
Commentary

Bendectin and Birth Defects: Hopefully, the Final Chapter

Robert Brent^{1,2*}

¹Jefferson Medical College, Philadelphia, Pennsylvania

²Alfred I. duPont Hospital for Children, Wilmington, Delaware
Nemours Foundation

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INTRODUCTION

The study published in this issue of *Birth Defects Research Part A*, "Bendectin and Birth Defects: Ecological Analysis," by Kutcher et al. (2002) deals with two aspects pertaining to the effects of Bendectin. It is an excellent research article. The first area investigated was related to the question as to whether Bendectin was a human teratogen based on ecological analysis. The second area investigated was whether admissions to the hospital for intractable nausea and vomiting of pregnancy increased after the withdrawal of Bendectin from the market.

The evaluation of the merits of the allegation as to whether Bendectin represents any reproductive risks has been reported in review articles in the teratology and legal literature (Brent, 1995a, 1997) utilizing a methodology that has been described previously (Brent, 1978, 1985c, 1986). This evaluative process has been utilized on several occasions for other drugs, chemicals and physical agents (Brent et al., 1991, 1992, 1993, 1995a, 1997, 1999a; Brent et al., 1991, 1993; Christian and Brent, 2001). The method of evaluation is listed in Table 1 and consists of five components of the evaluation process, which include 1) consistency of epidemiological studies, 2) secular trend analysis, 3) animal studies, 4) toxicokinetics and pharmacokinetics, and 5) basic science principles.

Kutcher et al. (2002) focused on two aspects of the Bendectin saga in their article: 1) ecological analysis, and 2) the impact of the withdrawal of Bendectin from the market on the treatment of nausea and vomiting and the clinical effects of the withdrawal of Bendectin from the market place.

ECOLOGICAL ANALYSIS

Kutcher et al. (2002) focused on one aspect of the methods that are used to evaluate the question of the risk of teratogenicity. Prior publications have used the term secular trend analysis and have suggested that the dramatic changes in the Bendectin exposure of pregnant women would not (Brent,

1985a,b, 1986) and did not (Brent, 1985a,c, 1995a, 1997) correlate with the incidence of birth defects alleged to be caused by Bendectin. But although these publications came to the same conclusion as the Kutcher et al. (2002), they did not provide the extensive analysis of all birth defect incidences or an extensive analysis of the exposure of the population to Bendectin. The ecological analysis provided by Kutcher et al. (2002) scientifically and convincingly demonstrates that there was no concomitant change in the incidence of birth defects, although there was a substantial change in the exposure of pregnant women to Bendectin. The strength of this lack of association is supported by the large decrease in population exposure (from 30–35% to a very low exposure) without a concomitant change in the incidence of birth defects. Secular trend analysis or ecological analysis is most convincing when a substantial portion of the population is exposed.

Kutcher et al. (2002) did not address other aspects of the evaluation of the alleged teratogenicity of Bendectin in the article, but they have been covered in the above-mentioned reviews and opinions (Brent et al., 1989; Brent, 1995a, 1997). They did refer to two meta-analyses that have been published, both of which concluded that Bendectin did not have any measurable teratogenic risks (Einarson et al., 1988, McKeigue et al., 1994). The extensive review by Brent (1995a, 1997) came to the same conclusion, and included extensive reviews of epidemiological literature, animal studies, pharmacokinetics, and the basic science principles of teratology and toxicology.

One other aspect of the Bendectin era was the fact that several researchers indicated in court testimony that in vitro studies utilizing Bendectin permitted them to conclude that Bendectin was teratogenic in humans. This conclusion is without merit (Table 2).

*Correspondence to: Dr. Robert Brent, Distinguished Professor of Pediatrics, Radiology, and Pathology, Jefferson Medical College, Alfred I. duPont Hospital for Children, Box 269, Wilmington, DE 19899.

