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The Treatment of Nausea and Vomiting in Pregnancy (NVP)

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Nausea and vomiting are the most common complaints of the first trimester, affecting between 60 and 70% of pregnant women. For most women, nausea begins between the 2nd and 5th week and ends between the 8th and 14th week post-conception. For 35% of pregnant women, nausea and vomiting are severe enough that they lose time from work (Gadsby et al, 1993).

Hyperemesis gravidarum is a severe form of pregnancy-induced nausea characterized by persistent vomiting, ketonuria and severe weight loss and dehydration. This condition affects approximately 0.5-2.0% pregnant women and, if left untreated, can lead to coma, convulsions and fetal loss. Up to 60% of women who suffer from hyperemesis gravidarum develop secondary clinical depression. Treatment may involve medication, IV fluids, acupuncture and enteral nutrition (Goodwin, 1998).

Although hyperemesis has been proposed as a potential teratogen, a 1996 retrospective case control study reported similar incidences of fetal outcomes between patients suffering from hyperemesis gravidarum and controls (Tsang et al, 1996). Several additional studies have replicated this finding.

Despite their discomfort, women can be reassured that their nausea may be serving as a predictor of good pregnancy outcome. A statistical meta-analysis of 11 epidemiological studies indicated a strong significant association of nausea and vomiting of pregnancy with decreased risk of miscarriage in the first 20 weeks of gestation (RR=0.36)(Weigel).

The use of any medication in pregnancy involves weighing the risks of the medication against the risks associated with maternal disease. Nausea and vomiting can pose a serious risk to the health of the mother and the developing fetus. In light of that fact, health care providers should be familiar with medications used to treat nausea and vomiting, including their potential teratogenic risks. The major types of these medications will be reviewed here.

Bendectin/ Diclectin

Bendectin is a combination drug, consisting of doxylamine (a sedative-antihistamine) and pyridoxine (vitamin B6), which was available in the US prior to 1983 for the treatment of nausea and vomiting of pregnancy. Amidst litigation over infants born with limb reduction defects, Merrell Dow, the manufacturer of Bendectin, removed it from the US market in 1983. At that time, nearly 40% of pregnant women had taken or were taking Bendectin. As a result of the removal of Bendectin from the US market, the incidence of hyperemesis gravidarum has increased three-fold. The product remains available in Canada under the name Diclectin. Doxylamine is marketed in the US as Unisom sleep tablets, and some physicians continue to treat affected patients with a combination of half a Unisom tablet and 10mg of vitamin B6.

More than 30 million women took Bendectin from 1956 to 1983. At least 25 epidemiological studies and 2 meta-analyses have been performed regarding its use during pregnancy, making it the world's most studied drug in pregnancy. Both of the meta-analyses and the large case-control studies support the conclusion that Bendectin is not teratogenic.

Individual case-control and cohort studies initially raised the possibility of specific types of defects associated with Bendectin use, including heart disease, cleft palate, cleft lip and limb-reduction defects. Most of these studies (including the case control study that identified limb reduction defects as a potential association) did not report a statistically significant increase for the specified association. The results of these studies were inconsistent and were not reproduced in later investigations.

Two case control studies (Eskenazi et al, 1982; Aselton P et al, 1984) suggested a possible association between first trimester use of Bendectin and pyloric stenosis in exposed newborns. However, an increased risk of pyloric stenosis was not observed in several larger case-control studies. Eskenazi et al suggested that a slightly increased risk for pyloric stenosis could result from a confounder such as an increase in nausea in pregnant women with a genetic predisposition to gastrointestinal malformations.

Diclectin is the only anti-emetic approved in Canada for the treatment of nausea and vomiting of pregnancy. The company that continues to make Diclectin (Duchesnay, Inc) will most likely be able to market the drug in the United States in the near future.

Vitamin B6 (pyridoxine)

Many women choose to take vitamin B6 as a "natural" alternative to medication to treat nausea during pregnancy. In fact, women who take a multivitamin containing vitamin B6 during the first six weeks of pregnancy experience significantly less nausea than women who do not take a multivitamin (Emelianova et al, 1999). Vitamin B6 use has been associated with a lower risk for congenital heart defects in human studies (Boneva et al, 1999) and oral clefting in rats (Jacobsson and Granstrom, 1997). Vitamin B6 may also play a role in the reduction in neural tube defects associated with multivitamin use.

Because pyridoxine is included in most multivitamins and in the preparation of Bendectin, which has been widely studied in pregnancy, data suggests that it is not teratogenic. Standard doses range from 10-25mg. As with most vitamins, megadoses of vitamin B6 are neither necessary nor recommended.

