist they may be reported instead of an anomaly discharge diagnosis and the anomaly would not

appear in the database.

This recoding study could not evaluate how often anomalies recorded on the hospital chart might be missing from the abstract and thus the SHSP database. Jick (1985) and Shapiro (1986) have pointed out that in most studies details of case histories are required to properly document clinical diagnoses, as important distortion from misclassification of diagnosis might occur. This concern has not been evaluated because of the prohibitive cost. The apparent overall shortfall in anomaly reporting could not be resolved in this study without examination of all the hospital charts of infants whose mothers were probably exposed to anticonvulsants and a large sample of offspring of women without anticonvulsant exposure.

However, the validation study that was undertaken at least confirmed the coding and data entry into the machine-readable SHSP dataset from the short written diagnoses on the admission-separation record.

Prescription drug data quality - claims records

Many administrative databases have limitations on use for epidemiologic research because data items not used administratively, but of interest to the health researcher, may be lacking in accuracy and completeness (Connell et al., 1987). However, the Drug Plan prescription information should be of high quality because: payment is involved for each transaction recorded; the amount of payment is directly related to the exact drug, strength and amount dispensed; the reporting process involves only 350 pharmacies interacting directly with SPDP on a regular basis and much of the pharmacy billing is automated. Furthermore, SPDP monitors the accuracy of the claims data weekly by asking a selected sample of individuals whether they received prescriptions as claimed by pharmacies.

Estimating first trimester anticonvulsant exposure

The problems inherent to evaluating drug use from the database are discussed here for anticonvulsants, the only prescriptions evaluated closely in this study, but it seems quite likely that similar problems might arise with other prescription drugs as well. A number of situations created complications for establishing the exposure window and estimating dose:

1) Although most drugs are dispensed in 30 day supplies, a few including anticonvulsants are also available in 100 day supplies. When the elapsed number of days between dispensing dates was close to 30 or 100, it was assumed that the supply was used over 30 or 100 days respectively. However, the elapsed number of days between prescription dispensing was less than 25, between 40 and 90 or over 130 days often enough to be of concern. Several different scenarios might explain the patterns, each with different repercussions on dose and exposure window. For example, elapsed times of between 40 and 90 days might indicate the individual took a reduced dose for a 30 day prescription, increased the dose on a 100 day prescription, or picked up the second prescription early out of convenience. In this type of situation in epidemiology one wants to make an assumption to maximise the chance of finding an association if it exists. Failing that, one would want to make a conservative assumption about exposure. However, the optimal and the conservative choice of assumption in this situation is unclear--higher dose over short duration or lower dose but over a longer duration.

2) It is difficult to estimate exposure if an anticonvulsant prescription is the last one dispensed. Is one to assume that each prescription was used as prescribed and then treatment discontinued, or did treatment cease before the prescription was used up? Similarly, there is a problem if only one prescription for a particular anticonvulsant was ever dispensed. There is no way to know if the full course of therapy was taken or whether it was discontinued.

3) If a prescription for a second type of anticonvulsant is recorded in mid therapy, were the anticonvulsants taken concurrently or was the first anticonvulsant discontinued? Treatment regimes vary enough between patients that either scenario is possible. If a second type of anticonvulsant is introduced, the dose of the first may need to be reduced or increased to maintain serum levels because the anticonvulsants often interact with each other.

For the majority of anticonvulsant-exposed women there was a long history of anticonvulsant use and the appearance of a continuous pattern of use through pregnancy. However, for a small percentage of women without a long and continuous history of anticonvulsant use, there could be non-differential misclassification into the exposed or unexposed groups, which would tend to dilute observed associations.

More sophisticated anticonvulsant use algorithms could have been developed (e.g. looking at the anticonvulsant prescribing pattern over several years) but it was felt that this would result in limited improvement in exposure assessment while complicating the calculations and understanding of them. Thus, because the individual data could not be examined, such an analysis had the potential to create unexpected complications.

Changes over time in the unique individual identifier

The unique personal identifier used for record linkage in this database changes when a woman reaches 18 years of age or gets married. We found that for 9% of the recorded pregnancies, the women's RBN's had changed during the one-year period before a pregnancy outcome. Thus prescriptions dispensed before the number change would not have been picked up and linked to the pregnancy. We decided against resolving this problem because the cost was prohibitive, estimated at more than the entire cost of the study as undertaken. (The process of resolving RBN's would require updating millions of prescription and hospital records for the entire study period to the most recent RBN's

through a several step process before beginning the linkage. The cost was roughly estimated at $75,000.)

Instead, we flagged all pregnancies where the mother's benefit number changed in the year preceding pregnancy in order to account for the pregnancies that might have missing data and evaluate the possible effects. In general, the effect would be a small amount of misclassification bias, i.e., missed drug exposure resulting in exposed women being classified as unexposed, and would tend to dilute the results toward the null, resulting in slightly conservative estimates of risk.

Other limitations of the database

The linked drug-birth outcome dataset has other limitations. No hospital outpatient information is available in machine readable form and therefore most therapeutic abortions are missed in the database. Birth weight is not included in the hospital discharge abstracts but the risk of low birth weight can be an important endpoint. Non-prescription drug use is unavailable for study, as are prescriptions dispensed in hospital.

6.3 Evaluation of the anticonvulsant study

Evaluating epilepsy status

Because we have no specific information in the database on the clinical diagnosis of epilepsy, anticonvulsant use was the sole marker for epilepsy and this could be problematic for reasons including the following:

1) Phenobarbital is often prescribed for conditions other than epilepsy. Anticonvulsants other than phenobarbital can be prescribed either for very rare indications (Krogh et al., 1987) or inappropriately, and this could result in some

individuals being assumed to be epileptic.

2) If a woman with epilepsy has not been on anticonvulsant treatment during the study period, or not on anticonvulsants while using the RBN at the time of pregnancy outcome, she will be misclassified as non-epileptic.

3) Even if the error rate in recording either the RBN or the type of drug is below one percent, when a huge volume of data is scanned--in this case over 32 million individual prescription transactions--a number of transcription or data entry errors may still occur. With the 489,000 anticonvulsant prescriptions recorded, incorrect RBN coding of 0.5% could result in almost 2,500 individuals who were never dispensed an anticonvulsant but who have a record indicating receipt of one. This might translate into approximately 75 pregnancy outcomes being misclassified into the group with any history of anticonvulsant use.

The summary anticonvulsant prescription profiles were examined carefully to assess the likelihood that an individual had epilepsy in light of the number of prescriptions and types of anticonvulsants used. It appeared that over 90% of the 359 reported pregnancy outcomes among those women treated with anticonvulsants in the first trimester, whose anticonvulsant history had included anticonvulsants other than phenobarbital, were very likely to be epileptic because of long prescription histories to anticonvulsants and prescriptions for more than one type of anticonvulsant. Similarly in over 90 percent of the pregnancies where a father had a history of non-phenobarbital exposure, it was very likely the father had epilepsy according to the criteria used.

Other limitations

Data on potentially important confounders were not available. Congenital anomalies in epileptic parents, in particular facial clefts, may result in higher risk for similar

anomalies in the offspring (Annegers et al., 1974). Details concerning the type, severity and history of the epilepsy which are likely to be associated with the choice of anticonvulsant therapy are not available for analysis. Alcohol consumption and smoking patterns, which may differ among epileptics and non-epileptics, also increase risk of adverse reproductive outcome (Abel, 1984; Abel and Sokol, 1986), but are unavailable.

How do the results in Saskatchewan compare to the meta-analyses?

This follow-up study was as large as any study executed to date in this field--628 pregnancies were assessed to involve first trimester anticonvulsant exposure. Nevertheless, the study was limited by a lack of power when specific anticonvulsants or outcomes were examined. A smaller percentage of the anticonvulsant-exposed women were on polytherapy than observed in most other studies of anticonvulsant teratogenicity. Furthermore, the overall anomaly rates were relatively low, and these two factors aggravated the analysis problems created by sample size limitations.

The overall risk estimate of congenital malformation of 1.24 (95% CI 0.75-1.94) associated with anticonvulsant exposure was half that found in the meta-analysis (RR 2.6, 95% CI 2.1-3.2). Many of the other studies are clinic-based where women with more serious epilepsy would be more likely to be treated, whereas this is essentially population based. This may be reflected by the fact that the percentage of women on polytherapy among those with anticonvulsant exposure varies in the studies located for the meta-analyses between 35 and 90% (average about 45%) whereas in the Saskatchewan study it was 27%. Unlike most of the other studies, there was no diagnosis of epilepsy and therefore it was not possible to confidently differentiate which women were epileptic, particularly for the large number who had taken only phenobarbital. Therefore, our sample may be diluted with non-epileptic women. If the pattern of anticonvulsant taking was different (e.g. lower doses) among non-epileptics this could reduce risk.

Furthermore, the congenital malformation definition may have been narrower in some of the other studies where hospital records could be examined and the seriousness of an anomaly assessed more carefully.

When heart and cleft anomalies were examined, the elevated risks described in many studies and the meta-analysis were observed. The association of three-drug therapy with higher risk of serious anomaly was observed but based on few exposures and few outcomes. Because we could not confidently differentiate epilepsy particularly in the unexposed women we could not compare the exposed with the unexposed in a precise way.

The finding of an increased risk of ectopic pregnancy with anticonvulsant polytherapy has not been reported in the literature (Dansky and Finnell, 1991). Although the RR is reasonably high at 5.74 and statistically significant (95% CI 2.62-10.86) it could easily be a chance finding because 1) it is based on only 9 cases, 2) it was not a hypothesis-based finding and 3) it was observed in the course of screening several outcomes and exposures. Furthermore, it seems unlikely that it would not have been observed or reported before, particularly in any of the 22 prospective studies of anticonvulsant teratogenesis, as it would be unlikely to have been missed because of its potentially fatal consequences and the fact that it would definitely come to medical attention.

On the other hand, it is possible that the effect could have been overlooked, particularly in the smaller studies, if the RR in other studies was lower, the effect was diluted by presenting the risk for monotherapy and polytherapy together, the overall incidence of ectopic pregnancy was lower in the study populations and/or the individual studies were focused only on congenital malformation. Proper evaluation of the association in this study would require examination of pelvic inflammatory disease which appears to be an important risk factor for ectopic pregnancy (Chow et al., 1987). A higher incidence of pelvic inflammatory disease (or risk factors associated with pelvic infection) among the women contributing to the high relative risk associated with polytherapy would have to

be ruled out before the finding would warrant further attention.

6.4 Undertaking pharmacoepidemiologic research using the Saskatchewan Health databases

Undertaking pharmacoepidemiologic research in Saskatchewan is made more difficult as a result of Saskatchewan Health's confidentiality policies which only allow researchers access to summary cross-tabulations of the data they wish to analyse. Data on individual study subjects, even with all potential identifiers removed or scrambled, can not be obtained.