E-mail: rbrent@nemours.org

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Table 1
Characteristics of Environmental Agents That Are
Teratogenic in Humans

1. Epidemiology studies *consistently* demonstrate an increase in the frequency of congenital malformations, and especially a recognizable syndrome in the exposed population.
2. Secular trend analysis reveals that the frequency of congenital malformations is associated with changes in population exposure, i.e., the introduction or withdrawal of environmental agents for which there has been a high population exposure.
3. An animal model has been developed that is similar to the reports in the human and can be produced with pharmacokinetically or toxicokinetically equivalent exposures.
4. In the appropriate animal model, the frequency and severity of the teratogenesis or embryopathology increases with a dose or exposure that is within the range of human exposures.
5. The teratogenic effect is consistent with the basic principles of embryology and teratology and does not contradict biologic principles or biologic common sense.
 - a. Is the exposure level above or below the NOEL?
 - b. The nature of the malformations. Is there an identifiable syndrome?
 - c. Are there receptors for the drug or chemical that would suggest organ specificity?
 - d. Is the agent cytotoxic or mutagenic at exposure levels that occur in the human?

NAUSEA AND VOMITING OF PREGNANCY

The second area focused on by Kutcher et al. (2002) was the impact of Bendectin withdrawal from the marketplace. The data presented in their article indicates quite clearly that the problem of severe nausea and vomiting of pregnancy (NVP) increased after the withdrawal of Bendectin from the marketplace. Although the authors of this study, and others, had indicated in previous publications that this was occurring, documentation is provided by Kutcher et al. (2002) on the basis of hospital admissions.

Kutcher et al. (2002) are conservative in their interpretation of their results, which is the essence of scholarship. They conclude:

"The National Ambulatory Medical Survey data indicated that the decrease in the use of Bendectin was not followed by a concomitant rise in the use of other anti-emetic agents. Thus, the lack of a decrease in birth prevalence rate for limb reduction defects with the cessation of Bendectin use cannot be explained by the substitution and use of an alternative teratogenic anti-emetic. The National Hospital Discharge Survey data demonstrate that the US hospitalization rate for NVP doubled after the reduction and subsequent cessation of Bendectin use. The pattern of NVP in Canada was similar to that seen in the USA when Bendectin sales also disappeared from their marketplace ...However in Canada, Diclectin, a generic form of Bendectin, remained on the market and in the 1990s as the sales of Diclectin markedly increased, the rate of NVP hospitalizations continued to fall (Neutel, 2000)."

"...despite the reduction and cessation of Bendectin sales during the period of 1980–1985, the rate of birth defects (limb reduction defects) was unaffected and the rate of NVP hospitalization had doubled. ...the pattern is quite consistent with the known purpose for which the

drug was taken and with the epidemiological studies that have shown no teratological association."

"Too often, epidemiologists speak of ecological fallacies without giving appropriate recognition to ecological truths. Ecological analyses serve an important and complementary role with epidemiological analyses in presenting public health information."

I would add two additional pieces of information to the authors' excellent analyses. It is important to note that a crucial aspect of secular trend or ecological analyses is that a substantial portion of the population has to be exposed, as has been demonstrated by the usage of Bendectin and the progestational drugs (Wilson and Brent, 1981; Corfman, 1988; Brent, 1989a). Although some courts and juries have focused positively on this data, others have ridiculed this approach out of ignorance.

THE PROBLEM OF NVP

The major perspective on this subject is that so-called normal nausea is a sign of a healthy pregnancy. To understand the problem that pregnant women must face when they have nausea or nausea and vomiting, we need to deal with the medical, social and legal implications of treating NVP. The problem arises when the symptoms become exaggerated and result in debilitation, dehydration, and hospitalization. It is common knowledge that once the symptoms progress beyond a certain stage, treatment becomes more difficult. Therefore, the treatment of NVP in early stages has the implication that it will prevent more serious complications, including hospitalization. Therapeutic modalities that have been utilized or are being tested are primarily symptomatic treatments (antihistamines, Bendectin, phenothiazines, hypnosis, acupuncture, relaxation behavioral modification, audiogenic feedback training, newer medications, diet and nutritional support) (Koren and Levichek, 2002; Magee et al., 2002; Matteson et al., 2002; Niebyl and Goodwin, 2002; Roscoe and Matteson, 2002). Some of them, such as Bendectin, have been studied extensively with regard to their reproductive effects. Bendectin is probably the most studied medication with regard to its reproductive effects, and the studies clearly (Brent, 1983, 1985a,b; Brent et al., 1989, Brent 1995a, 1997) demonstrate that exposure to Bendectin has no demonstrable deleterious or symptomatic effect on the mother or reproductive effect on the fetus. Other medications and therapies have been studied minimally or not at all.