Phenothiazines: Prochlorperazine, Chlorpromazine, and Promethazine

As a class, phenothiazines appear to confer little risk to the developing fetus. The Collaborative Perinatal Project followed 1309 pregnancies with first trimester exposure to phenothiazines. No statistically significant increase in birth defects was found. A statistically insignificant increase in the incidence of cardiac defects was observed. The authors suggest that the finding is of borderline significance (Slone et al, 1977). Milkovich et al (1976) reported a prospective observational study of nearly 2,000 women treated for nausea and vomiting at the Kaiser medical facilities in San Francisco. Of those, 543 took phenothiazines; no increase in congenital anomalies was observed.

Prochlorperazine (Compazine, prochlorpemazine)

Prochlorperazine is used as both an antipsychotic and an antiemetic. Prochlorperazine is currently the most commonly prescribed medication in the US for the treatment of nausea and vomiting in pregnancy. It is available in suppository form.

Of the 1309 women exposed to phenothiazines in the Perinatal project, 887 took prochlorperazine. In the Kaiser prospective study, 433 women took prochlorperazine during the first trimester. Both of these studies suggested that prochlorperazine is not teratogenic.

In a Swedish prospective study of women taking anti-emetic drugs in pregnancy, congenital dislocation of the hip (CDH) was seen more frequently among the 91 women taking prochlorperazine. Because the medication was only taken during the first trimester, biologic plausibility is hard to establish. The authors suggested that an endocrine disturbance leading to CDH may have resulted in increased nausea in these expectant mothers (Kullander and Kallen, 1976). No other studies have reported an association between prochlorperazine and CDH.

Chlorpromazine (Thorazine)

Chlorpromazine is a phenothiazine tranquilizer that is also used as an antiemetic.

An early animal study suggested that chlorpromazine might cause cleft palate in mice (Walker and Patterson, 1974). However, this malformation has never been reported with chlorpromazine use in human pregnancy.

In the Collaborative Perinatal Project, the frequency of congenital anomalies was no greater than expected among the children of 142 women treated with chlorpromazine during the first four months of pregnancy or the children of 284 women treated anytime during pregnancy (Heinonen et al, 1977).

Rumeau-Rouquette et al (1976) reported an increase in the rate of congenital anomalies in infants born to mothers who took phenothiazines in pregnancy. Congenital anomalies occurred in 3.5% of pregnancies with phenothiazine exposure and less than 1.6% in the control population. (The expected rate of congenital anomalies in control populations is approximately 3.5%.) In the study, no pattern of anomalies could be established. This study did not examine potential confounding factors such as maternal use of tobacco or alcohol, which could be important since phenothiazine therapy is known to decrease the clearance rate of ethanol from the blood (Rawat, 1980). Transient neonatal withdrawal symptoms have been described with high doses of chlorpromazine (150-250mg/day) used to treat psychiatric illness (Auerbach et al, 1992). When used for the treatment of nausea and vomiting, the typical dose is 10-25 mg/day, which has not been associated with neonatal withdrawal.

Promethazine (Phenergan)

Promethazine is a phenothiazine with antihistaminic activity. Promethazine is the medication most commonly used by practitioners to treat hyperemesis, the most severe form of nausea and vomiting of pregnancy. It is also used as an adjunct to narcotic analgesia during labor. It is typically given as a slow intravenous bolus.

Several studies have reported finding no association between use of promethazine during pregnancy and an increased risk of birth defects in the offspring (Golding et al, 1983; Heinonen et al, 1977). Fourteen pregnancies exposed to promethazine during the first trimester and a total of 746 pregnancies exposed to promethazine at any time during gestation were identified through The Collaborative Perinatal Project. The data obtained from this study suggests that promethazine is not associated with an increased risk of major or minor birth defects.

Some studies suggest that the use of promethazine during labor induces respiratory distress in the newborn (Crawford, 1963). Additionally, the use of promethazine during labor may impair platelet aggregation in both the mother and in the newborn. While this effect has not been associated with significant clinical bleeding problems, the degree of platelet impairment was comparable with that seen with aspirin use and therefore it may be advisable for pregnant women to avoid promethazine near term (Whaun et al, 1980; Corby and Shulman, 1971).

Antihistamines: Diphenhydramine, Dimenhydrinate, Meclizine, and Cyclizine

As a class, antihistamines have not been shown to increase the incidence of congenital malformations (Greenberger and Patterson, 1979), although some particular antihistamines have been associated with

birth defects in retrospective studies.

Diphenhydramine (Benadryl)

Diphenhydramine is a commonly used antihistamine.