This policy affects epidemiologic and biostatistical research in the following ways:

1) Trying to get "a feel" for the data is difficult. When one does an epidemiologic study a substantial amount of time is spent getting to know what the data "look like", cleaning up inconsistent coding and resolving potential problems. Each variable should be examined carefully for temporal and demographic patterns of missing or unlikely values. Where there is incomplete coding, one must look across an individual's record to evaluate closely whether the pattern applies to other variables. A close initial visual inspection of individual records is often particularly useful for picking up unexpected idiosyncrasies of the dataset, which could cause complications later and if overlooked could compromise the study results.

2) Communicating to a programmer the large number of details involved in data manipulation and summarisation is cumbersome and error prone. The problem is amplified if you are working from a remote location. For example, this project required communicating and checking the precise logic for each of the more than 15 programs developed in Saskatchewan to create the dataset and summarise it to create the anticonvulsant-birth defect cross-tabulations used in the analysis. If a researcher was inexperienced in dealing with the peculiarities of databases and record linkage, they

might easily end up with a cross-tabulation which was not precisely what they assumed it to be. If the algorithms are left up to the programmer there is even more chance for miscommunication. The need for fastidious checking at every stage of the linkage and analysis cannot be overemphasized.

Use of any dataset belonging to a third party obviously is involved. However, if anonymized individual "raw" data is made available to the researcher, only the initial few programs would have to be done within Saskatchewan thereby greatly decreasing the probability of the foregoing types of problems and the potential for unnoticed errors.

3) When an error in a cross-tabulation is discovered, much of the information in the tabulation often becomes useless. Furthermore, errors do not necessarily become apparent until one is well in to the analysis. When a problem arises in an analysis--e.g. something just doesn't make sense or "add up", an inappropriate assumption about the nature of a variable or a mistake in the logic used to manipulate a variable has generally been made. When this happens with an individual record dataset, recovery often involves just a simple recode, rerunning a couple of steps and continuation of the analysis. When it happens with an analysis based on a summary cross-tabulation, and the error was made before or during the multi-way cross-tabulation step, it requires going back to the original dataset, fixing the error, recreating the cross-tabulation and reworking the data through all of the analytic steps.

4)" What if" analysis is often impossible. After one analyses the relationships between certain variables, the results often suggest other analyses or slightly different ways of coding or examining a variable or grouping data to check out scenarios and explore the relationship further. These analyses can be very instructive and may turn up unexpected relationships in the dataset. An analysis starting with a cross-tabulation severely limits these possibilities or makes them impossible.

5) When an unexpected result turns up it is very useful to be able to go back to the

original unrecoded variables to verify that the variables or groups have not been inadvertently improperly coded somewhere in the processing. With individual data this is simple and provides reassurance about results; without individual data this kind of checking is difficult, expensive and time-consuming.

6) Data on individual subjects cannot be as closely evaluated. For example individuals with more complicated prescription dispensing patterns around the time of the first trimester and infants with several hospitalizations and several anomaly diagnoses could have been more accurately assessed with individual records. Anomaly coding conflicts arise when multiple records on a child are merged together. Detailed rules for making choices about when to drop specific codes (e.g. more detailed diagnoses are established on later hospitalizations), when to keep two similar codes, as well as many special rules for situations which do not conform to the general rules are required to resolve conflicts.

In summary, epidemiologic analysis based on data available only in cross-tabulated form simultaneously makes analysis more difficult to undertake and more prone to unrecognized error. This increases the probability that the research results could be incorrect or misleading.

6.5 Conclusions and Recommendations

This thesis has refined the understanding of the relationship between anticonvulsant therapy during the first trimester of pregnancy and the risk of congenital malformation through two meta-analyses. As well, it has demonstrated the utility and highlighted limitations of the Saskatchewan Prescription Drug and Hospital Services databases for studies of maternal drug use and certain reproductive outcomes.

The meta-analyses have clarified the risks associated with anticonvulsant use and quantified the differences in risk associated with different anticonvulsant therapies. Specifically, the meta-analyses found the following: 1) study reporting was often poor--vague descriptions of methods restricted assessment of study quality and incomplete reporting of results made many reports unusable; 2) there was no indication of increased risk of congenital malformation among offspring of women with epilepsy not taking anticonvulsants during the first trimester; 3) first trimester anticonvulsant monotherapy was associated with an approximately a doubling of congenital malformation risk relative to no anticonvulsant exposure; 4) available published data are insufficient to demonstrate statistically significant differences in overall malformation risk among the various monotherapies commonly in use, although phenobarbital and carbamazepine appear to have the lowest risks; 5) two drug therapy is associated with a 20% increase in malformation risk relative to monotherapy; and 6) three-drug therapy is associated with more than a two-fold increase in risk relative to monotherapy. Although confounding by type and severity of epilepsy may play a role, the results suggest that women with epilepsy who are considering pregnancy not be treated with anticonvulsant polytherapy, particularly with three or more types of anticonvulsants.

The Saskatchewan study yielded results reasonably consistent with those of the meta-analysis. However, evaluation of the drug-reproductive outcome dataset raised questions about the utility of Saskatchewan Health's databases for pharmacoepidemiologic research into congenital anomalies. Although the linked dataset was created, a comparison of the

Saskatchewan congenital anomaly birth prevalences to those in other Canadian hospitalization-based congenital anomalies reporting systems suggested that anomalies were likely to be significantly underreported in SHSP's admission/discharge database. Furthermore, Saskatchewan Health's confidentiality policies resulted in severely limited access to the data, making proper epidemiologic analysis most difficult.

Recommendations

1. It is likely that meta-analysis will play an increasingly important role in the epidemiologic evaluation of many risk factor-adverse health outcome issues where it is difficult to undertake studies with adequate statistical power. When this is the case, as it is with the issue of anticonvulsant teratogenicity, it is imperative that study reporting be improved so that the results of different studies can be consolidated. In particular, with anticonvulsant studies it is imperative that the number of women on each anticonvulsant therapy is clearly presented along with the specific outcomes, even though little evaluation on an individual study basis will be possible.

2. The decision to treat a woman who has epilepsy with antiepileptic therapy which involves more than two types of anticonvulsants during the first trimester of pregnancy should be very carefully evaluated, and avoided if at all possible. Further studies will be required to elucidate the relationship of epilepsy type, severity and polytherapy, and the relative teratogenicity associated with specific polytherapies. Obtaining more details concerning specific anticonvulsant therapies and malformation risk from the authors of studies which were incompletely reported would also contribute to clarifying risks.

3. Congenital anomaly reporting on SHSP's admission-separation records requires further evaluation before more research into maternal drug use and congenital anomalies should be undertaken using the linked database. The underreporting of anomalies needs to be evaluated at the ICD 4-digit level after suitable code melding for individual cases has been done. A reabstraction study would be required to pinpoint when and how often

congenital malformations do not get coded on the abstract. SHSP needs to increase the number of discharge diagnoses fields on the admission-separation form and in the database as well as finding ways to ensure that personnel completing discharge summaries make sure that anomalies reported on the hospital chart are recorded on the discharge summary.

It is not clear that an easy solution is available for the existing database. Therefore, careful consideration of the potential bias that may be introduced by missing diagnoses must be carefully evaluated in any study undertaken using the existing database.

4. Saskatchewan Health should give strong consideration to modifying the restrictive policies regarding data access, i.e. only allowing release of data as summary cross-tabulations. Confidentiality is a very important concern. However, epidemiologists regularly use data of equal sensitivity in the form of individual records, generally anonymized but often with identifying information, without breaches of confidentiality. The current policy seems excessively restrictive, may limit the number of researchers interested in using the databases and increases the probability of undetected errors which could threaten the integrity of study results.

STATEMENT OF ORIGINALITY

At the time this study was begun, the potential of the Saskatchewan databases for pharmacoepidemiologic study had been recognised. However, this study was one of the first large-scale cross-database linkages undertaken using the Saskatchewan Health databases and the first large epidemiologic study to use the databases to study prescription drug teratogenicity. Therefore, I was required to design the study and formulate the detailed logic required to implement the design in order to efficiently access and link the databases. I wrote the flowcharts and provided detailed program logic for the more than 15 computer programs required to search, extract, sort, merge, check, consolidate and categorise the drug and hospital data for the 125,000 pregnancy outcome cohort. Saskatchewan Health's confidentiality rules restricted me from actually doing the record-linkage computer programming, so my instructions were carried out by a computer programmer working for Saskatchewan Health. The anticonvulsant study undertaken from cross-tabulations received from Saskatchewan is one of only a few large-scale population-based studies of anticonvulsants and birth defects.

The meta-analyses contribute important knowledge to the anticonvulsant teratogenicity issue because they are the first analyses to systematically consolidate and appropriately quantify the existing epidemiologic literature. In particular, the second meta-analysis has synthesized the published literature in a way not previously done--by systematically contrasting the risks associated with specific anticonvulsant therapies. This analysis should be of direct and specific use to the clinician attempting to decide on appropriate anticonvulsant therapy for a women with epilepsy considering pregnancy.

When I conceived and undertook the meta-analyses, there were few examples in epidemiology of the use of meta-analysis to consolidate information that did not come from randomized controlled trials. I came up with the idea, designed the meta-analyses, did the analyses and wrote the papers. Dr Sherman provided only minor guidance and editorial feedback.

I conceived the idea for the confidence band technique for improving the graphical presentation of a series of confidence intervals. I also formulated the computer program, provided substantial feedback on refinements to the visual presentation as the computer program was developed, and wrote the paper. Jocelyn Rouleau wrote the code for the computer program. The technique I have developed is a substantial improvement over existing graphical display techniques used to present a series of risk estimates. Because in many epidemiologic studies the results are presented as a series of risk estimates and confidence intervals, I am optimistic that the technique will gain considerable currency.

In conclusion, this dissertation contributes new knowledge to the field of pharmacoepidemiology by testing the utility of using Saskatchewan Health's prescription drug and hospital databases for teratogenicity research and by synthesizing the results of the existing epidemiologic studies of anticonvulsant teratogenicity. The confidence band technique is a distinct contribution to the area of graphic presentation of epidemiologic results.

REFERENCES

Abel EL. Smoking and pregnancy. J Psychoactive Drugs 1984; 16(4):327-338.

Abel EL, Sokol RJ. Maternal and fetal characteristics affecting alcohol's teratogenicity. Neurobehav Toxicol Teratol 1986; 8(4):329-334.

Albengres E, Tillement JP. Phenytoin in pregnancy: a review of the reported risks. Biol Res Pregnancy 1983; 4:71-74.

Anderson RC. Cardiac defects in children of mothers receiving anticonvulsant therapy during pregnancy. J Pediatr 1976; 89:318-39.

Annegers JF, Elveback LR, Hauser WA, Kurland LT. Do anticonvulsants have a teratogenic effect? Arch Neurol 1974; 31:364-373.

Annegers JF, Kurland LT, Hauser WA. Teratogenicity of anticonvulsant drugs. In: Ward AA, Penry JK, Purpura D, eds. Epilepsy. New York City: Raven Press, 1983:239-248.