The following discussion pertains to the ethical and legal issues surrounding this topic and how they have been amplified by the Bendectin era. Before Bendectin litigation, nonmeritorious congenital malformation lawsuits were filed and went to trial, and junk science was presented at these proceedings (Brent, 1967, 1968, 1977, 1982, 1987, 1992a,b). But the Bendectin era focused our attention on the area of nonmeritorious litigation (Brent 1995a,b,c) and junk science.

Although some aspects of this discussion may seem to be critical of the legal profession, it is important to place this criticism in perspective. Physicians, as a group, tend to be hypercritical of the legal profession because of the escalation of malpractice litigation and malpractice insurance premiums. Recommendations from the medical community for modification of the law, to reduce the frequency of nonmeritorious litigation and the size of the awards, have

Table 2
Utilization of Bendectin in In-vitro Studies*

Authors	Test	Results
Simmon and Marx, 1979	Ames test (test for mutagenicity)	Negative
Budroe et al., 1984	Hepatocyte DNA repair assay	Minimal effect
Greenberg, 1982	Differentiating neural crest cells	No effect at 250 µg/ml or 50 µg/ml
Braun et al., 1982	Inhibition of ascites tumor attachments	Bendectin used in very high doses; no effect
Guntakatta et al., 1984	Limb bud culture proteoglycan synthesis	No effect of Bendectin at 15 µg/ml (100 times the human peak blood level)
Hassell and Horigan, 1982	Teratogenic potential utilizing limb bud mesenchyme cells for 6 days and staining with Alcian Blue. This test is inappropriate for determining the etiology of limb reduction defects that do not have a problem with cartilage formation.	Bendectin, 50 µg/ml (300 times the human peak blood level) inhibited proteoglycan synthesis
Steele et al., 1988 The authors concluded that "in vitro systems are limited" in their ability to determine risk for the reasons they explain in their paper.	Utilized the human embryonic palatal mesenchymal cell growth inhibition assay (HEPM) and the mouse ovarian tumor cell attachment inhibition assay (MOT)	Forty-four compounds were tested with these assays. The authors considered the MOT assay to negative for doxylamine succinate. The HEPM assay was positive at concentrations far above the levels reached following the administration of Bendectin to humans.
Muller et al., 1989	Transplacental exposure of mouse embryos to doxylamine succinate followed by analysis of mouse cells for sister chromatid exchange (SCE), bone marrow micronuclei, human lymphocytes for SCE and chromosomal aberrations in mouse cells.	The authors concluded that "relevant mutagenic potential" could not be concluded from these studies.

*Most of these in vitro tests were negative and the two that were positive were at drug concentrations far above the human therapeutic range. Furthermore, in vitro tests are useless in predicting human risks if the human epidemiology studies and in-vivo animal studies do not indicate the presence of reproductive toxicity. There is not a single human teratogen that has been identified by the scientific community from in vitro studies, whose epidemiological and in vivo animal studies are negative.

been minimally successful, primarily because lawyers dominate the legislatures. I have suggested that physicians and scientists focus their attention on junk scientists and junk science, because this is an area over which physicians and scientists should establish professional standards and control. (Brent 1968, 1977, 1982, 1987, 1992a, 1995a,c).