In a retrospective case-control study, Saxen (1974) found that first trimester use of diphenhydramine was more common among 599 children born with oral clefts (20 exposures) than among 590 controls without clefts (6 exposures). Another retrospective case-control study observed that significantly fewer infants with malformations were prenatally exposed to antihistamines, particularly diphenhydramine, than were controls (Nelson and Forfar, 1971). In a retrospective study of drugs used during the first trimester, only one of 361 infants born to women taking diphenhydramine was found to have a congenital anomaly (Jick et al, 1981).

Heinonen et al. (1977) conducted a prospective cohort study and observed no significant increase in the incidence of major or minor malformations among 595 infants exposed to diphenhydramine in the first trimester or 2948 infants exposed at any time during pregnancy.

Dimenhydrinate (Dramamine)

Dimenhydrinate is an antihistamine commonly used for the prevention of motion sickness. Chemically, dimenhydrinate is the chlorotheophylline salt of diphenhydramine. Several cohort studies, including the Collaborative Perinatal Project, have examined the use of dimenhydrinate in pregnancy and have not found any increased rate of congenital anomalies.

Meclizine (Antivert, Bonine)

Meclizine is a piperazine antihistamine used as an antiemetic in the treatment of vertigo and motion sickness.

The reproductive effects of this drug have been studied extensively in the rat where cleft palate and other oral abnormalities are noted after exposure to doses 25 to 50 times the human therapeutic dose (King et al, 1966). Meclizine has not been shown to be teratogenic in mice, rabbits, pigs, or monkeys (Girugea and Puigdevall, 1966; Wilson, 1972). Fetal edema has been suggested as the mechanism by which this and related compounds induce orofacial malformations (Posner and Darr, 1970).

Several epidemiologic studies have reported an increased incidence of cleft palate among infants born to mothers exposed to meclizine during early in pregnancy (Mellin and Katzenstein, 1963). One study of more than 3000 infants exposed to meclizine during pregnancy found 12 with cleft lip or palate (just under 0.4%)(Lenz, 1966), compared with a population incidence of 0.1%. However, the difference was not statistically significant. In contrast, Michaelis et al (1983) reported on 628 women who had used either meclizine or one of three other antiemetic drugs during the first 10 weeks of pregnancy. This and other epidemiologic studies, encompassing several thousand births and including the Kaiser prospective study, have failed to associate meclizine use during pregnancy with an increase in congenital anomalies (Shapiro, 1978; Slone et al, 1977).

Although outcome data is limited, other piperazines have not been shown to be associated with oral clefting.

Cyclizine

Cyclizine is an antihistamine used as an antiemetic for the prevention of motion sickness and postoperative nausea and vomiting.

Animal studies regarding the use of cyclizine in pregnancy indicate a potential association with cleft palate and micromelia (King and Howell, 1966; Steffek et al, 1968). A proposed mechanism of teratogenic action involves the binding of an active metabolite of these compounds to cartilage by

displacing calcium, and the induction of fetal edema as a simple mechanical cause for the observed orofacial malformations.

Epidemiological investigations have not indicated an increase in malformations after fetal cyclizine exposure. Retrospective cohort studies found no increase in the number of cyclizine exposures among infants with cleft palate or limb malformations. Subsequently, both prospective and retrospective cohort studies have failed to identify an association between the first trimester use of antihistamines (including cyclizine) and oral clefts or other malformations (Milkovich and Van den Berg, 1976; Nelson and Forfar, 1971; Saxen, 1974).

Trimethobenzamide (Tigan)

Although trimethobenzamide is structurally related to the antihistamines, it has little activity as a histamine blocker. Its mechanism of action is unknown.

A prospective study evaluating the teratogenicity of several antiemetic drugs followed 193 women who took trimethobenzamide during the first trimester (Milkovich and Van den Berg, 1976). The incidence of major congenital anomalies discovered by age 5 was 3.5% in women who had received no medications for nausea and 5.8% in women who had received trimethobenzamide. This difference was significant at the $p=0.05$ level. However, no particular type of anomaly was predominant in this group. The Collaborative Perinatal Project followed the infants of 340 women treated with trimethobenzamide during the first four months of pregnancy and the infants of 700 women who used trimethobenzamide at any time during gestation (Heinonen et al, 1977). The frequencies of major and minor anomalies were no greater than expected among the treated groups. Similarly, no malformations were observed among the infants of more than 120 women treated with trimethobenzamide during the first trimester of pregnancy in the Boston Collaborative Drug Surveillance Program (Jick et al, 1981; Aselton et al, 1984).