Beghi E, Di Mascio R, Tognoni G. Drug treatment of epilepsy. Outlines, criticism and perspectives. Drugs 1986; 31:249-265.

Bertollini R, Kallen B, Mastroiacovo P, Robert E. Anticonvulsant drugs in monotherapy. Effect on the fetus. Eur J Epidemiol 1987; 3:164-171.

Bossi L. Fetal effects of anticonvulsants. In: Morselli PL, ed. Antiepileptic Drug Therapy in Pediatrics. New York City: Raven Press, 1983:37-64.

Calle EE, Khoury MJ. Completeness of the discharge diagnoses as a measure of birth defects recorded in the hospital birth record. Am J Epidemiol 1991; 134:69-77.

Chalmers I, Enkin M, Keirse MJNC, eds. Effective Care in Pregnancy and Childbirth (2 vols). Oxford: Oxford University Press, 1989.

Chalmers TC, Berrier J, Sacks HS, Levin H, Reitman D, Nagalingam R. Meta-analysis of clinical trials as a scientific discipline. II: replicate variability and comparisons of studies that agree and disagree. Stat Med 1987, 6:733-744.

Chow WH, Daling JR, Cates W,Jr., Greenberg RS. Epidemiology of ectopic pregnancy. Epidemiol Rev 1987; 9:70-94.

Coatsworth JJ. Studies on the clinical efficacy of marketed antiepileptic drugs. NINDS Monograph No. 12, 1971: 1-35.

Connell FA, Diehr P, Gary Hart L. The use of large data bases in health care studies. Ann Rev Public Health 1987; 8:51-74.

Dansky L, Andermann E, Andermann F, Sherwin AL, Kinch RA. Maternal epilepsy and congenital malformations: correlation with maternal plasma anticonvulsant levels during pregnancy. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:251-258.

Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 2: human studies. Reproductive Toxicology 1991; 5(4):301-335.

Dean J, Dean A, Burton A, Dicker R. Epi Info Version 5.01. Atlanta, Georgia: Centres for Disease Control, Epidemiology Program Office, i990.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Treatment of Early Breast Cancer: A Systematic Overview of All Available Randomized Trials of Adjuvant Endocrine & Cytotoxic Therapy, Volume 1: Worldwide Evidence, 1985-1990. Oxford University Press, 1990.

Finnell RH. Preliminary findings of the fetal hydantoin syndrome in a mouse model. In: Hassell TM, Johnston MC, Dudley KH, eds. Phenytoin-induced Teratology and Gingival Pathology. New York: Raven Press, 1980:59-66.

Finnell RH. Genetic differences in susceptibility to anticonvulsant drug-induced developmental defects. In: Kucheria K, ed. Pharmacol Toxicol. In press 1992;

Finnell RH, Bennett GD, Karras SB, Mohl VK. Common hierarchies of susceptibility to the induction of neural tube defects in mouse embryos by valproic acid and its 4-propyl 4-pentenoic acid metabolite. Teratology 1988; 38:313-320.

Finnell RH, Dansky LV. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 1: animal studies. Reproductive Toxicology 1991; 5(4):281-299.

Finnell RH, Moon SP, Abbott LC, et al. Strain differences in heat-induced neural tube defects in mice. Teratology 1986; 33:247-252.

Fraser FC. Antenatal factors in congenital defects: problems and pitfalls. NY State J Med 1959; 59:1597.

Fraser FC. Experimental teratogenesis in relation to congenital malformations in man. In: Fishbein M, ed. Proceedings of the Second International Conference on Congenital Malformations. Philadelphia: Lippincott, 1964:277-287.

Friis ML. Facial clefts and congenital heart defects in children of parents with epilepsy: genetic and environmental etiologic factors. Acta Neurol Scand 1989; 79:433-459.

Fritz HD, Müller D, Hess R. Comparative study of the teratogenicity of phenobarbital, diphenylhydantoin and carbamazepine in mice. Toxicology 1976; 6:323-330.

Gaily E, Granström ML, Hiilesmaa V, Bardy A. Minor anomalies in offspring of epileptic mothers. J Pediatr 1988; 112:520-59.

German J, Kowal A, Ehlers KH. Trimethadone and human teratogenesis. Teratology 1970; 3:349-362.

Gibson JE, Becker BA. Teratogenic effects of diphenylhydantoin in Swiss Webster and A/J mice. Proc Soc Exp Biol Med 1968; 128:905-909.

Glass GV, McGaw B, Smith ML. Meta-analysis in social research. Beverly Hills CA: Sage, 1981.

Gram L, Drachmann-Bentsen K, Parnas J, Flachs H. Controlled trials in epilepsy: a review. Epilepsia 1982; 23:491-519.

Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9:1-30.

Guess HA, Lydick EG, Small RD, Miller LP. Exact binomial confidence intervals for the relative risk in follow-up studies with sparsely stratified incidence density data. Am J Epidemiol 1987; 125:340-347.

Hanson JW. Teratogen update: fetal hydantoin effects. Teratology 1986; 33:349-353.

Hanson JW, Myrianthopoulos NC, Harvey MAS, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976; 89:662-668.

Hanson JW, Smith DW. The fetal hydantoin syndrome. J Pediatr 1975; 87:285-90.

Harbison RD, Becker BA. Relation of dosage and time of administration of diphenylhydantoin to its teratogenic effect in mice. Teratology 1969; 2:305-312.

Harbison RD, Becker BA. Effect of phenobarbital and SKF 525 A pretreatment on diphenylhydantoin teratogenicity in mice. J Pharmacol Exp Ther 1970; 175:283-288.

Harbison RD, Becker BA. Diphenylhydantoin teratogenicity in rats. Toxicol Appl Pharmacol 1972; 22:193-200.

Hierholzer WJ,Jr.. Health care data, the epidemiologists's sand: comments on the quantity and quality of data. Am J Med 1991; 91(3B):21S-26S.

Hill RM, Verniaud WM, Horning MG, McCulley LB, Morgan NF. Infants exposed in utero to antiepileptic drugs. A prospective study. Am J Dis Child 1974; 127:645-53.

Hopkins A. Prescribing in pregnancy. Epilepsy and anticonvulsant drugs. Br Med J [Clin Res] 1987; 294:497-501.

International Clearinghouse on Birth Defects. Anticonvulsants in monotherapy: Methodological problems. International Clearinghouse on Birth Defects Annual Report. 1981: (UnPub)

Janz D. On major malformations and minor anomalies in the offspring of parents with epilepsy: review of the literature. In: Janz D, Bossi L, Dam M, Helge H, Richens A, Schmidt D, eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:211-222.

Jeavons PM. Non-dose-related side effects of valproate. Epilepsia 1984; 25:S50-S55.

Jenicek M. Meta-analysis in medicine. Where we are and where we want to go. J Clin Epidemiol 1989; 42:35-44.

Jick H. Use of automated data bases to study drug effects after marketing. Pharmacotherapy 1985; 5(5):278-279.

Johnson KC. The feasibility of using HMRI hospital data for birth defects surveillance in Canada. 1990: (UnPub)

Kao J, Brown NA, Shull G, et al. Chemical structure and teratogenicity of anticonvulsants. Fed Proc 1979; 38:438.

Kelly TE. Teratogenicity of anticonvulsant drugs. I: Review of the literature. Am J Med Genet 1984; 19:413-434.

Khera KS. Adverse effects in humans and animals of prenatal exposure to selected therapeutic drugs and estimation of embryo-fetal sensitivity of animals for human risk assessment. A review. Issues and Reviews in Teratology 1984; 2:399-445.

Krogh CME, Gillis MC, Shave DG, Bisson R, Blais D, eds. Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmaceutical Association, 1987.

Lammer EJ, Sever LE, Oakley GP Jr. Teratogen update: valproic acid. Teratology 1987; 35:465-473.

Lawson DH. Pharmacoepidemiology: a new discipline. Br Med J 1984; 289:940-941.
Light RJ, Pillemer DB. Summing up: The science of reviewing research. Cambridge, MA:Havard University Press, 1984.

Light RJ, Smith PV. Accumulating evidence: Procedures for resolving contradictions among different research studies. Harv Educ Rev 1971; 41:429-471

Lindhout D. Teratogenesis in maternal epilepsy: new aspects of prevention. Ph.D. Thesis. Amsterdam: University of Amsterdam, 1985.

Lindhout D, Höppener RJ, Meinardi H. Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation (of carbamazepine). Epilepsia 1984; 25:77-83.

Lindhout D, Meinardi H. Spina bifida and in-utero exposure to valproate. Lancet 1984; 2:396.

Lindhout D, Schmidt D. In-utero exposure to valproate and neural tube defects [letter]. Lancet 1986; 1392-1393.

Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA 1988; 260:652-656.

Louis TA, Finberg HV, Mosteller F. Findings for public health from meta-analyses. Ann Rev Public Health. 1985; 6:1-20.

Mastroiacovo P, Morandini S, Saracino P, Pedrotti D, Clerici Bagozzi D. Spina bifida e acido valproico: Risultati di un'analisi preliminare. Boll Epidemiol Nazionale (Ital) 1982; 47:1-6.

Mauritsen R. EGRET. Seattle, Washington: Statistics and Epidemiology Research Corporation 1990.

Meadow R. Anticonvulsants in pregnancy. Arch Dis Child 1991; 66:62-65.

Meadow SR. Anticonvulsant drugs and congenital abnormalities. Lancet 1968; 2:1296.

Mercier-Parot L, Tuchman-Duplessis H. The dysmorphogenic potential of phenytoin: Experimental observations. Drugs 1974; 8:340-353.

Miller RP, Becker BA. Teratogenicity of oral diazepam and dyphenylhydantoin in mice. Toxicol Appl Pharmacol 1975; 32:53-61.

Nakane Y. Congenital malformation among infants of epileptic mothers treated during pregnancy--the report of a collaborative study group in Japan. Folia Psychiatr Neurol Jpn 1979; 33:363-369.

Nakane Y. The teratological problem of antiepileptic drugs. Folia Psychiatrica et Neurologica 1980; 34:277-287.

Nau H, Hendrickx AG. Valproic acid teratogenesis. ISI Atlas of Science: Pharmacology 1987; 1:52-56.

Paulson RG, Paulson GW, Jreissaty S. Phenytoin and carbamazepine in production of cleft palates in mice. Comparison of teratogenic effects. Arch Neurol 1979; 36:832-836.

Pica LA. The relationship between case rates and reporting practices in the Canadian Congenital Anomalies Surveillance System, 1970-1982. Masters Thesis. Montreal, Quebec: McGill University, 1987.

Rating D, Nau H, Jäger-Roman E, et al. Teratogenic and pharmacokinetic studies of primidone during pregnancy and in the offspring of epileptic women. Acta Paediatr Scand 1982; 71:301-11.

Rosa FW. Teratogenesis in epilepsy: birth defects with maternal valproic acid exposures. In: Porter RJ et al., ed. Advances in Epileptology: XVth Epilepsy International Symposium. New York: Raven Press, 1984:309-314.

Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991; 324:674-677.

Rothman KJ. Modern Epidemiology. Boston/Toronto: Little, Brown and Company, 1986.

Saskatchewan Health. Annual Report 1982-83: Saskatchewan Prescription Drug Plan. 1983.

Saskatchewan Health. Annual Report 1982-83: Saskatchewan Hospital Services Plan. 1983.

Saskatchewan Health. International symposium on drug data base uses, Regina, Canada, 7-8 November 1984. 1984.

Schmidt D. The effect of pregnancy on the natural history of epilepsy: review of the literature. In: Janz D, Dam M, Richens A, et al , eds. Epilepsy, Pregnancy and the Child. New York: Raven Press, 1982:3-14.

Seller MJ, Embury S, Polani PE, Adinolfi M. Neural tube defects in curly-tail mice: 2: effect of maternal administration of vitamin A. Proc R Soc Lond [Biol] 1979; 206:95-107.

Sever LE, Gilbert ES, Hessol NA, McIntyre JM. A case-control study of congenital malformations and occupational exposure to low-level ionizing radiation. Am J Epidemiol 1988; 127(2):226-242.

Shapiro S. Reasons for the successes and failures of specific models in drug epidemiology. In: Epidemiologic concepts in clinical pharmacology. New York: Springer-Verlag, 1986:11-22.

Smith DB, Delgado Escueta AV, Cramer JA, Mattson RH. Historical perspective on the choice of antiepileptic drugs for the treatment of seizures in adults. Neurology 1983; 33:2-7.

Speidel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and the newborn. Lancet 1972; 2:839-843.

Staples RE. Teratology. In: Woodbury DM, Penry JK, Schmidt RP, eds. Antiepileptic Drugs. New York: Raven Press, 1972:55-62.

Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. Epidemiol Rev 1990; 12:87-107.

Strom BL, Carson JL, Morse ML, LeRoy AA. The computerized on-line Medicaid pharmaceutical analysis and surveillance system: a new resource for postmarketing drug surveillance. Clin Pharmacol Ther 1985; 38:359-364.

Sullivan FM, McElhatton PR. Teratogenic activity of the antiepileptic drugs phenobarbital, phenytoin, and primidone in mice. Toxicol Appl Pharmacol 1975; 34:271-282.

Sullivan FM, McElhatton PR. A comparison of the teratogenic activity of the antiepileptic drugs carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin and primidone in mice. Toxicol Appl Pharmacol 1977; 40:365-378.

Thunem NY, Lowry BR, Linde KM. Assessment of the quality of congenital anomaly data in birth notification documents. 1988: (UnPub)

Tilson HH. Getting down to bases - record linkage in Saskatchewan. Can J Public Health 1985; 87:222-223.

Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does Breathing Other People's Tobacco Smoke Cause Lung Cancer? Br Med J 1986; 293:1217-1222.

West R, Sherman GJ, Downey W. A record linkage study of valproate and malformations in Saskatchewan. Can J Public Health 1985; 76:226-228.

Wilson JG, Fraser FC, eds. Handbook of Teratology, Volume 1, General Principles and Etiology. New York: Plenum Press, 1977.

Woodbury DM, Penry JK, Pippenger CE, eds. Antiepileptic Drugs. New York: Raven Press, 1982.

Young GB, Ashenhurst EM, Eder S. Treating epilepsy: one drug or several? Can Med Assoc J 1982; 126:1134-1136.

APPENDIX A

The prevalence of individual identifiers in Saskatchewan HMRI admission/discharge summary data including a diagnosis for a congenital anomaly 1978-1988.

Table A.1

Prevalence of identifiers in Hospital Medical Records Institute dataset for admission/discharge summaries which included a birth defect diagnosis in the first year of life – Saskatchewan 1978–1988.

Year	Hospital Insurance Number		Geocode		Postal Code		Total Records
	Count	Percent	Count	Percent	Count	Percent	Count
78	0	(0.0%)	0	(0.0%)	0	(0.0%)	9
79	0	(0.0%)	0	(0.0%)	0	(0.0%)	66
80	0	(0.0%)	0	(0.0%)	0	(0.0%)	227
81	0	(0.0%)	0	(0.0%)	0	(0.0%)	495
82	0	(0.0%)	0	(0.0%)	17	(2.3%)	745
83	7	(0.6%)	30	(2.5%)	85	(7.1%)	1,198
84	84	(5.5%)	192	(12.5%)	272	(17.%)	1,535
85	279	(16.9%)	749	(45.4%)	362	(21.5%)	1,650
86	583	(35.9%)	731	(45.0%)	735	(45.3%)	1,624
87	629	(40.3%)	781	(50.1%)	799	(51.2%)	1,560
88	754	(63.1%)	532	(44.6%)	891	(74.6%)	1,194
Total	2,336	(22.7%)	3,015	(29.3%)	3,161	(30.7%)	10,303

APPENDIX B

Differences in Anomaly Ascertainment - Ontario 1973-1977 versus Ontario 1978-1988

Ascertainment plays a key role in explaining reported differences in birth defect rates. In this appendix, differences in ascertainment are examined for two quite different ascertainment schemes in Ontario, the multi-source system prior to 1979 without automated searching of hospital discharge records and the system after 1978 based exclusively on automated search of HMRI admission/discharge abstract data.

In Table B.1.1 the birth prevalences of 57 specific and 15 summary birth defect categories developed by CCASS for routine monitoring are compared for the Ontario 1973-1977 system and the HMRI-based 1978-1988 system. The differences in birth prevalence are plotted in Figure B.1 after sorting the defects in the order of decreasing percentage differences in birth prevalence. To make an approximate adjustment for trend over time in the defect ascertainment, risk differences between 1979-1981 and 1986-1988 were subtracted from the overall difference.

In all but eight of the categories the birth prevalence is lower in the earlier system. Two-thirds of the defects are reported at least 25% less often prior to 1978. Several of the defects where a higher de-trended rate is reported before 1978 such as anencephaly, spina bifida and stillbirths probably result because the trend changed after 1978. In the case of cystic kidney, other urinary anomalies and autosomal syndromes, changes in technology greatly improved ascertainment during the 1980's.

Table B.1

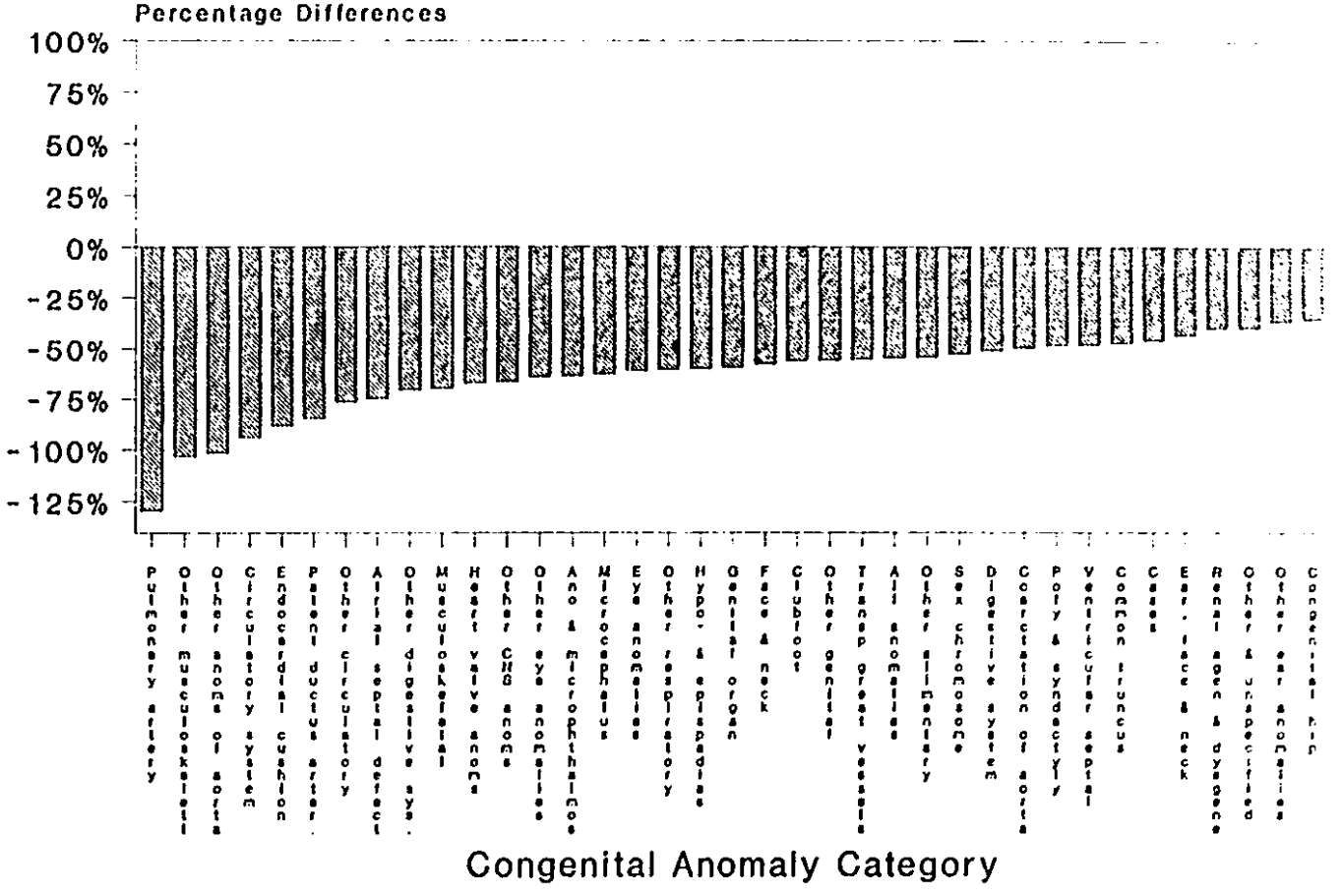
Differences in congenital anomaly ascertainmnet – Ontario 1973–1977 relative to Ontario 1978–1988