More importantly, we should respect and admire the importance and accomplishments of the legal profession, because it is the foundation of any thriving democracy. Without the law, we could never have rid ourselves of a sitting president, or protected all of the constitutional rights bestowed on individuals. Because a very small percentage of attorneys exploit the power of the law to their advantage does not indicate that the legal system has to be replaced or eliminated. A functioning legal system with its benefits and risks is to the advantage of all, although there are modifications of the legal system that could ameliorate the present negligence litigation crisis, such as capping punitive damages and eliminating or reducing contingency fees. Remember that many nonmeritorious lawsuits could not proceed, if it were not for the testimony of a junk scientist who appears before a judge, and testifies that the case has merit. Many of these junk scientists are obstetricians and pediatricians, as well as other members of the clinical and scientific community (Brent, 1982, 1995a, 1997).

The problem of managing the clinical care of pregnant women with nausea and vomiting is epitomized by the Bendectin era, the period from 1960–2000. A review of this history delineates the problems we face and potential solutions.

HISTORICAL PERSPECTIVE 1960s

Lawsuits alleging that various phenothiazines and antihistamines caused birth defects. There was an increase in the number of lawsuits involving malformed children and their families as plaintiffs (Brent, 1967). Many lawsuits involved an anti-nausea medication, such as meclizine. The first meclizine lawsuit, with which I was acquainted, involved a child with ectrodactyly, ectodermal dysplasia, and cleft palate (EEC) syndrome, which is a genetic disease (Cockayne, 1936; Tentamy and McKusick, 1969; Rudiger et al., 1970; Brill et al., 1972). Scientists from a prestigious university and the National Institutes of Health testified that meclizine caused this child's defect, which, of course, was present at the time of conception, before there was any exposure to the medication, because the EEC syndrome is either a dominant mutation or dominantly inherited.

Bendectin containing doxylamine succinate, dicyclomine, and pyridoxine was listed as appropriate for the treatment of NVP. The Federal Drug Administration (FDA) approved labeling for Bendectin as the only drug recommended previously for the treatment of nausea and vomiting in pregnant women

1970s

National Academy of Sciences listed Bendectin as possibly effective. A committee of the National Academy of Sciences (NAS) evaluated a long list of medications with regard to their effectiveness. The manufacturer of Bendec-

tin was of the opinion that the therapeutic benefits were greater than that expressed by the NAS and commissioned further studies of effectiveness in a double blind study.

A peer review group of 15 toxicologists, epidemiologists, obstetricians, and teratologists reviewed the NAS opinion and suggested that a double-blind study be carried out utilizing various combinations of the constituents in Bendectin. The results of these studies indicated that dicyclomine did not contribute to the effectiveness of Bendectin, but that the combination of doxylamine and pyridoxine was effective. A new Bendectin compound was reformulated without dicyclomine.

1980s and 1990s

FDA Maternal Health Drug Committee deliberations. In the early 1980s, the FDA Maternal Health Drug Committee discussed Bendectin at several of their meetings and actually held open hearings on the merits of the allegation that Bendectin caused congenital malformations. Before the committee could complete their report, the deliberative process was terminated through political intervention by a governmental official whose grandchild had been born with a birth defect and whose mother was prescribed Bendectin during her pregnancy.

Mekdeci lawsuit initiated, followed by the Ohio class action lawsuit and numerous individual lawsuits. The plaintiff in the Mekdeci lawsuit had Poland Syndrome, with a unilateral limb defect. Poland Syndrome is thought to be due to vascular disruption (Bouwes-Bavinck and Weaver, 1986; Der Kaloustian et al., 1991). In some cases, the disease is familial (Fuhrmann et al., 1971; David, 1982; David and Winter, 1985; Cobben et al., 1989). The only epidemiological data available in the early 1980s did not support the allegation that Bendectin could cause Poland Syndrome. In the first trial, the jury determined that Bendectin did not cause the malformations, but they awarded \$20,000.00 to the family. The explanation given by the jury was that they wanted to compensate the family; the judge reversed the decision. In the second trial, another jury rendered a defense verdict.

The class-action lawsuit in Ohio was supervised by Judge Hoffman, who negotiated a settlement of \$120,000,000.00 (Bendectin litigation, 1984). There were over 1,000 plaintiffs in this class-action lawsuit. The plaintiff attorneys rejected the negotiation and the cases went to trial; the trial resulted in a defense verdict.

