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The National Birth Defects Prevention Study: How to communicate data

Anthony R. Scialli*

Tetra Tech Sciences, 2200 Wilson Blvd Ste 400, Arlington, VA 22201, USA

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SUMMARY

The National Birth Defects Prevention Study is a population-based case–control study. The study has actively sought to identify children with any of 34 specified types of malformation. The mothers of affected and unaffected children have been interviewed with regard to demographic information, lifestyle factors, and exposures. A large number of published studies have appeared and continue to appear on diverse exposures and outcomes. An example of such a study identified an increased odds ratio for ondansetron use among the mothers of children with cleft palate. Possible explanations for associations between exposures and outcomes are chance, error, and causation. The ondansetron–cleft palate association may have arisen by chance given the large number of comparisons made in the study. Error appears unlikely as an explanation of the association. The assessment of causation in teratology uses a systematic evaluation based on the Hill criteria or similar criteria of Shepard or Brent.

1. Introduction

Because we counsel families about the risk for developmental abnormalities from exposures, we find ourselves in the business of interpreting data. Our pregnant patients who have been exposed to a medication or an environmental chemical want to know, 'Is it safe?', and our patients who have had a child with a developmental problem want to know, 'What caused this problem?' The published literature does not give us a direct answer to these questions. Instead, the literature gives us data, and we have to bring our expertise and analytical skills to bear on turning the data into answers that are useful to our patients. In this paper, I describe the National Birth Defects Prevention Study (NBDPS), which has become an important source of data, and I suggest how these data can be incorporated into our practices using as an example a study of medications for nausea and vomiting of pregnancy.

2. What is the National Birth Defect Prevention Study?

The NBDPS is an ongoing population-based case–control study sponsored by the US Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA). The study saw its origins in an act of Congress in 1996 that directed CDC to establish Centers for Birth Defects Research and Prevention. These centers include the birth defects surveillance and research programs of Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah.

The centers identified infants with any of 34 congenital malformations or types of malformation (Box 1). The selection and classification of abnormalities followed detailed guidelines that were used by all centers in the program [1]. These guidelines provided criteria for case definition and policies for the exclusion of genetic syndromes and for the categorization of infants with multiple malformations. There were differences between centers in whether stillborn infants and elective terminations of prenatally diagnosed malformations were included [2]. Control children were randomly selected from birth certificates or birth hospitals. Mothers were interviewed by female personnel using a standard computer-assisted telephone interview in English or Spanish. Prior to the interview, each mother was mailed an information packet, a calendar that included the dates of her pregnancy, and a money order for $20. Interviewing was stopped on 31 March 2013.

Questions were asked about exposures that occurred from three months before conception through the end of the pregnancy. Most questions were structured with coded response lists, but some questions were open-ended, for example questions about occupation and occupational exposures. Interviews were performed no sooner than 6 weeks after the estimated date of delivery and no later than 24 months after the estimated date of delivery, with a target date of 6 months after the estimated date of delivery [2]. The information collected by the maternal interview is summarized in

* Tel.: +1 571 527 1709.
E-mail address: Tony.Scialli@TetraTech.com.

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Box 1
Malformations included in the National Birth Defects Prevention Study[a]

Cardiovascular

Anomalous pulmonary venous return
Conotruncal heart defects
Heterotaxy
Hypoplastic left heart syndrome
Obstructive heart defects
Septal heart defects
Single ventricle

Central nervous system

Anencephaly
Dandy–Walker malformation
Encephalocele
Holoprosencephaly
Spina bifida

Eye

Anophthalmia/microphthalmia
Congenital cataract
Glaucoma

Ear

Anotia/microtia

Orofacial

Choanal atresia
Cleft lip
Cleft palate

Gastrointestinal

Biliary atresia
Esophageal atresia and tracheo-esophageal fistula
Intestinal atresia

Genitourinary

Hypospadias (2nd or 3rd degree)
Renal agenesis (bilateral)

Musculoskeletal

Bladder exstrophy
Cloacal exstrophy
Craniosynostosis
Diaphragmatic hernia
Gastroschisis
Limb deficiency
Omphalocele
Sacral agenesis/caudal regression

Non-system-specific

Amniotic band sequence

[a]Terminology as presented on the NBDPS web site at http://www.nbdps.org/aboutus/bd.html.