	Congenital Anomaly Birth Prevalences Rate/10,000 livebirths		Percentage Differences Adjusted for Trend
	1973–77	1978–88	1973–77/1978–88
Anencephalus & similar anomalies	7.8	4.3	40%
Spina bifida	11.9	8.8	10%
Encephalocele	1.7	1.7	–9%
Microcephalus & brain reduction	3.5	6.4	–63%
Congenital hydrocephalus	10.0	9.5	–18%
Other specified & unspecified CNS an	1.1	7.2	–66%
Anophthalmos, microphthalmos	0.7	1.3	–64%
Other eye anomalies	2.4	6.1	–64%
Anomalies of ear causing impairment	0.6	0.7	–14%
Other ear anomalies	6.0	6.8	–37%
Anomalies of face & neck	2.8	5.2	–58%
Common truncus	0.6	1.2	–47%
Transposition of great vessels	2.5	4.8	–55%
Tetralogy of Fallot	1.3	3.6	–22%
Ventricular septal defect	11.4	23.8	–48%
Atrial septal defect	3.2	12.2	–75%
Endocardial cushion defects	0.5	4.2	–88%
Heart valve anomalies	2.5	7.6	–67%
Other heart anomalies	24.5	25.0	–5%
Patent ductus arteriosus	4.1	20.5	–84%
Coarctation of aorta	2.4	4.3	–50%
Other anomalies of aorta	0.8	2.5	–101%
Pulmonary artery anomalies	2.1	10.7	–129%
Other circulatory system anomalies	2.7	12.8	–76%
Nose anomalies	1.9	3.1	–30%
Lung agenesis & hypoplasia	3.1	5.5	–23%
Other respiratory system anomalies	1.0	3.3	–61%
Cleft palate	5.8	6.3	–31%
Cleft lip	4.5	3.6	17%
Cleft palate with cleft lip	6.3	7.0	–27%
T–E fistula, esophageal atresia & ste	2.5	3.0	–31%
Other upper alimentary tract anomali	23.5	36.2	–54%
Intestinal, anorectal atresia & stenosi	4.5	4.7	–19%
Other digestive system anomalies	4.1	11.8	–71%
Hypospadias, epispadias	14.9	25.5	–60%
Other genital organ anomalies	6.2	9.4	–56%
Renal agenesis & dysgenesis	2.4	4.0	–40%
Cystic kidney disease	1.3	2.4	33%
Other urinary system anomalies	5.3	11.1	7%
Congenital dislocation of hip	16.5	42.0	–35%

Table B.1 (continued)

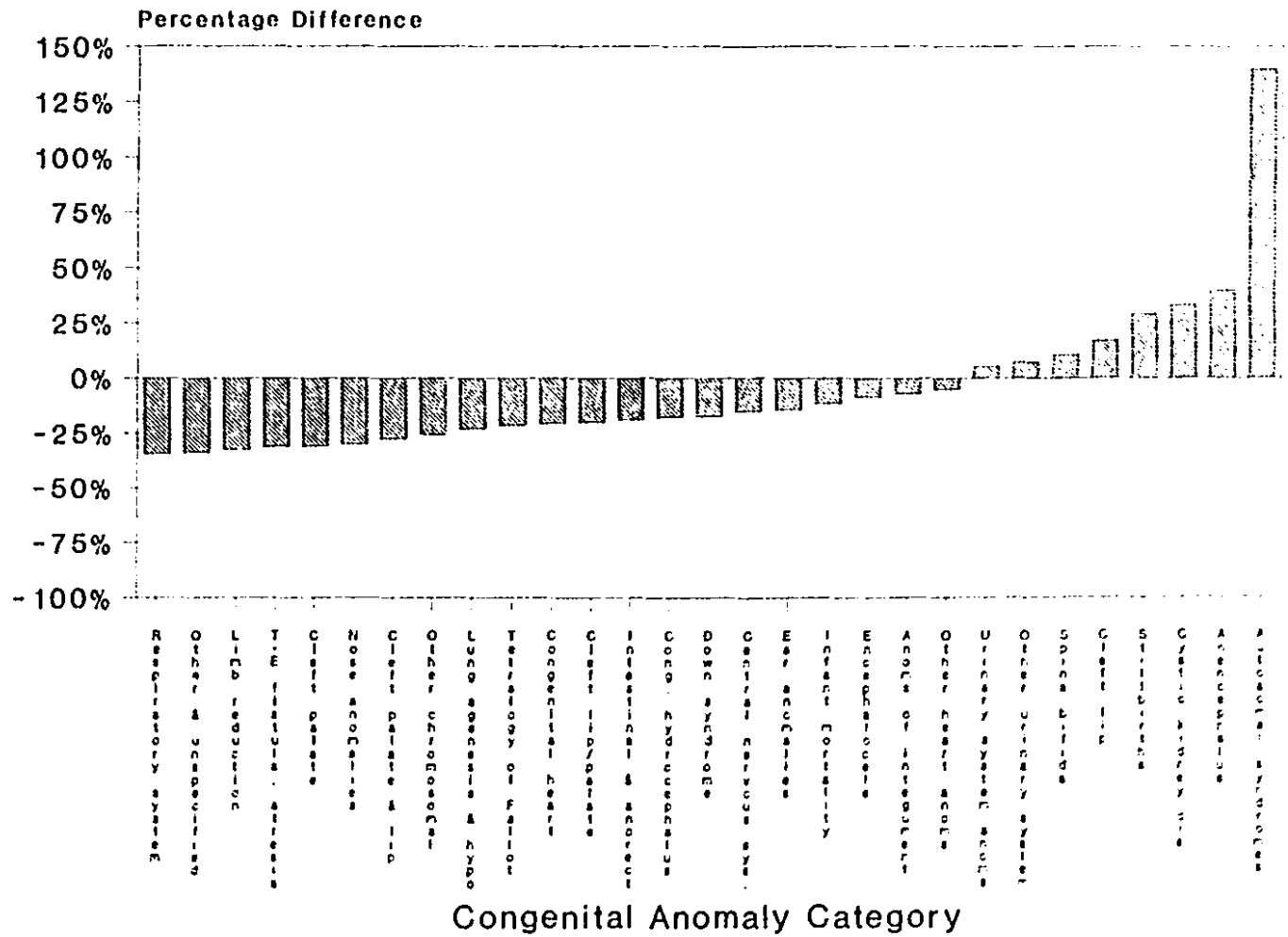
	Congenital Anomaly Birth Prevalences Rate/10,000 livebirths 1973–77	1978–88	Percentage Differences Adjusted for Trend 1973–77/1978–88
Clubfoot	32.2	48.7	–56%
Polydactyly, syndactyly	12.6	15.5	–49%
Limb reduction anomalies	3.6	4.2	–33%
Other musculoskeletal anomalies	1.5	27.8	–103%
Anomalies of integument	1.9	4.9	–7%
Down syndrome	8.6	12.0	–17%
Autosomal syndromes	2.3	1.0	140%
Sex chromosome conditions	0.5	1.2	–53%
Other & unspecified anomalies	10.1	14.2	–40%
Summary Categories			
Cases	233.2	384.8	–46%
All anomalies	279.9	520.1	–55%
Central nervous system	33.7	33.7	–15%
Eye anomalies	3.0	7.0	–61%
Ear, face & neck anomalies	9.0	12.3	–43%
Congenital heart defects	41.9	60.2	–21%
Circulatory system anomalies	7.7	27.7	–94%
Respiratory system anomalies	6.0	11.8	–35%
Cleft lip and/or palate	16.6	16.9	–20%
Digestive system anomalies	34.2	53.6	–51%
Genital organ anomalies	20.8	34.5	–59%
Urinary system anomalies	8.3	15.5	5%
Musculoskeletal anomalies	64.5	158.9	–70%
Other chromosomal anomalies	2.8	4.6	–26%
Other & unspecified anomalies	12.0	19.0	–34%

Fig B.1 Differences in Ontario anomaly ascertainment rates 1973-77 relative to 1978-1988, adjusted for trend



Reference ▪ Ontario 1978-1988

Fig B.2 (continued)



Reference ▪ Ontario 1978-1988

APPENDIX C

Saskatchewan SHSP Congenital Anomaly Recode Validation Study

Before September 1979, ICD coding was done according to ICD-8, after that date the ICD-9 system was used. Computer equivalencing of ICD-8 to ICD-9 had been done at SHSP for the data up until September 1979, so the validation study involved ICD-9 coding only. There were quite limited changes between the eight and ninth revisions of the ICD for the congenital anomalies chapter and only a few anomalies caused equivalencing problems. None of the recoding problems discovered involved an equivalencing problem and the recoding of records from the time before September 1979 indicated that among the anomalies observed the equivalencing had been correctly done.

Table C.1 summarises which records were chosen for extraction and comparison. The summary results of the comparison of the machine-readable and recoded anomalies are presented in Table C.2. In 210 of the 234 (90.5%) records, the anomalies recorded were identical between the SHSP computer file and the recode done from the copy of the microfiche. In 22 records (9%) the anomalies were recoded differently. In 14 of these records the difference was only at the fourth digit of the code, in eight of the records the codes did not agree at the three-digit level. Tables C.3 and C.4 provide details of the differences in codes that were observed in the comparison. For some of these codes choosing the correct code at the four-digit level can be difficult and discretionary when only a two or three word description is available.

The recoder was also able to code 17 additional anomalies that had appeared on the separation form but could not be accommodated on the computer record which was limited to two diagnostic codes, one of which was often a birth code or other infant problem. Twelve of these anomaly codes were different at the three-digit level from the

anomaly or anomalies already coded for that record. Where anomalies were recoded differently or another new anomaly was found, the analysis dataset was updated to reflect the more accurate or complete data.

Table C.1

Description of the 182 infants with anomalies used in the validation study to compare anomaly descriptions on hospital discharges with ICD coding on Saskatchewan Hospital Services Plan machine-readable records

Parent's anticonvulsant prescription history 1976–1983	1st trimester anticonvulsant exposure	Phenobarbital only		
		No	Yes	Total
None				50
Mothers	Not exposed	24*	31	55
	Exposed	21	10	31
	Total	45	41	86
Fathers	Not exposed	31	7	38
	Exposed	8	0	8
	Total	39	7	46
Total infants				182
Total discharge summaries examined **				234

* Number of infants with anomalies selected (includes infants with minor anomalies later removed from birth defect analysis)

** On average there were 1.28 hospital discharges with anomalies noted per child.

Table C.2

Saskatchewan anomaly validation study - Comparison of hospital discharge summaries with Saskatchewan Hospital Services Plan machine-readable records for 234 records reporting anomalies - Summary

	Number	Percent of total records
Records checked	234	
Original codes and recodes agree	212	(90.5%)
Codes different at 4th digit only	14	(6.0%)
Codes different at 3rd digit	8	(3.4%)
Codes different	22	(9.4%)
Additional codes discovered in recode*		
Different at 4th digit only	5	(2.1%)
Different at 3rd digit	12	(5.2%)
Total	17 **	(7.3%)

* anomalies reported on discharge summary were not reported on machine-readable record

** 17 codes for 15 infants

Table C.3

Congenital anomalies not reported on Saskatchewan Hospital Services Plan machine-readable record but present on the hospital discharge summary

Existing defect code(s)*	Code(s) not reported	Description on paper abstract	Different at 3 digits
7492	7454	Interventricular septal defect	Y
7590	3795	Congenital nystagmus	N
7451,7454	7460	Pulmonic stenosis	Y
745	7470	Patent ductus arteriosus	Y
7453	7451	Transposition of great vessels	N
7468	7566	Diaphragmatic hernia	Y
7455	7466	Mitral incomplete	Y
7454	7423	Hydrocephalus	Y
7454	7451,7473	7451,7473	Y
7559	7543	7543	Y
7597	7410	7410	Y
7597	7421	7421	Y
7515	7512	7512	N
7580	7468	7468	Y
7456,7468	7466,7580	7466,7580	Y
Total 17	17		12