Insurance premiums exceeded gross sales for Bendectin, and the manufacturer stopped marketing Bendectin in the early 1980s. Unavailability of Bendectin resulted in an increase in admissions to hospitals in the United States for severe NVP. With the withdrawal of Bendectin from the U.S. market, the rate of exposure among pregnant women dropped markedly. In the 1970s, the percentage of pregnant women taking Bendectin was as high as 30–35% (Harron and Griffiths, 1980; Anonymous, 1983; Congenital Malformation Surveillance Bulletin, 1993). The frequency of limb reduction defects and congenital heart disease remained the same during the 1980s, when pregnant women had practically no exposure to Bendectin (Congenital Malformation Surveillance Bulletin, 1993). The allegation that Bendectin is a human teratogen is not supported by this type of secular trend divergence in the frequency of exposure and malformations.

Peer review group convened by the Canadian government and the preparation (Diclectin) is continued on the market. A Canadian Member of Parliament, concerned about all the notoriety that Bendectin was receiving in U.S. newspapers, requested that the Canadian equivalent of the FDA review the data pertaining to the teratogenicity of Bendectin (the equivalent drug in Canada is Diclectin).

The review panel consisted of members of the drug approval branch of the Canadian government, Drs. G. Koren, A. Scialli, E. Zimmerman, and myself. The panel published their findings, and Diclectin was kept on the market in Canada (Brent et al., 1989).

Relevant Publications and Lawsuits

Numerous negative cohort, case-control human studies, animal studies, in vitro studies, commentaries, and meta-analyses of the potential fetal effects of Bendectin have been published. Interestingly, not a single review article was written by any of the plaintiff experts about Bendectin. The most recent complete review of the subject was published in 1995 and reprinted with some modifications in 1997 (Brent, 1995a, 1997).

Other Important Bendectin Lawsuits

Several important lawsuits have been discussed, but others are equally important:

1. Hagaman case (1987): Split-hand syndrome
2. Daubert (1989): Supreme Court decision (Brent, 1995b)
3. Depyper (1995): Friend of the court testimony
4. Blum (1999) Length of the litigation process.

The Hagaman case (1987) involved a plaintiff with a typical split-hand, split-foot syndrome that is due to an autosomal dominant gene (Pearson, 1908; McMullen and Pearson, 1913; MacKenzie and Penrose, 1951; Neugebauer, 1962; David, 1972; Bujdoso and Lenz, 1980), either inherited, or mutated during oogenesis or spermatogenesis. Alleging that an exposure to Bendectin during pregnancy caused this malformation is scientifically inappropriate.

The Daubert (1989) decision allows judges to prevent the testimony of an expert if that witness does not utilize acceptable scientific methodology. Many experts for the plaintiff in the Bendectin litigation had their testimony rejected by the courts. This was an important and monumental decision (Brent, 1989b, 1992a,b, 1995a,b, 1997).

In the Depyper trial (1995), the judge requested experts to testify as friends-of-the-court, which had been suggested previously (Brent, 1967).

The Blum case (1999) involved a child who was born with clubfeet and had to have surgery more than once. A clinical geneticist examined the family, and concluded that the family had mild symptoms of Ehlers-Danlos syndrome that accounted for the failed surgery and the presence of clubfeet. The first and second trial resulted in plaintiff verdicts, but was reversed by appeals to superior courts. This case is an example of the length of time (1982–1999) that a family can be involved in litigation.

