Is vomiting during pregnancy teratogenic?

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Abstract

The possibility that antiemetics used during pregnancy are teratogenic has been hotly debated; the effect of vomiting itself, however, has been largely ignored. The relation between vomiting and congenital malformations was examined in a prospective study of 16 398 women who registered for prenatal care at or before 20 weeks' gestation. The odds ratios for malformations among women who vomited compared with women who did not were 1·14 for major malformations (p=0·13), 0·88 for deformations (p=0·39), 1·03 for hernias or undescended testes (p=0·82), 1·06 for any of these three conditions (p=0·38), 1·09 for minor anomalies (p=0·14), and 1·10 for any anomaly (p=0·03). After adjustment for use of antiemetics and five other confounding variables vomiting was not associated with a significantly increased risk of any of the above malformations.

These data suggest that the increased risk, if any, among women receiving antiemetics during pregnancy is due to the drugs, not the vomiting.

Introduction

The teratogenicity of drugs used to treat nausea and vomiting during pregnancy is controversial. Several studies have found specific defects or defects of organ systems to be associated with these drugs,[1-4] but other studies have not.[5-8] The possibility that vomiting per se is associated with malformations has been raised,[3 9] yet only two studies have investigated this hypothesis. One found vomiting to be unassociated with malformations,[10] and the other noted that malformations were more common in pregnancies in which vomiting occurred,[11] even when antiemetics were not taken. We used data from a large, prospective perinatal study to test the hypothesis that vomiting is itself associated with delivery of a malformed infant.

Methods

The data for this study were from the Collaborative Perinatal Project, the design of which has been previously described.[12] At each prenatal visit trained interviewers asked each woman about the occurrence of complications of pregnancy, including vomiting. To categorise women with respect to vomiting during early pregnancy we studied only first study singleton pregnancies in which the woman had registered by 20 weeks (20 294 women). All livebirths and fetal losses that could be examined for malformations were included. Women for whom the duration of gestation was uncertain were eliminated (1054), as were those who had no follow up obstetric visits (657), leaving 18 583 women for analysis.

At her first obstetric visit each woman was asked whether she had had symptoms including vomiting, diarrhoea, and fever since her last menstrual period. At each subsequent visit she was asked if she had had any of the same events since her last visit. The 1593 women who reported vomiting only in conjunction with fever or diarrhoea were considered to have had gastroenteritis and were analysed separately. If a woman reported gastroenteritis at one visit and isolated vomiting at another she was classified as having vomiting related to pregnancy. The 86 women with hyperemesis gravidarum requiring intravenous treatment were analysed separately. Among the remainder, data on malformations were unavailable for 488 offspring and vomiting state was unknown for 18 women. The remaining study group consisted of 9255 women who reported vomiting and 7143 women who did not.

Methods for collecting data on drug use during pregnancy have been previously described.[13] Antiemetics were defined as those drugs classified as "antinauseants, antihistamines and phenothiazines" by Heinonen *et al*[13] and listed in the 1965 *Physicians' Desk Reference* as being indicated for hyperemesis gravidarum, vomiting, nausea, or motion sickness.[14] As the possible teratogenic effects of antiemetics have been reported from this data set,[5 13] and as our objective was not to evaluate the teratogenicity of antiemetics, these drugs were not individually scrutinised. Antiemetic users were defined as women exposed to any of the above drugs during the first four lunar months of pregnancy.[13]

Malformations were noted up to 1 year of age[15]; major malformations were defined as congenital structural abnormalities that were of functional or cosmetic importance. Abnormalities of the legs currently believed to be secondary to intrauterine position or neurological dysfunction (for example, congenitally dislocated hip or clubfoot) were classified as deformations. Hernias (except diaphragmatic or hiatus hernia) and undescended testes were coded separately. All other congenital structural anomalies were classified as minor. This classification was established without knowledge of maternal vomiting state (a full listing of the abnormalities included in each category is available on request).