* on machine-readable records

Table C.4

Code conflicts between Saskatchewan Hospital Services Plan machine-readable records and recoding from admission-discharge abstracts

Machine-readable code	Recode	Description on abstract	Same at 3 digit
7421	7422	7422	Y
7424	No description or code on abstract		-
7424	7422	7422	Y
7436	7438	7438	N
7443	7441	7441	N
7455	7450	7450	Y
7468	7451	7451	Y
7483	7528	7528	Y
7525	7545	7545	Y
7543	7547	7547	Y
7546	7547	elbow	N
7547	7548	transposition of great artery	N
7547	7548	hip	N
7555	7548	elbow vs limb	N
7555	7548	7548	Y
7556	7556	specified vs unspecified	Y
7556	7556	cranial stenosis	Y
7559	7560	syndrome & trisomy	N
7565	7560	7560	N
7582	7560	provisional diagnosis	N
7596	7582	7582	Y
7597	7585	7585	Y
Total			12/22

APPENDIX D

Confidence Bands: Improved Graphical Presentation of Multiple Confidence Intervals

Kenneth C. Johnson and Jocelyn Rouleau

Birth Defects and Poisonings Section
Diseases of Infants and Children Division
Bureau of Chronic Disease Epidemiology
Laboratory Centre for Disease Control
Health Protection Branch
Health and Welfare Canada

Abstract: Plotting point estimates and confidence intervals is often a useful technique for understanding and presenting epidemiologic data. In meta-analysis the technique has been used to particular advantage. However, current presentation techniques result in graphic representations of confidence intervals that poorly reflect important underlying characteristics of the intervals. Plotting confidence bands is an attempt to present a series of confidence intervals in a more visually appropriate and thus more analytically useful way. The heights and shadings of the confidence bands are used to reflect, respectively, the precision of the risk estimates and the probability function associated with the confidence interval.

Keywords: confidence intervals, epidemiology, graphics, meta-analysis.

"Humans drew before they wrote. For much of our brain, I suspect, drawing is thinking. It may be that computers will be releasing that brainpower in the next few years, as we learn to express ourselves graphically as easily as we use the car or telephone."

Stewart Brand[1]

". . . Furthermore, of all methods for analyzing and communicating statistical information, well-designed data graphics are usually the simplest and at the same time the most powerful."

Edward R Tufte[2]

Introduction

Point estimates and confidence intervals are the main statistical measures for presenting results in much epidemiologic research. When several confidence intervals and point estimates are involved, plotting the estimates and intervals allows one to present a large amount of information in a concise way.

Where the estimates and intervals come from different studies, as in meta-analysis, graphic presentation allows studies to maintain their individual integrity and unlike most statistical synthesis, no assumptions about homogeneity are required. The results can be "seen" and are not buried in statistical calculations. Furthermore, the reader can informally evaluate "what if" scenarios by removing specific intervals or by grouping or by ordering them according to specific criteria. Graphic presentation has been used to advantage in a number of meta-analyses of the results of controlled trials of health care[3,4] and to evaluate risk factors for disease[5,6].

Galbraith has suggested improvements to the graphical presentation of confidence intervals[7] while Walker et al. have suggested a different way of using them in analysis[8]. The Early Breast Cancer Trialists' Collaborative Group plotted a confidence interval for each trial in a summary comparison and used a shaded square for the point estimate

which was sized according to the studies' variance.[4,9]

In 1987, Poole suggested that plotting confidence intervals as a p-value function provided a more useful and appropriate display of the statistical information contained in a confidence interval.[10] More recently Sullivan and Foster have demonstrated the use of the confidence interval function and have made software available.[11] Although the function and software are a most welcome addition to the presentation of individual study results, their practical use in meta-analysis or for reporting a number of confidence intervals is questionable because of the space they require, the complexities of visual overlap that often result and problems of relative visual attention discussed below.

Limitations of Current Presentation Methods

In this paper we present a number of refinements to the graphic presentation of several confidence intervals which solve three major graphic limitations with the way they have generally been presented to date. The problems are:

1) a confidence interval drawn as a line fails to visually express the probability function which underlies a point estimate and confidence interval;
2) the quantitative importance of a particular point estimate is related to the inverse of the length of the confidence interval, whereas the visual impact of the interval is related directly to its length; and
3) it is difficult to compare the differences in precision of intervals with different lengths.

The first problem tends to makes one visualize the whole confidence interval as of equal probability; the second problem results in the natural tendency to focus one's visual attention on the less precise and thus less informative intervals; the third problem makes it difficult to see the relative contribution of various studies to a summary risk estimate. The result is that often a graphic presentation of results, although a tremendous

improvement over a table of point estimates and confidence intervals, is still difficult to "see" and interpret readily--particularly where there are a number of intervals of disparate size and varying risk.

The widespread use of high quality laser printers provides the opportunity to improve the graphic presentation of results using the following graphical procedure.

Improvements in Graphical Presentation

The graphical presentation of a series of confidence intervals has been improved in the following ways:

1) The line used to represent the interval has been replaced by a band made up of a series of shaded rectangles such that values in the confidence interval function with higher probabilities are darker. (See Figure 1.)

2) The height of the band correlates with the precision of the risk estimate. The "visual importance" or "visual attention" that an interval receives is thus correlated with the precision of the risk estimate. The precision of an estimate is displayed as a one-dimensional linear measurement.

3) The point estimate and the 95% limits are not highlighted. This reinforces the fact that the interval is a continuous function, the actual underlying risk is unlikely to be the actual point estimate, and that the specific interval limit cutoff (i.e. 95%) is an arbitrary choice.

4) In situations where a summary risk estimate is appropriate, the precision of the plotted summary risk estimate can be compared directly to the precision of the individual study risks from which it is created.

Graphical Methods

In this algorithm, confidence band heights could be calculated by various schemes including the variance of the estimates[4], according to the weights calculated for each

strata to combine strata in a Mantel-Haenszel summary risk estimate[12], or other schemes for combining risk estimates[5]. Heights are scaled so that the individual risk estimate with the most precision is given a height close to the height chosen for each line of data. Alternatively, the height could be used to represent study quality, with the studies with the highest quality score represented by the tallest bands.

The results are generally displayed on a log scale in the horizontal dimension to balance the visual distance of an estimate from the null for estimate increases or decreases of similar value[7], for example a doubling or halving of the risk. In a series of confidence intervals where few of the 95% limits extend below .1 or above 10, the algorithm truncates the intervals and expands the scale, improving readability of the plots. Where both case-referent data and cohort data are to be summarised on a graph, study weights are calculated according to the methods described in the appendix of the paper by Wald et al[5].

Visual Presentation - Technical Details

The graphs were produced on a Hewlett Packard LaserJetIII printer using Hewlett Packard's Printer Control Language. Some people find the graphs somewhat difficult to look at because they appear slightly fuzzy. We have found that once one is familiar with the graphs, this is no longer a problem. One option would be to use continuous grey scaling (available in popular graphics software such as CorelDRAW) to draw the confidence bands, but our experimentation with continuous grey scaling resulted in only a marginal improvement in the look but a more involved process.

Meta-Analysis Examples

Figure 2 is reproduced from the meta-analysis of Wald et al on the relationship between passive tobacco smoke exposure and lung cancer.[5] The wide confidence intervals of the small studies tend to swamp and take attention away from the narrower confidence

intervals of the few larger studies.

Figure 3 presents the same data using the confidence band algorithm. With the confidence bands, one's eye is immediately attracted to the more precise studies and to the most important part of the confidence intervals. Studies with the lowest precision (the thin long lines) are virtually ignored by the eye. The relative precision of the more important intervals--difficult to pick out from their logged length--can be quickly evaluated from their band heights which are plotted on a linear scale.

The Early Breast Cancer Trialists' Collaborative Group has presented graphic summaries of their overview results of randomized controlled trials of treatment of early breast cancer[4,9]. (See Figure 4.) They use black squares for point estimate indicators which are sized according to the variance of the individual study. Although this presentation is a clear improvement over traditional representation, the following visual limitations still exist:

1) Individual's interpretation of the relative areas represented by different sized boxes vary. Comparing areas is more difficult than comparing heights. As Tufte has pointed out, "there are considerable ambiguities in how people perceive a two-dimensional surface and then convert that number into a one-dimensional number. Changes in the physical area on the surface of a graphic do not reliably produce appropriately proportional changes in perceived area"[2].

2) The more informative the study, the wider the point estimate appears, when in fact the tighter the interval will be and more precise the point estimate. In fact, in some of the graphs presented, the point estimate square is wider than the interval with which it is associated.

3) The summary interval containing the most information has the weakest visual presentation of any of the intervals while it is clearly the interval containing the

most information.

In Figure 5 these studies are replotted using confidence bands. An option in the program allows one to present the data subdivided into groups according to some study characteristic (in this example planned duration of tamoxifen use), each with a typical odds ratio.

Other Applications

A series of crude and adjusted risk estimates and 95% confidence intervals are often presented in epidemiologic studies. In case-referent studies, the risks associated with a number of potential risk factors are often presented, while in cohort studies the risks of a series of different diseases are presented according to exposure status. Graphic presentation generally makes it faster and easier to "see" and get a feel for the magnitude and precision of a series of risks than through a table. As well, it down plays the role of specific confidence limits and point estimates.

An example of a series of risks of different health outcomes is presented in Figure 6 which describes the birth defect experience in one municipality relative to a referent population. Because graphic presentations can often be reduced to quite a small size, confidence bands like in Figure 6 could be produced for a series of municipalities and presented to advantage in a confidence band matrix, by placing size-reduced plots for different places beside one another like a table (i.e specific birth defects (rows) by specific regions (columns)). In this way a large amount of data could be presented in a particularly concise, informative and easy-to-see manner.

Discussion

We feel that the confidence band is a useful technique for presenting a series of confidence intervals which has inherent visual advantages over plotting confidence

intervals or confidence interval functions. The technique is particularly useful for meta-analysis but is potentially useful in many applications. We think that confidence band presentation of results will facilitate investigator understanding of the quantitative dynamics of the studies that go into a synthesis and enhance the message the readers of an article will receive.

In an informal visual survey of recent issues of several leading epidemiologic journals, the authors noted that the publication prevalence of graphical presentation was low while the use of tables was epidemic. Because we believe that in many situations "graphics reveal data"[2] better than tables, we hope that this confidence band algorithm will be a tool that encourages epidemiologists to present results graphically.

Note: C.IT source code for creating confidence band graphs from user provided point estimates and confidence intervals is available from the authors. The main control program is written in the fourth generation database language Sculptor. All output is produced using Hewlett Packard's Printer Control Language. The program runs on an IBM-compatible microcomputer.

FIGURE 1. Confidence interval function with two-sided confidence levels and *P*-values: risk ratio = 2.0, standard deviation = 0.354.