Box 2. There were also questions about paternal demographic and lifestyle factors. After the interview, women were sent a kit for collecting buccal cells from the child, if living, and the parents, and parents were sent another $20 money order. These cells are being used for genetic studies.

The data collected from study participants were pooled and are available to all participating centers. Investigators at the centers have published and continue to publish study data, often in conjunction with additional authors. Since the first results appeared in 2001, there have been more than 170 publications covering diverse exposures including medications, diet, obesity, and lifestyle factors among others (see Appendix).

Box 2
Categories of information collected by maternal interview[a]

Maternal health

Illnesses
  Diabetes
  Fever
  Hypertension
  Respiratory illnesses
  Seizure disorder
  Urinary tract infection
  Other illnesses
Injuries
Medication exposure (prescription and non-prescription)
X-ray exposure

Pregnancy

Assisted reproductive techniques
Contraception
Nausea and vomiting
Prenatal care
Pregnancy history

Substance use and diet

Alcohol
Caffeine
Food supplements
Illicit drugs
Tobacco
Vitamins
Assessment of diet

Home and work

Hot tub/sauna
Military service
Occupation
Residence

Water

Bathing
Drinking water sources
Swimming pool use
Other water uses

[a]Adapted from Yoon et al. [2]

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3. Epidemiology study designs

Epidemiology studies can be descriptive, that is, reporting statistics on the incidence or prevalence of a condition, or they can evaluate associations between exposures and outcomes. Two frequently used designs that evaluate associations between exposures and outcomes are cohort studies and case–control studies. Cohort studies define two or more groups based on their exposures or other potential risk factors and measure the occurrence of outcomes of interest in the group members. Case–control studies define groups by outcome and measure the previous occurrence of exposures or other risk factors of interest. As indicated above, the National Birth Defects Prevention Study is a case–control study.

There are strengths and weaknesses of each type of design. Because cohort studies define group membership based on exposure, ascertainment of exposure is, in theory, straightforward. For unusual outcomes, however, cohort study designs require large samples in order to have the power to detect a meaningful difference between exposed and unexposed groups in the prevalence of the outcome. Case–control studies define group by outcomes, so a study population is enriched by including only individuals with the outcome of interest. In case–control studies, it can be a challenge to reliably ascertain exposure status, which can be based on maternal recall, medical/pharmacy record evaluation, or insurance claims. Errors in ascertaining exposure status may be systematic, meaning that they are more likely in one group (e.g. cases) than the other, which can affect the findings of the study.

In case–control studies, the end-points that can be evaluated are limited to those selected by the investigators prior to the collection of data. Exposures that cause an increase in birth defect risk usually do so with respect to a syndrome or pattern of birth defects. A criticism of case–control studies is that they address individual birth defects rather than syndromes or patterns of birth defects. For example, exposure to isotretinoin during pregnancy can be associated with micrognathia, ear abnormalities, and conotruncal heart defects. A study of isotretinoin using the National Birth Defects Prevention Study would be expected to identify an association with conotruncal heart defects and possibly with microtia/anotia, but would not identify an association with micrognathia, which is not a malformation included in the study. Identification of the isotretinoin syndrome, then, might not arise from this study. Elements of a proposed syndrome could be investigated, but some prior knowledge of these elements would be needed in order to direct the investigators' attention to the right combination of abnormalities.