Table 3
Bendectin and Congenital Malformation Cohort Studies*

	Study group	Exposed total	Exposed malformed	Nonexposed total	Nonexposed malformed	Relative risk	95% CI
Heinonen et al., 1977	50,282	1169	79	49,113	3169	1.05	0.84–1.30
Fleming and Knox, 1981	22,977	620	31	22,357	1208	0.93	0.65–1.31
Michaelis and Gluck, 1983	1748	874	18	874	19	0.95	0.50–1.79
Milkovich and van den Berg, 1976	10,205	628	14	9577	343	0.62	0.37–1.06
Morelock et al., 1982	1690	375	31	1315	93	1.17	0.79–1.73
Aselton and Jick, 1983	5254	1364	2	3890	4	1.43	0.26–7.78
Gibson et al., 1981	7456	1685	78	5771	245	1.09	0.85–1.40
Jick et al., 1981	6837	2255	24	4582	56	0.87	0.54–1.40
General Practitioner Research Group, 1963	661	72	2	589	18	0.91	0.22–3.84
Newman and Correy, 1977	7933	1192	6	6741	70	0.48	0.21–1.11
Smithells and Sheppard, 1983	3426	1173	28	1713	31	0.89	0.54–1.51
Bunde and Bowles, 1963	4436	2218	11	2218	21	0.52	0.25–1.08
Shiono and Klebanoff, 1989	31,564	2720	51	28,793	520	1.0	0.8–1.4
Summary						0.95	0.62–1.45

*Adapted from Einarson et al., 1988 (64). A second met-analysis was performed by McKeigue et al., 1994 (65) with similar results.

BENEFITS AND RISKS OF INTRODUCING MEDICATION AND TREATMENT FOR NVP

Benefits of Effective Treatment

There are many clinical, psychological, and social benefits that will result from any effective therapy that reduces or eliminates the symptoms of NVP in pregnant women. These benefits include: 1) symptomatic improvement and comfort; 2) optimal nutrition for mother and fetus; 3) decreased risk of some pregnancy complications; 4) psychological benefits; 5) decrease in absenteeism for working mothers; and 6) decrease in the difficulty of managing the home and family.

Medical Risks of Therapeutic Intervention

The medical risks of any therapy have two implications. The therapy may be 1) unacceptable to the patient, or 2) represent a medical risk that is unacceptable to the physician and the patient. The risk of a new therapy could represent a risk greater than the benefits of relieving nausea and vomiting. Some of these risks, if they occur, could lead to litigation. The most serious medicolegal risk is the occurrence of embryonic and fetal malformations (Brent, 1977). The risks of therapy include: 1) side effects of the therapy in pregnant woman; 2) deleterious effects of the therapy on the embryo or fetus; 3) idiosyncratic reactions; 4) ineffectiveness of therapy; and 5) risk of the patient selecting untested medications such as herbal or home remedies.

Legal Risks of Therapeutic Intervention

Legal risks of therapeutic intervention include allegations that: 1) the therapy was not effective; 2) side effects of therapy are the result of negligence by the physician or drug manufacturer; 3) maternal reproductive problems are the result of negligence by the physician or drug manufacturer; and 4) birth defects, abortion, or fetal pathology are the result of negligence by the physician or drug manufacturer.

Many therapies for the treatment of NVP were mentioned in the study (introduction section) by Kutcher et al. (2002); these other therapies have minimal data on which to base an evaluation of the risk of reproductive effects. Unfortunately, attorneys can be creative in generating hy-

potheses and in obtaining witnesses willing to support hypotheses that suggest teratogenic or reproductive effects of the therapy. Even when therapies such as acupressure, hypnosis, psychotherapy, or psychological conditioning seem very unlikely to harm the fetus, the initiation of lawsuits is not prevented if a severely malformed fetus resulted from that pregnancy. Therefore, the best protection for patients, physicians, drug manufacturers, and those who develop therapeutic techniques is abundant data indicating that the therapy has no measurable harmful effects on the developing embryo or fetus, as well as the pregnant woman. Unfortunately, there is only one therapy that fits these criteria now, and that is the administration of Bendectin. There are over 13,000 patients in 12 cohort studies and numerous case-control studies that indicate that Bendectin does not represent a measurable risk to the developing mother or fetus (Tables 3, 4) (Bunde and Bowles, 1963; Bunde and Leyland, 1965; Yerushalmy and Milkovich, 1965; Milkovich and van den Berg, 1976; Heinonen et al., 1977; Newman and Correy, 1977; Shapiro et al., 1977; Rothman et al., 1979; Michaelis and Gluck, 1980; Bracken and Holford, 1981; Clarke and Clayton, 1981; Cordero et al., 1981; Correy and Newman, 1981; Fleming and Knox, 1981; Gibson et al., 1981; Mitchell et al., 1981; Eskenazi and Bracken, 1982; Morelock et al., 1982; Bracken and Berg, 1983; Golding et al., 1983; Jick et al., 1983; Mitchell and Shapiro, 1983; Smithells and Sheppard, 1983; Hearey et al., 1984; McCredie et al., 1984; McCredie and Krickler, 1984; Elbourne et al., 1985; Zierler and Rothman, 1985; Shiono and Klebanoff, 1989; Brent 1995a, 1997). Furthermore, animal studies and in vitro studies support this conclusion. No other treatment of NVP has demonstrated the low-risk record of Bendectin.