In the first analysis the risk of malformations in pregnancies complicated by vomiting was compared with the risk when vomiting was absent. The statistic used to estimate this relative risk was the odds ratio. The odds ratio is calculated by dividing the number of subjects with malformations by the number without in the vomiting and non-vomiting groups and then dividing the results in the vomiting group by the results in the non-vomiting group. With equal risks in the two groups the odds ratio would equal one. The 95% confidence limits of the odds ratios were derived using the test based method.[16] As expected, use of antiemetics was more common among women with vomiting, and it has been suggested that malformations are more common among offspring of women who used this class of drugs.[13] The odds ratios were therefore adjusted for use of antiemetics by the Mantel-Haenszel procedure.[17] Multiple logistic regression was used to adjust the odds ratios further for the following factors associated with vomiting or malformations, or both[15 18]: maternal age, gravidity (primigravida/other), race (white, black, Puerto Rican), infant sex, and use of antiemetics. As the prevalence of both vomiting and malformations varied by study centre an adjustment for centre was included. Vomiting is associated with a reduced risk of stillbirth and miscarriage,[18] and malformations may be more common among stillborn than liveborn infants. Therefore, all of the above analyses were repeated for livebirths only, and also with malformations organised by organ system. Next, the prevalence of vomiting during pregnancy was compared between infants with 230 specific defects and normal infants.

A possible association between the use of Bendectin (Debendox) and pyloric stenosis has been described,[3 9] but the possibility that maternal vomiting per se might be teratogenic has been raised.[9] The relation between vomiting and pyloric stenosis was therefore explored.

Results

Among all 16 398 pregnancies 596 children had a major malformation (3·6%), 198 had a deformation (1·2%), and 303 had a hernia or undescended testis (1·8%). In all, 1046 had one or more of these three conditions (6·4%) and 1387 had a minor anomaly (8·5%). Table I shows malformation rates for the vomiting and non-vomiting groups. Although no single category of malformations was significantly more common among the vomiting group, the probability of having any malformation was slightly but significantly greater among offspring of women who vomited. The proportion of malformations among offspring of women who vomited but did not use antiemetics were: major malformations 3·7%, deformations 1·1%, hernias or undescended testes 1·8%, any of above 6·3%, minor anomalies 8·2%, and any abnormality 13·9%. None of these percentages was significantly different from those offspring of women who did not vomit.

Table II shows the crude and adjusted odds ratios for malformations

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TABLE I—*Numbers (%) of malformations among offspring by mother's vomiting state*

Type of anomaly	Vomiting (n=9255)	Non-vomiting (n=7143)	p Value*
Major	353 (3·8)	243 (3·4)	0·13
Deformation	105 (1·1)	93 (1·3)	0·39
Hernia or undescended testis	172 (1·9)	131 (1·8)	0·82
Any of above†	602 (6·5)	444 (6·2)	0·38
Minor	807 (8·7)	580 (8·1)	0·14
Pyloric stenosis	25 (0·3)	14 (0·2)	0·31
Any anomaly†	1347 (14·6)	955 (13·4)	0·03
No anomaly	7908 (85·4)	6188 (86·6)	

*Reference group=those with no anomaly. p Values from χ^2 analysis.
†Composite outcome.

among women who vomited compared with women who did not. After adjustment for use of antiemetics vomiting was no longer associated with a significantly increased overall rate of anomalies. None of the odds ratios was significant. When the analyses were repeated for live births only, all of the odds ratios for vomiting remained within 2% of the values shown in table II and none was significant after adjustment.

the combined independent effects of these factors. This finding is important if women who vomited and received antiemetics were assumed to have had more severe vomiting than women who vomited and did not receive antiemetics, because it would then indicate a lack of a dose-response effect of vomiting on malformations. Offspring of women who did not vomit but received antiemetics did not show significant increases in any category of malformations when compared with offspring of women who neither vomited nor received antiemetics.