4. Risk estimates

Epidemiology studies assess associations between exposures and outcomes. An estimate of the strength of an association is called a risk estimate. In a cohort study, the risk estimate may be expressed as a relative risk. The term 'risk' is used for the proportion of affected individuals in a population. Relative risk is a ratio between the risk in one population (often an exposed group) and the risk in another population (often an unexposed group). In a case–control study, relative risk can be approximated by the odds ratio if the incidence of the outcome in the population is not too high. In the context of a case–control study, an 'odds' is the likelihood of having been exposed (the number of exposed individuals divided by the number of unexposed individuals), and an odds ratio is the odds of having been exposed in cases (affected individuals) divided by the likelihood of having been exposed in controls.

A risk estimate of 1 indicates no association between the exposure and the outcome. For a case–control study, a risk estimate of 1 means that affected individuals are no more or less likely to have been exposed to the risk factor of interest than unaffected individuals. Risk estimates of >1 may indicate an increase in risk, and risk estimates of <1 may indicate a decrease in risk. However, the risk estimate is not used by itself because of the recognition that there will be variability in the risk estimate as the putative association is examined in different studies of similar populations. The variability or precision of the risk estimate can be expressed as a confidence interval (CI), often a 95% CI. The 95% CI is the range of risk estimates that would be expected in 95% of repetitions of the study if the study were repeated an infinite number of times in similar populations. Any value within the 95% CI could be the true risk of the exposure–outcome relationship under consideration.

A related concept is the estimation of the likelihood that an apparent association arose by chance. This estimate is expressed as a *P*-value. $P = 0.05$ indicates a 5% likelihood that an association arose by chance. No *P*-value guarantees that an association must have arisen by chance, and no *P*-value guarantees that an association could not have arisen by chance. A 95% CI that includes 1.0 is consistent with the conclusion that the putative association is not statistically significant at $P < 0.05$. If a 95% CI excludes 1.0, it is statistically significant. It cannot be concluded that the association could not have arisen by chance, only that it is less likely to have done so than if the 95% CI included 1.0.

5. Multiple comparisons

As an example of data from the National Birth Defects Prevention Study, we now consider a paper from 2012 on medications used to treat nausea and vomiting of pregnancy [3]. The study evaluated a subset of the available malformation end-points within the NBDPS, including cleft lip with or without cleft palate, cleft palate, neural tube defects, and second- or third-degree hypospadias. According to the study authors, 75 different medications and a number of herbal products were used for nausea and vomiting of pregnancy. Medications were grouped into classes by a research pharmacist for the purposes of analysis. The classes included antihistamine antiemetics, other antihistamines, antihistamine antiemetics plus vitamin B_6, phenothiazines, prokinetics, 5-hydroxytryptamine-3 (5-HT_3)-receptor antagonists, coke syrup, bismuth subsalicylate, antacids, histamine H_2-receptor blockers, proton pump inhibitors, pyridoxine (vitamin B_6), steroids, and herbal products.

The results for cleft palate showed an elevated odds ratio for ondansetron (a 5-HT_3-receptor antagonist) adjusted for maternal age, race or ethnicity, education, parity, plurality, previous miscarriage, smoking, body mass index, infant sex, folic acid use, use of unknown antiemetic, study site, and expected year of delivery. The adjusted odds ratio was 2.37 with a 95% confidence interval of 1.18–4.76. This number tells us that after adjustment, children with cleft palate in the study were 2.37 times as likely to have mothers reporting the use of ondansetron as children without birth defects. The 95% CI excluded unity. This study also reported a statistically significant association between steroid use and hypospadias, but we now concentrate on the ondansetron–cleft palate findings.

Does this study mean that use of ondansetron during pregnancy causes cleft palate in the offspring? When an association is identified in a study, causation is one possible explanation, but there are two other possible explanations: chance and error.