CLINICAL AND RESEARCH RECOMMENDATIONS

Research On Physiology and Mechanism of NVP, and Benefits and Risks

We should design therapy based on basic science aspects Of NVP. Most of the therapies and research discussed

Table 4
Bendectin Case Control Studies

Authors	Malformations	OR	Confidence limits	Significance ²
Greenberg et al., 1982 ¹		0.84	0.62–1.17	–
Rothman et al., 1979 ¹	Congenital heart disease	1.8	1.2–2.7	+
Zierler and Rothman 1985 ¹	Congenital heart disease	1.09	0.76–1.55	–
Golding et al., 1983 ¹	Cleft lip and palate	2.88	1.19–6.96	+
Eskenazi and Bracken, 1982 ¹	Pyloric stenosis	4.33	1.75–10.75	+
Mitchell et al., 1981	Oral clefts	0.9	0.5–1.5	–
	Cleft palate			
	Cleft lip and palate	0.6	0.4–0.8	–
Elbourne et al., 1985		0.64	0.12–3.34	Oxford results
	Oral clefts	0.37	0.09–1.44	Aberdeen results
				–
Mitchell et al., 1983	Pyloric stenosis	0.9	0.6–1.2	–
McCredie et al., 1984	Limb reduction defects	1.1	0.8–1.5	First trimester
		1.0	0.7–1.4	–
Cordero et al., 1981	Limb reduction defects	1.18	0.65–2.13	–
David, 1982	Poland anomaly			–
Bracken and Berg, 1983	Diaphragmatic hernia	1.6	0.3–8.7	–
Mitchell and Shapiro, 1983	Diaphragmatic hernia			–
Cordero et al., 1981	Diaphragmatic hernia	1.74	0.81–3.76	–

¹The first five case control studies were the only studies utilized in the meta analysis performed by Einarson et al., 1988. (64)

²The notation (positive + or negative –) in the last column indicates whether the authors concluded that their results were statistically significant.

above can be labeled as symptomatic treatment, although there are studies dealing with susceptibility, etiology and methods of evaluation (Attard et al., 2002; Black, 2002; Buckwalter and Simpson, 2002; Heinrichs, 2002; Koren et al., 2002; Magee et al., 2002a,b). The answer to any clinical problem is best derived from mechanistic research. For example, what pregnancy metabolic product is interacting with what brain receptor that induces nausea and vomiting in pregnant women? It would seem most logical that major research efforts should be directed toward brain receptors involved in these physiological effects. Furthermore, it seems imperative to study the array of molecules, both natural and manufactured, that can interact with these receptors. We have models of angiotensin II receptor blockers (Bumpus, 1977) and endothelin receptor blockers (Kurihara et al., 1994; Love and McMurray, 1996; Pernow and Wang, 1997; Schiffrin et al., 1997; Bauersachs et al., 1999) that are used for the treatment of hypertension. A similar approach could be utilized to study the mechanism of nausea and vomiting during pregnancy, and to develop an effective, safe therapy.

Standardization of Anti-Nausea Medication Use With Regard to the Most Appropriate Dose, and Type of Phenothiazine, Antihistamine, or Combination of Agents

Many phenothiazines and antihistamines would be effective therapies for NVP and would represent very low risks to the embryo (Koren and Levichek, 2002); however, there has been very little epidemiological data collected in pregnant women for many of these products. Thus, it would be difficult to establish that these medications represent no measurable risk to the developing embryo or fetus.