Malformations were divided according to organ system and odds ratios calculated. The unadjusted odds ratios were 0·98 for defects of the central nervous system, 2·01 for those of the eye, 1·01 for the musculoskeletal system, 1·08 for the upper respiratory tract and mouth, 1·26 for the thorax, 1·21 for the cardiovascular system, 1·10 for the gastrointestinal system, and 0·77 for the genitourinary system. None of these odds ratios was significant either before or after adjustment. When each defect was evaluated individually only microcephaly (odds ratio=3·3, p=0·03), preauricular skin tag (odds ratio=8·5, p=0·02), and hairy pigmented naevus (odds ratio=1·6, p=0·048) were associated with vomiting at a p=0·05 level. Vomiting was not significantly associated with pyloric stenosis (odds ratio=1·40, p=0·31). Given 9255 women in the vomiting group and 7143 in the non-vomiting group, a minimum of five cases of an anomaly would be required to show significance. There were 70 defects that occurred at least five times, and three comparisons would be expected to be significant at p=0·05 by chance

TABLE II—*Crude and adjusted odds ratios (and 95% confidence limits) for malformations among vomiting women compared with non-vomiting women, all births*

Type	Crude odds ratio	Odds ratio adjusted for antiemetic use	Odds ratio adjusted for antiemetic use, gravidity, age, race, infant's sex, study centre
Major malformations	1·14 (0·96, 1·35)	1·13 (0·95, 1·35)	1·10 (0·92, 1·31)
Deformations	0·88 (0·66, 1·18)	0·85 (0·64, 1·14)	0·84 (0·63, 1·13)
Hernia or undescended testis	1·03 (0·80, 1·32)	0·99 (0·78, 1·26)	1·05 (0·83, 1·34)
Any of above†	1·06 (0·94, 1·20)	1·03 (0·90, 1·18)	1·03 (0·90, 1·17)
Minor anomalies	1·09 (0·97, 1·22)	1·05 (0·93, 1·18)	1·05 (0·94, 1·18)
Any abnormality†	1·10 (1·01, 1·20)*	1·07 (0·97, 1·17)	1·06 (0·97, 1·17)

*p=0·03.
†Composite outcome.

The ability (power) of the study to identify a significant increase in risk, if present, was investigated for each category of malformations. For these calculations the expected rate for each category of malformations was taken from the non-vomiting group (table I). The smallest increases in odds ratios that had an 80% chance of being identified at a p value <0·05 were: major malformations 1·26, deformations 1·43, hernias or undescended testes 1·36, any of above 1·19, minor malformations 1·17, and any anomaly 1·14.

Of the 9255 women who vomited, 1964 (22%) received antiemetics, 475 (7%) of the 7143 women who did not vomit also received antiemetics. The reasons for prescribing antiemetics to women who did not vomit were not specified, but most of these drugs had other indications such as allergic or psychiatric diseases. We were thus able to investigate the independent and synergistic effects of vomiting and antiemetics. Table III shows the adjusted odds ratios for the isolated and combined effects of vomiting and use of antiemetics (including the interaction effect) on major malformations; the results were similar for other types of malformations. The risk of malformations associated with both vomiting and use of antiemetics was not significantly different from the risk that would have been expected based on

TABLE III—*Joint effects of vomiting and use of antiemetics (odds ratio) on risk of major malformation**

Antiemetic use	Vomiting: No	Vomiting: Yes
No	1·00	1·10
Yes	1·17	1·31

*Adjusted for gravidity, age, race, study centre, and infant's sex.

alone. None of these defects was significant after correction for multiple comparisons. One method used to correct for multiple comparisons, dividing the usual p<0·05 by the number of tests performed (p<0·05/70= p<0·0007), could be too extreme when the observations may not be independent. If the significance level were set 10 times higher than this procedure dictates, however, it would still result in these three associations being considered to be non-significant.

Women with hyperemesis and gastroenteritis were analysed separately. The malformation rates for women with hyperemesis were: major 6·0%; deformations 0%; hernias or undescended testes 1·7%; any of the preceding 7·1%; minor 9·5%; and any anomaly 16·7%. None of these rates was significantly different from those in either the vomiting or non-vomiting groups. As we were uncertain whether women with fevers or diarrhoea as well as vomiting should be considered with the vomiting or non-vomiting group odds ratios were calculated both ways. All of the crude odds ratios were within 5% of those presented in table II.