The finding of a 95% CI that excludes unity suggests that the likelihood of chance explaining the findings is $<5\%$, but, when there are multiple comparisons in the study, the interpretation changes. Consider a comparison of two groups of people, say a group of epidemiologists and a group of obstetricians. A large number of measurements are taken from these groups – for example, height, weight, intercanthal distance, IQ, etc. – until there are 20

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independent measurements that are intended for comparison. If statistical testing of the comparisons uses a *P*-value of 0.05, it is implied that we will accept a comparison as being statistically significant if there is less than a 1 in 20 (5%) chance that a difference arose by chance. If it became apparent that the only difference between the group of epidemiologists and the group of obstetricians was a higher IQ in the obstetricians, we would not be so confident that the difference was a real finding as opposed to a chance finding. Epidemiologists might, indeed, insist that such a difference must have arisen by chance.

The relationship between the number of independent comparisons and the likelihood of a chance association with an apparent *P*-value of 0.05 is given by the equation

$$P = 1 - (0.95)^n,$$

where *P* is the likelihood of a chance finding, and *n* is the number of independent comparisons. This relationship is shown graphically in Fig. 1. As the number of comparisons increases, the likelihood of a chance finding being identified as statistically significant at $P < 0.05$ increases asymptotically towards 1. In the study of nausea and vomiting of pregnancy, the NBDPS evaluated 75 different medications and four different birth defect groups, potentially giving 300 comparisons. The likelihood of finding a chance association to be statistically significant for 300 independent comparisons is 0.99999979247.

In fact, there were fewer than 300 independent comparisons, because not all medications were counted and not all exposures were independent of one another. The study authors estimated that they made 70 comparisons, which would give a likelihood of $1 - (0.95)^{70} = 97\%$ likelihood of identifying a chance association as statistically significant. All the same, it is not possible to say that the association between cleft palate and ondansetron must be due to chance — only that it could be. The study authors recognized this possibility and wrote, 'Perhaps of most importance is the possibility of chance as an explanation for the statistically significant associations that we observed.'

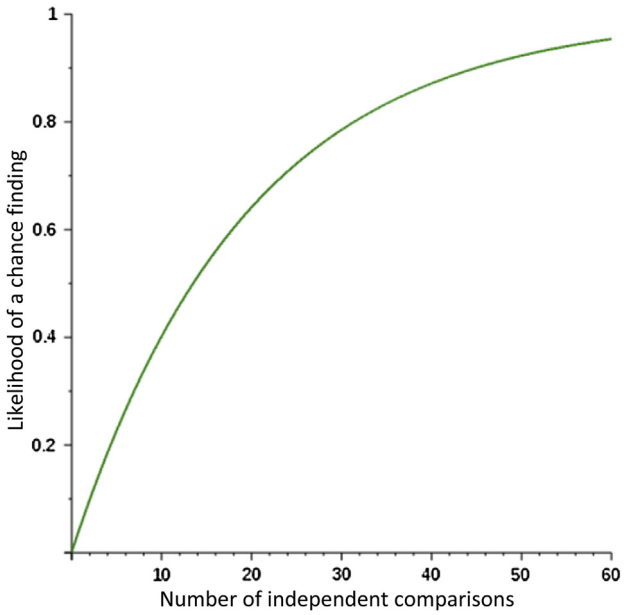

Fig. 1. The relationship between the number of independent comparisons being made in a study and the likelihood of finding a statistically significant difference at $P = 0.05$ by chance alone.

6. Error

The term 'error' is used to include features of a study or of biology that predispose the study to giving the wrong answer. Error is sometimes divided into bias and confounding.

6.1. Bias

Bias is a feature of the study design that increases the likelihood of the study giving the wrong result. A commonly mentioned source of error is recall bias, which in birth defect studies refers to the likelihood that the parents of affected children will search their memories more diligently than parents of unaffected children and will be more likely to report an exposure, whether or not the exposure actually occurred. Recall bias does not refer to non-differential memory errors, i.e. both case parents and control parents make mistakes in their reporting. If memory errors are non-differential, the effect on the study will be to make it harder to show a difference between the groups. Differential errors such as recall bias, on the other hand, predispose a study to show a difference that may not be real.