Ondansetron (Zofran)

Ondansetron is a selective antagonist at the 5-HT₃ serotonin receptor. Traditionally, it is used as an antiemetic in conjunction with surgery and cancer chemotherapy and radiation. Ondansetron is also occasionally used to treat severe cases of hyperemesis gravidarum.

Several case reports describe successful pregnancy outcomes following the use of ondansetron in pregnancy, including one case in which high doses of ondansetron were administered repeatedly throughout the first trimester (Guikontes et al, 1992; World, 1993). Still, epidemiological studies have not been reported. In 1996 Sullivan et al published the results of a randomized clinical trial to determine the efficacy of ondansetron in pregnancy, but pregnancy outcomes were not included in the data and have not been published by the authors.

Metoclopramide (Reglan)

Metoclopramide is a dopamine receptor-blocking drug that has is used to treat gastroesophageal reflux, chemotherapy-induced nausea, and nausea associated with cesarean section. It is also effective for women who vomit after eating.

Metoclopramide crosses the placenta readily. When administered before cesarean section, clinically significant neonatal effects have not been observed, even in the presence of measurable serum drug levels in the newborn (Bylsma-Howell et al, 1983). Controlled studies regarding first trimester use of metoclopramide have not been performed.

Teratogenic effects of metoclopramide have not been observed in mice, rats, or rabbits (Watanabe et al, 1968).

Ginger Root (*Zingiber officinale*)

Ginger has been used for centuries as a natural remedy to nausea. However, because ginger has been used to promote menstruation, megadoses of ginger are contraindicated in pregnancy. Fischer-Rasmussen, et al (1991) conducted a double-blind randomized trial of the efficacy of powdered ginger root (250 mg) compared with placebo in hyperemesis gravidarum. Twenty-seven women participated; all received ginger and placebo at some point in the trial. A significantly greater relief of the symptoms was found after ginger treatment compared to placebo, and no side effects were observed. Pregnancy outcomes included 1 spontaneous miscarriage, 1 elective termination, and 25 liveborn infants with no evidence of congenital malformations.

Summary

Because it has been studied extensively, Bendectin/ Diclectin (doxylamine plus pyridoxine) is the drug of choice for the treatment of nausea and vomiting in pregnancy. Its reintroduction into the US market will provide welcome relief to millions of women. Data suggests that chlorpromazine, diphenhydramine, dimenhydrinate and cyclizine are also good choices. Although trimethobenzamide and meclizine are probably not teratogenic, additional data is needed to fully evaluate their effects on the developing fetus. Ondansetron, metoclopramide and ginger should be used with caution, particularly during the first trimester, as epidemiological studies have not been performed to evaluate their potential teratogenicity.

References

- Aselton P et al: Pyloric stenosis and maternal Bendectin exposure. *Am J Epidemiol* 1984;120:251-6.
- Aselton P, Jick H, Milunsky A, et al.: First-trimester drug use and congenital disorders. *Obstet Gynecol* 1985;65:451-455.
- Auerbach JG, Hans SL, Marcus J, Maeir S. Maternal psychotropic medication and neonatal behavior. *Neurotoxicol Teratol.* 1992;14(6):399-406.
- Boneva RS, Moore CA, Botto L, Erickson JD. *Am J Epidemiol.* Nausea during pregnancy and congenital heart defects: a population-based case-control study. 1999;149(8):717-25.
- Bylsma-Howell M et al: Placental transport of metoclopramide: assessment of maternal and neonatal effects. *Can Anaesth Soc J* 1983;30:487-92.
- Corby DG, Shulman I: The effects of antenatal drug administration on aggregation of platelets of newborn infants. *J Pediatr* 1971;79:307-13.
- Cordero JF et al: Is Bendectin a teratogen? *J Am Med Assoc* 1981;245:2307-10.
- Crawford JS. The effects of drugs used in labor on the fetus and newborn. *Clin Pharmacol Ther* 1963;4:628-53.
- Emelianova S, Mazzotta P, Einarson A, Koren G. Prevalence and severity of nausea and vomiting of pregnancy and effect of vitamin supplementation. *Clin Invest Med* 1999;22(3):106-10.
- Eskenazi B, Bracken MB: Bendectin (Debendox) as a risk factor for pyloric stenosis. *Am J Obstet Gynecol* 1982;144:919-924.
- Fisher-Rasmussen W et al. Ginger treatment of hyperemesis gravidarum. *Eur J OB Gyn Reprod Biol.* 1991;38:10.
- Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract.* 1993;43:245-8.

Girugea M, Puigdevall J: Experimental teratology with meclozine. *Med Exp* 1966;15375-15388.