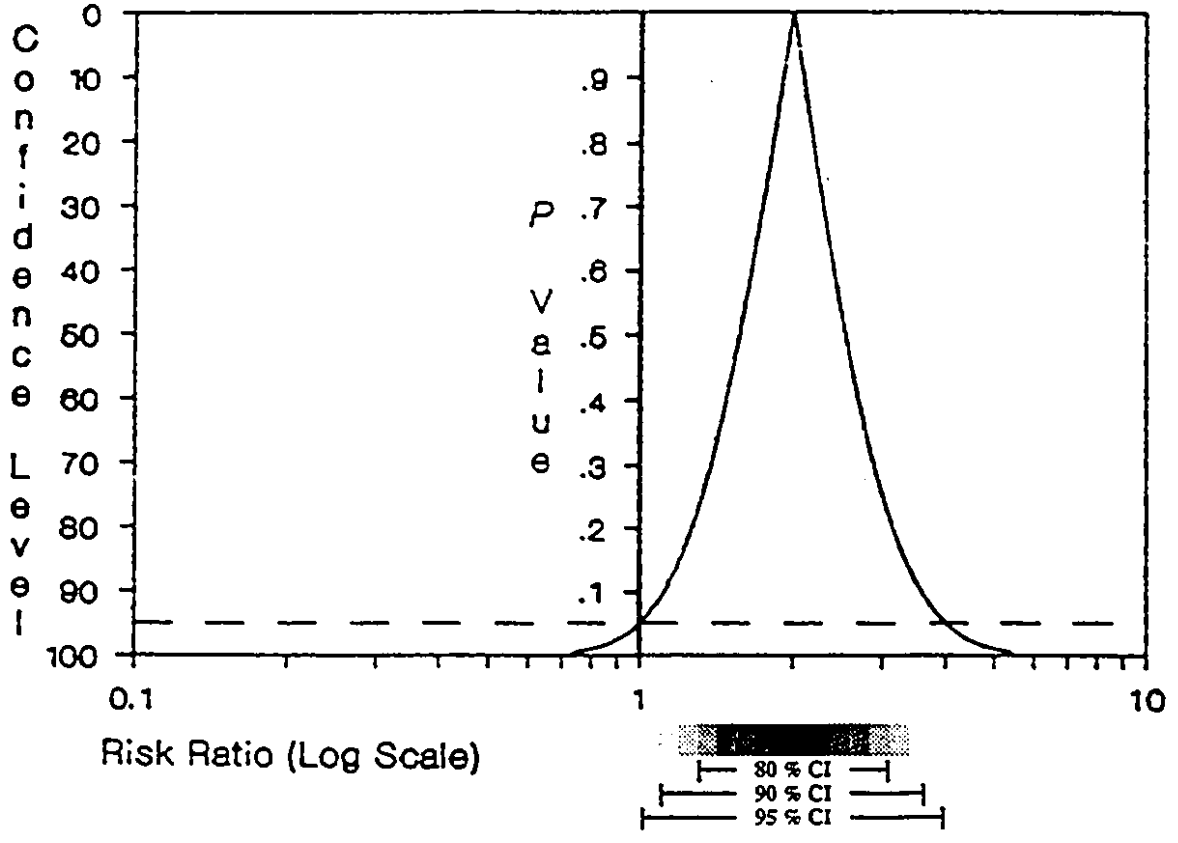
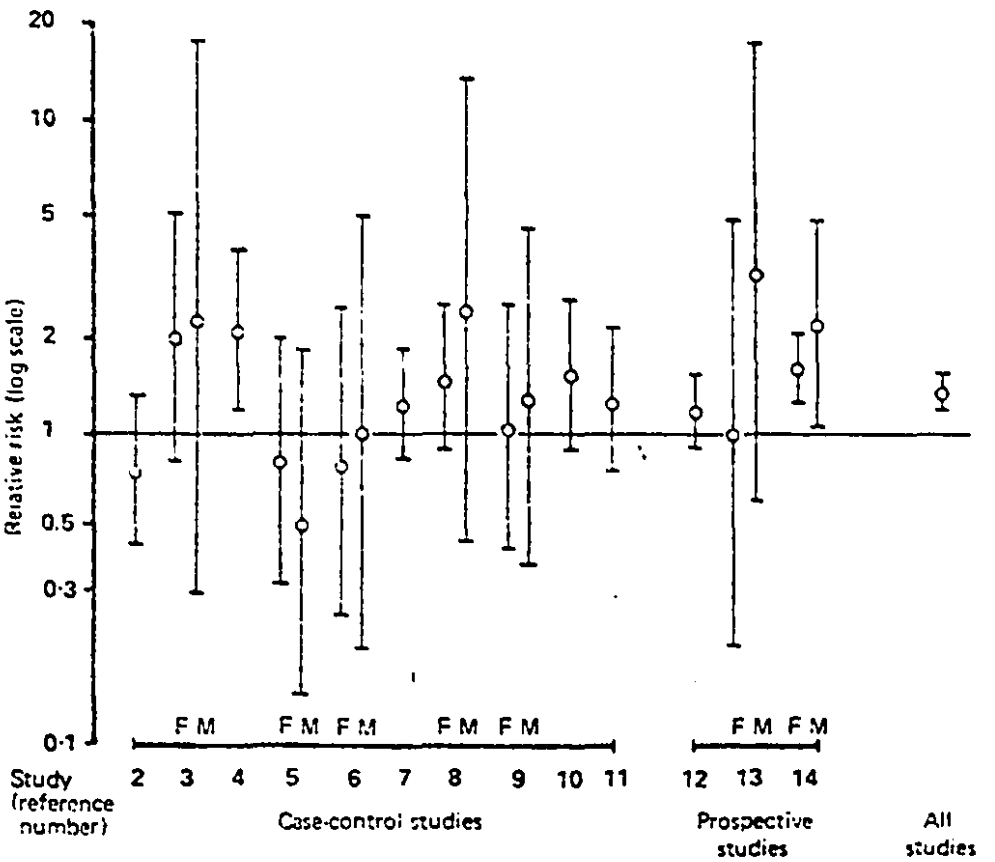


Figure 2: Passive smoking and lung cancer meta-analysis (Wald et al., British Medical Journal, 1986)



—The relative risk of lung cancer (estimate and 95% confidence interval) in non-smokers who live with smokers compared with non-smokers who live with non-smokers for each of the studies given in table I and the summary estimate based on all the studies combined. The estimate for females is shown first for studies based on both male and female subjects.

Figure 3: Passive Smoking and Lung Cancer Meta-Analysis (Wald et al., British Medical Journal 1986)

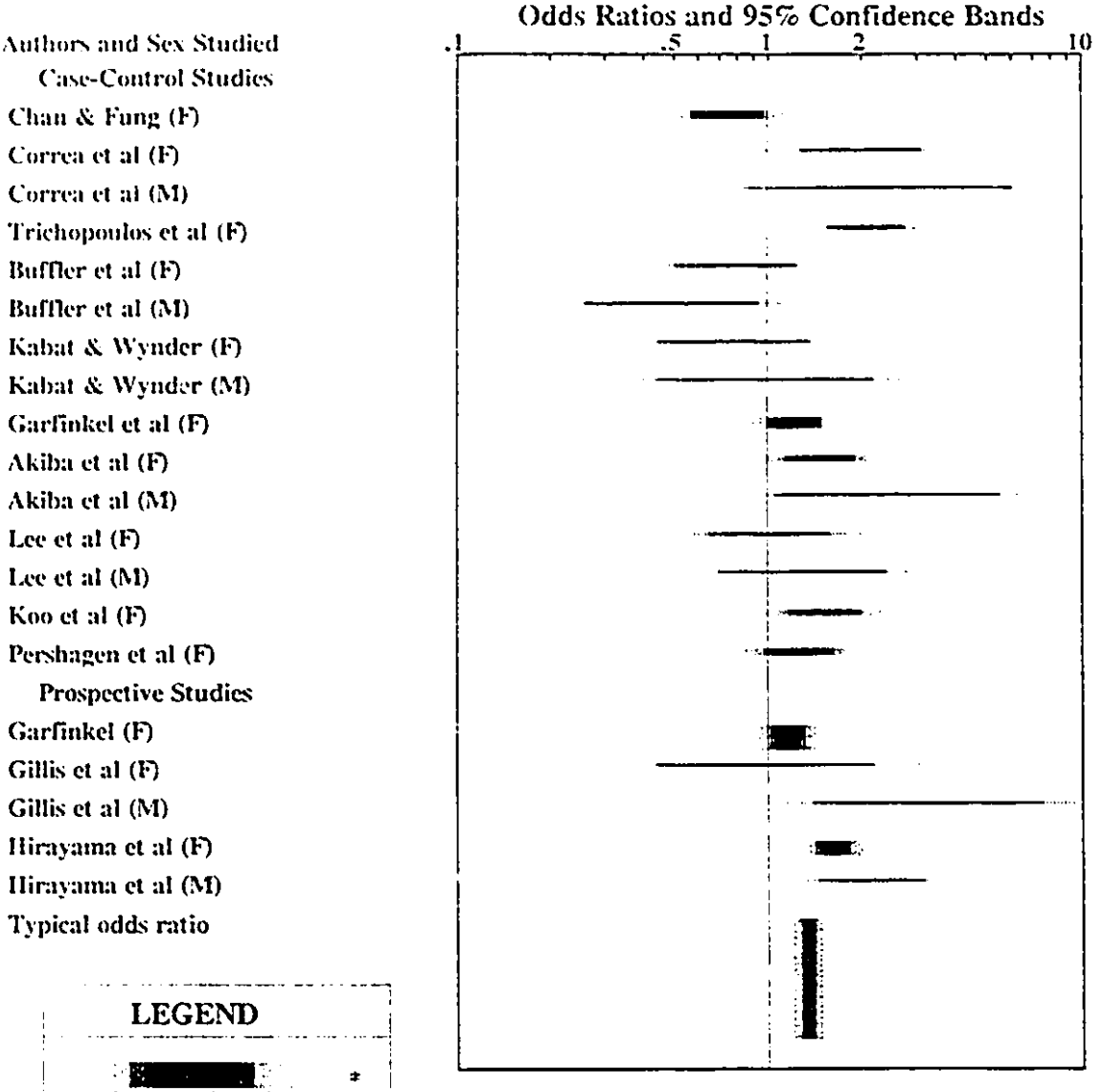


Figure 4: Mortality (all ages) in tamoxifen trials, subdivided by scheduled tamoxifen duration (EBCTCG, Lancet 1992)