It is unlikely that the ondansetron finding was due to recall bias, because mothers had the opportunity to over-recall many other drug exposures and to over-recall exposures for other defects, not just cleft palate. The finding that the association was present just for ondansetron and just for cleft palate makes recall bias a less convincing explanation.

Response bias is another potential source of error. If a small proportion of invited subjects agreed to participate, the question arises whether the participants had a special story to tell. In other words, perhaps the basis for their participation was some connection in their minds between the exposure of interest and the outcome of interest. In such instances, the participants might not faithfully represent the larger universe of affected or exposed individuals.

The NBDPS has evaluated the extent to which participants in the control group represent the general population from which they were drawn [4]. The control participation rate was 65.8%. The participating control pregnancies did not differ from pregnancies in the background population with respect to maternal age, maternal education, previous live births, trimester during which prenatal care began, or diagnosis of diabetes. Infants born to participants were less likely to weigh <2500 g at birth, less likely to be born at <37 weeks of gestation, and less likely to be multiples (twins, triplets, or more). There were small differences between the participating controls and the background population in maternal race/ethnicity, paternal age, and maternal smoking. A comparison of the participating control women and the invited non-participating control women showed participants to be more likely to be white non-Hispanic, aged ≥30 years, to have completed more than a high school education, and to have started prenatal care in the first trimester. Participants were less likely than invited non-participants to have had more than three previous live births and to be smokers. The other differences between participating control women and the general population were also seen in the non-participating invited control women and did not differ by the decision to participate.

In the antiemetic study, there was no information about the response rate of invited cases and controls, so possible response bias cannot be assessed based on participation rates. However, response bias does not appear to be a likely explanation for the ondansetron findings. It is implausible that participation was based on a perceived relationship between ondansetron and cleft palate without also affecting perceived relationships between other defects and ondansetron or other drugs.

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Another type of bias is diagnosis bias, sometimes called ascertainment bias. If women with a particular exposure are more likely to have their children examined for a particular birth defect, that birth defect might be more likely to be diagnosed in the exposed group. As an example, if anxious women are more likely to compel their children's pediatricians to order an echocardiogram than women who are not anxious, heart defects that might otherwise go undetected might be ascertained with greater frequency in the offspring of women exposed to medications used to treat anxiety. In the antinauseant paper we are discussing, it is unlikely that women who were treated with ondansetron would be more likely to prompt a thorough palate examination in their children. Of course, after a study such as this one is published, it is possible that practices will change and that a history of ondansetron exposure will, in fact, prompt a more thorough palate examination in newborns.

6.2. Confounding

Whereas bias is a feature of study design, confounding is a feature of the biology of an association that may escape consideration by investigators. In birth defect studies, it is frequent practice for investigators to consider whether there is confounding by exposure to tobacco, alcohol, and other medications and to adjust for potential confounders. If, for example, pregnant women who drink alcohol are more likely to be nauseated than women who abstain, women who are treated for nausea may have babies with alcohol-related malformations. The malformations might be blamed on antinauseant medication rather than on alcohol unless the results are adjusted for exposure to alcohol.

A related source of confounding is the illness or indication for which a medication is being used. If we accept that maternal diabetes mellitus causes birth defects, a study of antidiabetic medications might show an association between these medications and birth defects that is mediated in reality by the underlying maternal disease.

Is it likely that confounding by indication explains the ondansetron results? Could it be that something about maternal nausea and vomiting causes cleft palate in the offspring? Perhaps, but this study did not show a statistically significant increase in cleft palate associated with other antinauseants, making confounding by indication a less likely explanation. Perhaps ondansetron is preferentially used in women with particularly severe nausea and vomiting, which might explain the apparent association with cleft palate. There are no data with which to evaluate this possibility.