Discussion

Despite the controversy over the possible teratogenic effects of antiemetics[1-11] little attention has been paid to vomiting itself as a potential teratogen. Textbooks on teratology do not discuss vomiting[19,20] or the associated metabolic derangements such as hypochloraemic alkalosis and ketosis. Dehydration has been associated with an increased incidence of cleft palate in studies of mice.[21,22] It is not certain that the dehydration per se was teratogenic, as the decreased food intake seen in the mice deprived of water caused similar results in the absence of water deprivation.[22]

There are no human studies whose primary focus has been vomiting and malformations, although two studies of the teratogenicity of antiemetics also examined malformation rates in women who vomited but did not use antiemetics. Milkovich and van den Berg found slightly lower rates of severe malformations in the

offspring of women who vomited but did not use antiemetics (3·2%) than of women who did not vomit (3·7%).[10] The difference was not significant. Kullander and Källén reported contradictory results.[11] In their study 72% of women producing malformed infants had had morning sickness, compared with only 60% of those producing a normal infant ($p<0·001$). The reasons for these conflicting results are not evident from the study methods. Milkovich and van den Berg's non-vomiting group consisted of 3900 women, 2336 of whom were classified as non-vomiting based on no mention of vomiting in their medical record. Misclassification of vomiting was thus possible. Kullander and Källén relied on a questionnaire completed at registration to obtain data on vomiting in the first trimester. No information was included on when the women registered, making it difficult to determine whether recall might have been a problem.

Fetal losses are less common among women who vomit.[18] Theoretically, this could result in a greater proportion of malformed fetuses surviving to term. This could not account for the observed lack of an association between vomiting and malformations, as it would increase the rate of malformations among offspring of women who vomited and would magnify rather than conceal any risk from vomiting. Including in the analysis fetal losses that could be examined for malformations did not substantially change the results.

We found vomiting during the first 20 weeks of pregnancy to be unassociated with any broad class of malformations. Infants of mothers who vomited were slightly more likely to have a defect than infants of mothers who did not vomit. Women who vomited, however, were more likely to take antiemetics, which in turn are associated with a slightly though not consistently significant increased risk of malformations in this data set.[13] After adjustment for use of antiemetics vomiting was no longer associated with a significant increase in the risk of malformations. Only three of the 230 specific defects studied were found to be significantly associated with vomiting (microcephaly, preauricular skin tag, and hairy pigmented naevus). These findings can be explained by chance as none persisted after adjustment of the level of significance for multiple comparisons.

Some possible limitations of the present study should be considered. It was limited to women who registered in the first 20 weeks of pregnancy to minimise the elapsed time between symptoms and recall. Slightly under half of the study participants registered at or before 20 weeks. Nevertheless, vomiting remained unassociated with any of the categories of malformations when the entire study population was evaluated. Embryogenesis is essentially complete by week 12 of gestation, and therefore a 20 week cut off might be inappropriately late. When the analyses were repeated using only women who registered in the first trimester, however, no associations were found. Time constraints are therefore unlikely to account for the observed results.

A final caveat concerns the age of the data: although they were collected during the 1960s there is no reason to believe that this influences the relevance of our conclusions. The drugs most commonly used to treat nausea or vomiting in pregnancy in 1984, trimethobenzamide and promethazine,[23] were both marketed during the time of the Collaborative Perinatal Project. Furthermore, epidemiology of vomiting during pregnancy is unlikely to have changed since then.

In conclusion, this large, prospective study carefully collected information on vomiting and use of antiemetics from all participants and used a thorough, consistent protocol to evaluate all offspring for malformations. It indicated that vomiting during pregnancy, though distressing to the woman, does not increase her risk of having a malformed infant. The preponderance of evidence indicates that Bendectin is not teratogenic.[5-8] If, however, future investigations find an association between use of antiemetics and malformations this study indicates that the treatment, rather than the underlying condition, is probably responsible.

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