Golding J et al. Maternal Antinauseants and Clefts of Lip and Palate. *Hum Toxicol* 1983;2:63-73.

Goodwin TM. Hyperemesis gravidarum. *Clin Ob & Gyn* 1998;41(3):597-605.

Greenberger P, Patterson R: Safety of therapy for allergic symptoms during pregnancy. *Obstet Gynecol Surv* 1979;34:284-6.

Guikontes E, Spantideas A, Kiakakis J. Ondansetron and hyperemesis gravidarum. *Lancet* 1992;340:1223.

Heinonen OP, Slone D, Shapiro S: *Birth Defects and Drugs in Pregnancy*. Littleton, Mass. Publishing Sciences Group, 1977, pp 323-324, 327, 330, 437, 489.

Jacobsson C, Granstrom G. Effects of vitamin B6 on beta-aminopropionitrile-induced palatal cleft formation in the rat. *Cleft Palate-Craniofacial J.* 1997;34(2):95-100.

Jick H, Holmes LB, Hunter JR, et al.: First-trimester drug use and congenital disorders. *JAMA* 1981;246:343-346.

King CTG and Howell J: Teratogenic effect of buclizine and hydroxyzine in the rat and chlorcyclizine in the mouse. *Am J Obstet Gynecol* 1966;95:109-111.

King CTG et al: Antihistamines and teratogenicity in the rat. *J Pharmacol Exp Ther* 1965;147:391-8.

Kullander S, Kallen B. A Prospective Study of Drugs and Pregnancy. II. Anti-emetic drugs. *Acta Obstet Gynecol Scand* 1976;55:105-111.

Lenz W: Malformations caused by drugs in pregnancy. *Am J Dis Child* 1966;112:99-106.

McKeigue PM, Lamm SH, Linn S, Kutcher JS: Bendectin and birth defects: I. A meta-analysis of epidemiologic studies. *Teratology* 1994;50:27-37.

Mellin GW, Katzenstein M: Meclozine and foetal abnormalities. *Lancet* 1963;1:222-3, 1963.

Michaelis J et al: Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformation. *Teratology* 1983;27:57-64.

Milkovich L, Van den Berg BJ: An evaluation of the teratogenicity of certain antinauseant drugs. *Am J Obstet Gynecol* 1976;125:244-8.

Mitchell AA et al: Birth defects in relation to Bendectin use in pregnancy. *Am J Obstet Gynecol* 1983;147:737-742.

Nelson MM, Forfar JO: Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. *Br Med J* 1971;1:153-7.

Posner HS, Darr A: Fetal edema from benzhydrolypoperizines as a possible cause of oral-facial malformations in the rat. *Toxicol Appl Pharmacol* 1970;17:67-75.

Rawat AK: Psychotropic drug metabolism in fetal alcohol syndrome. *Adv Exp Med Biol* 1980;132:561-8.

Rumeau-Rouquette C et al: Possible teratogenic effect of phenothiazines in human beings. *Teratology* 1976;15:57-64.

Saxen I: Cleft palate and maternal diphenhydramine intake. *Lancet* 1974;1:407-8.

Shapiro S et al: Meclizine in pregnancy in relation to congenital malformations. *Br Med J* 1978;1:483.

Slone D et al: Antenatal exposure to the phenothiazines in relation to congenital malformations,

perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 1977;128:486-8.

Steffeck AJ et al.: Chlorcyclizine produced cleft palate in the ferret. *Arch Oral Biol* 1968;13:1281-1283.

Sullivan CA, Johnson CA, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. *Am J Obstet Gynecol* 1996;174:1565-8.

Tsang IS, Katz VL, Wells SD. Maternal and fetal outcomes in hyperemesis gravidarum. *Intl J Gyn Ob.* 1996;55(3):231-5.

Walker BE, Patterson A: Induction of cleft palate in mice by tranquilizers and barbiturates. *Teratology* 1974;10:159-64.

Watanabe N et al: Teratogenicity of metoclopramide. *Yakugaku Kenkyu* 1968;39:92-106.

Weigel RM, Weigel MM. Nausea and vomiting of early pregnancy and pregnancy outcome. A meta-analytical review. *Br J Ob Gyn.* 1989;96(11):1312-8.

Whaun JM et al. Effect of prenatal drug administration on maternal and neonatal platelet aggregation and PF4 release. *Haemostasis* 1980;9:226-37.

Wilson JG: Abnormalities of intrauterine development in non- human primates. *Acta Endocrinol* 71(suppl 166):261-292, 1972.

World MJ: Ondansetron and hyperemesis gravidarum. *Lancet* 1993;341:185.