7. Causation

We come now to the question a patient might ask us in light of the NBDPS: does ondansetron use during pregnancy cause cleft palate? We should be clear from the outset that single studies do not establish causation. Rather, causation is considered using evidence from multiple sources, and causation analysis considers several elements.

Criteria for causation were specified in the mid-1960s by Sir Austin Bradford Hill [5] and an advisory committee to the US Surgeon General with regard to cigarette-related disease [6]. These 'viewpoints', as Sir Austin called them, are listed in Box 3. The Hill criteria have given rise to variations and interpretations in the half-century since they were published. Sir Austin used examples largely from occupational exposures and cancer. In the field of teratology, notable contributions came from Drs Thomas Shepard [7] and Robert Brent [8]. These authors included components of the Hill list modified to apply to teratology. The Public Affairs Committee of the Teratology Society published principles to be applied to causation analyses in a litigation context [9].

Box 3
The Hill criteria[a]

1. Strength of the association (the likelihood that the association is not due to chance, bias, or confounding).
2. Consistency of the association (the association is reproduced in different populations).
3. Specificity (uniqueness of the association both with respect to the exposure and with respect to outcome).
4. Temporal relationship (the putative cause comes before the effect).
5. Coherence (the association is compatible with related knowledge).
6. Biologic gradient (there is a dose–response effect).
7. Biologic plausibility (the association does not violate known principles).
8. Experiment (reducing the putative cause reduces the effect).
9. Analogy (evidence is similar to that for similar cause–effect relationships).

[a]Adapted from Hill [5]

I review below some of the Hill criteria in terms of how they might be used to assess the relationship of ondansetron therapy during pregnancy and cleft palate. There is no threshold number of criteria required for a conclusion of causation, but the more criteria that are met, the more confidence we have that a conclusion of causation is correct.

7.1. Strength of the association

Strength of the association refers to the size of the risk estimate. The higher the risk estimate, the less likely it is that chance or error can explain the result. How high a risk estimate is needed? Dr Shepard suggested that a risk estimate of 6 would show a strong association [7]. In the antinauseant study, the risk estimate for ondansetron and cleft palate was 2.37 with a 95% CI that started at 1.18, which is not very much above 1.0. As discussed above, chance might explain this association based on the multiple comparisons that were made.

7.2. Consistency of the association

The demonstration of a consistent association in different populations is an important element of causation analysis, and if an association appears only once, we cannot be confident that the association is causal. In considering ondansetron, there are three studies other than the NBDPS that can be used to evaluate a possible association with cleft palate.

A paper from teratology information services in Canada and Australia compared pregnancy outcome among 176 women who called with concerns about ondansetron and the same number of women who called with concerns about exposures that were not believed to increase the risk of birth defects [10]. There were 169 live births in the ondansetron group among which six children had major malformations compared with three malformed infants among 160 live births in the comparison group ($P = 0.52$). The malformations in the ondansetron group included three instances of hypospadias and one child each with duplication of the renal collecting system, pulmonic stenosis, and duodenal atresia. Although these results might appear reassuring with respect to cleft palate, the risk estimate in the NBDPS predicts an increase in the incidence of cleft palate from about 6/10 000 to 15/10 000. Such

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an increase could not have been detected with the limited sample in the teratology information service study.

A study using the Swedish Medical Birth Registry reported an odds ratio for use of antiemetic medications in infants with orofacial clefts of 0.75 (95% CI: 0.55–1.03) [11]. Although this odds ratio is not increased, the result applies to antinauseant medications as a group and lacks the requisite specificity for conclusions about ondansetron. Indeed, there were few instances of ondansetron use among these drugs.

A study from Denmark using a prescription registry to identify exposures and a patient registry to identify outcomes reported that among 1233 women believed to have been exposed to ondansetron in the first trimester, there was no increase in major malformations compared with an unexposed group [12]. Although individual malformations were not analysed, there were no instances of cleft palate among the 1233 infants with presumed maternal ondansetron exposure. This sample is much larger than the sample in the teratology information service study, but 1233 pregnancies is still not sufficient to identify an increase in cleft palate from 6/10,000 to 15/10,000. The issue of consistency remains open.