Reintroduction of Doxylamine Succinate-Pyridoxine Combination as the Only Medication Used for NVP

At this time, it would seem that the most conservative approach to the problem of providing effective therapy for NVP is the reintroduction of Bendectin for use in pregnant women. The first reason for making this recommendation is that the therapy is effective. Second, the massive amount of data on the lack of reproductive risks would provide a bulwark against any litigation that might be initiated by families of malformed children from Bendectin-treated pregnancies.

Of course, that should not stop investigation into the mechanism of nausea and vomiting in pregnancy and the development of more specific therapies based on receptor physiology and modern drug development techniques.

RECOMMENDATIONS PERTAINING TO THE LEGAL RISKS

Introduce Legislation Similar to the Vaccine Injury Compensation Act

If we followed the model of the Vaccine Injury Compensation Act (Department of Health and Human Services, 2002), it would be a serious error. The question of vaccine injury to immunized children was a very controversial issue in the medical community (Department of Health and Human Services, 2002). Although the risks were very small, the number of lawsuits initiated was very large. The data pertaining to Bendectin is much more decisive and, from the scientific vantage point, not controversial with regard to its reproductive effects. Therefore, there is a better approach to solve the problem of potential litigation than to pursue legislation similar to the Vaccine Injury Compensation Act.

Reintroduce Bendectin

Until we understand the mechanism and specific therapy for nausea and vomiting, it would seem that the reintroduction of Bendectin (doxylamine succinate-pyridoxine) is the logical intermediate course to follow. Accompany the introduction of Bendectin with an educational campaign with regard to the lack of reproductive risks for this medication.

In 1999 the FDA published a statement in the Federal Register, which summarizes the organizations opinion on the lack of teratogenicity of Bendectin (Federal Drug Administration, 1999b):

“Summary: The Food and Drug Administration has determined that the drug product Bendectin, a tablet composed of pyridoxine hydrochloride, 10 milligram (mg), and doxylamine succinate, 10 mg, for the prevention of nausea during pregnancy was not withdrawn from sale for reasons of safety or effectiveness. This determination will permit FDA to approve abbreviated new drug applications (ANDAs) for the combination product pyridoxine hydrochloride, 10 mg, and doxylamine succinate, 10 mg, tablets.”

The FDA has set the stage for the reintroduction of Bendectin by republishing their conclusion that Bendectin does not represent an increase in reproductive risks to the fetuses of pregnant women. Therefore, the FDA and other organizations should be very much involved in physician and patient education in the use of this combination drug for treatment of NVP. Position articles from various research and clinical societies should review the subject and publish their views on the reproductive risks of Bendectin. The American Bar Association should be approached and requested to issue a statement similar to the FDA and many of the clinical and research societies. In this way, a program to diminish and neutralize any attempt by some attorneys to capitalize on the fact that 3% of mothers receiving any treatment for nausea and vomiting will have a child with a congenital malformation (the background incidence of major birth defects) (Congenital Malformation Surveillance Bulletin, 1993; Brent, 1995 a, 1997).

ACKNOWLEDGMENTS

I became familiar with Bendectin from several vantage points: as an investigator and teacher in the fields of teratology, genetics and epidemiology; a participant in a peer review of Bendectin with regard to its efficacy and risks; as a member of the Maternal Health Drug Committee of the FDA when Bendectin was a topic discussed at its committee meetings; a member of an expert panel appointed by the Canadian government to review the data pertaining to the reproductive risks of Bendectin; an author of commentaries indicating that my opinion was that Bendectin did not produce a measurable increase in congenital malformations in women exposed to the drug during pregnancy; and as an expert witness for the defense in several Bendectin lawsuits and as a reviewer of materials in several others. Some of the material in this commentary was presented at a recent NICHD symposia on nausea and vomiting of pregnancy and published (Brent, 2002).

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