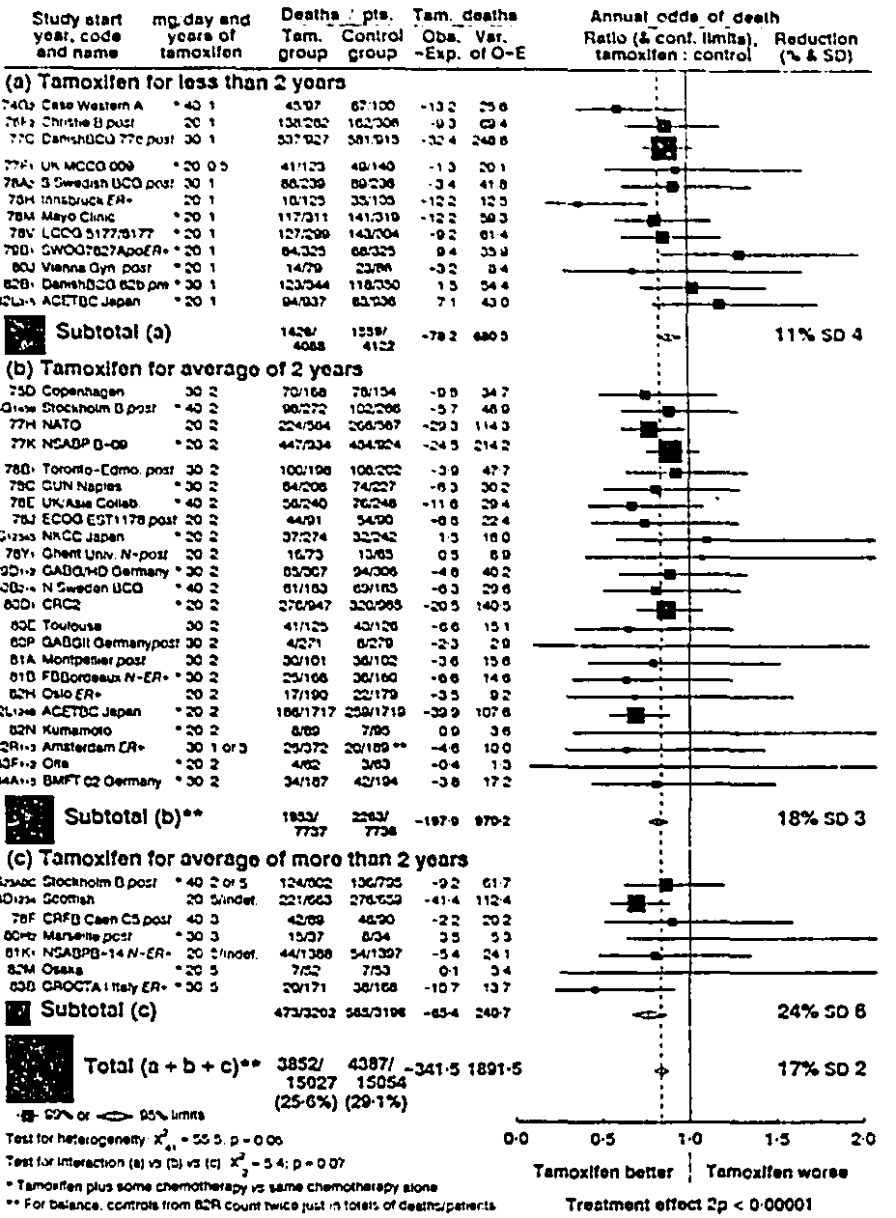


Figure 5: Mortality (all ages) in Tamoxifen trials, Subdivided by Scheduled Tamoxifen Duration (EBCTCG, Lancet 1992)

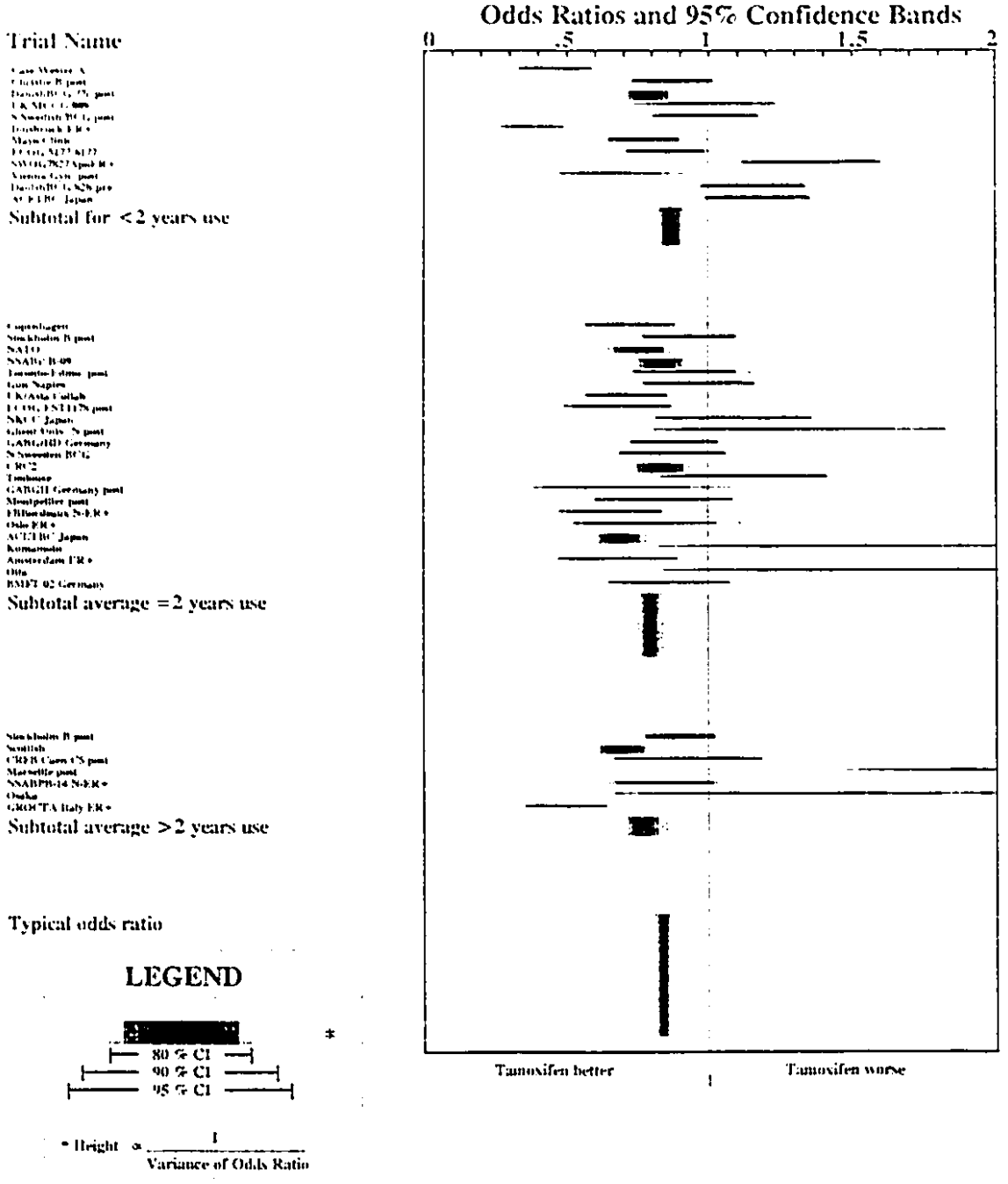
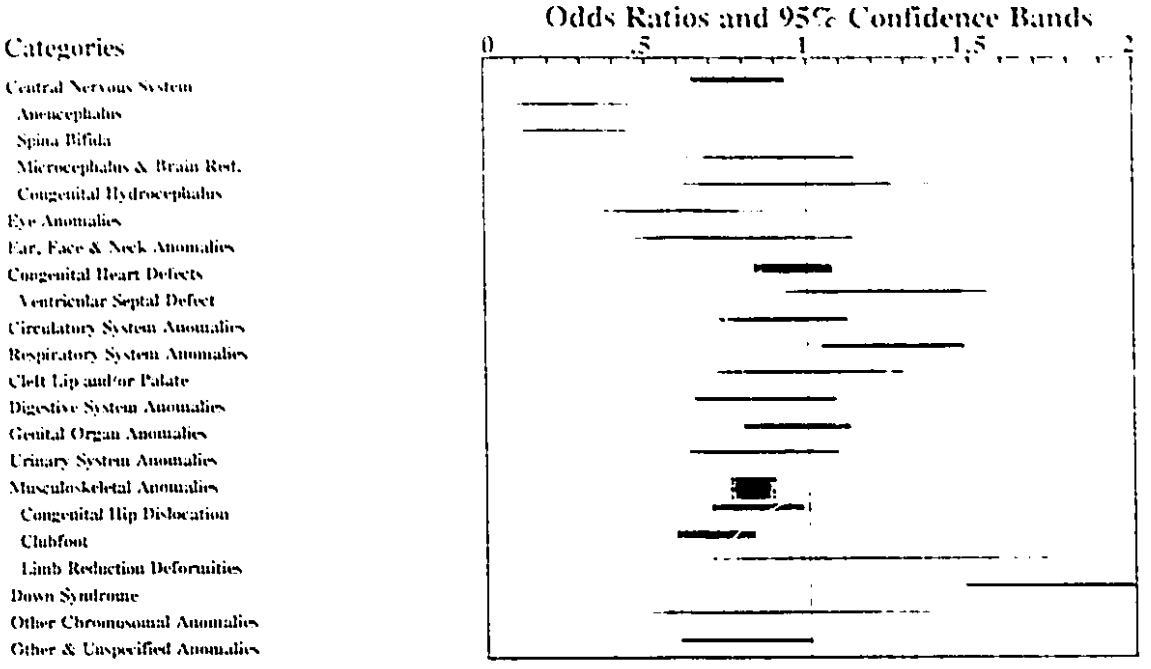


Figure 6: Birth Defect Birth Prevalence Ratios for Pickering (1973-1988), Reference all Ontario (1973-1988)



References

1. Brand S. Editorial, Whole Earth Review 1985; 45:5.

2. Tufte ER. The Visual Display of Quantitative Information. Cheshire, Connecticut: Graphics Press, 1983.

3. Chalmers I, Enkin M, Keirse MJNC, eds. Effective Care in Pregnancy and Childbirth (2 vols). Oxford: Oxford University Press, 1989.

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) . Treatment of Early Breast Cancer: A Systematic Overview of All Available Randomized Trials of Adjuvant Endocrine & Cytotoxic Therapy, Volume 1: Worldwide Evidence, 1985-1990. Oxford University Press, 1990.

5. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does Breathing Other People's Tobacco Smoke Cause Lung Cancer? Br Med J 1986; 293:1217-1222.

6. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA 1988; 260:652-656.

7. Galbraith RF. A note on graphical presentation of estimated odds ratio from several clinical trials. Stat Med 1988; 7:889-894.

8. Walker AM, Martin-Moreno JM, Artalejo FR. Odd man out: a graphical approach to meta-analysis. Am J Public Health 1988; 78:961-966.

9. Early Breast Cancer Trialists' Collaborative Group. Systematic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992; 339:1-15, 71-85.

10. Poole C. Beyond the Confidence Interval. Am J Public Health 1987; 77:195-199.

11. Sullivan KM, Foster DA. Use of the Confidence Interval Function. Epidemiol 1990; 1:39-42.

12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Natl Cancer I 1959; 22:719-748.