7.3. Specificity

The report of the NBDPS satisfies the requirement for specificity. The malformation under consideration was cleft palate – not all malformations or even all facial clefts – and the exposure was ondansetron, not all antiemetics.

7.4. Temporality

The requirement that the putative cause comes before the effect seems easily to be satisfied by the NBDPS; however, it is possible to be more critical in requiring the temporal relationship between exposure and outcome to make embryological sense. In the study on antinauseants, women were considered exposed if they took a medication any time in the first trimester, but not all birth defects can be caused by an exposure any time in the first trimester, and some birth defects are caused by exposures after the first trimester. Some authors recommend considering exposures during specific critical periods as relevant for specific malformations [13]. Using this approach, ondansetron exposures during the third month after the last menstrual period might be considered informative for cleft palate and exposures at other times might be considered uninformative. This approach has not been widely adopted.

7.5. Biological gradient

It is expected that as the dose level of an exposure increases, the response will increase, either in terms of frequency or severity of adverse effects. The NBDPS paper on antinauseants has no information on dose level, and this criterion cannot be evaluated.

7.6. Biological plausibility

The requirement for biological plausibility is considered by some people to be a low hurdle; as long as the proposed causal association does not involve unicorns or Martians, it might be considered biologically plausible. However, in teratology, it is customary to require either an experimental animal model for the putative causal relationship or a well-established mechanism by which the causal association could be mediated. With respect to ondansetron, a 5-HT_3 receptor antagonist, nonclinical embryofetal toxicology studies did not show an increase in cleft palate or in any other malformation at up to 4 mg/kg body weight in rats and up to 10 mg/kg body weight in rabbits. The human intravenous dose is 0.45 mg/kg body weight/day [14,15].

There are no published data on possible developmental toxicity of other 5-HT_3 inhibitors. Mice with knockout of the 5-HT_3 receptor are healthy [16]. Because cleft palate precludes suckling in mice, the viability of knockout mice is evidence that antagonism of this receptor does not produce cleft palate.

8. Counseling

Counseling patients who are contemplating exposure to ondansetron during pregnancy can take the approach that there are alternatives in the treatment of nausea and vomiting. One small study showed no difference in the effectiveness of treatment with promethazine versus ondansetron for patients hospitalized with excessive nausea and vomiting of pregnancy [17]. Ondansetron is expensive compared to promethazine, but it is less sedating. Favorable experience has also been published for the combination of droperidol and diphenhydramine in the management of excessive nausea and vomiting of pregnancy [18].

Patients who have been exposed to ondansetron can be advised that the increase in risk identified by the NBDPS has not been confirmed. Moreover, the absolute risk is small, with an increase of $<$0.09% in the incidence of cleft palate.

9. Conclusions

The NBDPS is a large, population-based case–control study that has collected information in a systematic manner on the exposures and lifestyle characteristics of the mothers and fathers of children with and without congenital malformations. The study has produced a large number of publications on a variety of exposures. As is true of all case–control studies, the outcomes under study are selected before the data are collected, limiting the ability of the study to identify new birth defect syndromes. Nonetheless, case–control studies provide important information to be used in the consideration of birth defect causation questions. These questions are not decided by a single study but are addressed using information from multiple sources.

Conflict of interest statement

Dr Scialli has provided testimony for the defense in Paxil® litigation. Paxil® is marketed by GlaxoSmithKline, which also markets the Zofran® brand of ondansetron. Dr Scialli has not consulted or testified on Zofran® or generic ondansetron.

Appendix A. Supplementary data

Additional further reading sources related to this article can be found online at http://dx.doi.org/10.1016/j.siny.2013.09.007.

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