

Medications that Cause Fetal Anomalies and Possible Prevention Strategies



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KEYWORDS

• Teratology • Medications • Frequently used drugs during pregnancy

KEY POINTS

- It is commonly, but incorrectly, believed that prenatal exposure to most drugs is a high risk for fetal development.
- It is not possible at the present time to document the safety of drugs in the prenatal period.
- Most of the known human teratogens are associated with a pattern of 3 or more minor anomalies, not a single major malformation.

INTRODUCTION

Before 1960 all birth defects were believed to have a genetic cause. The fetus was thought to occupy a privileged site within an iron-clad uterus, safe from the ravages of the external environment. That all changed in the early 1960s when Lenz in Germany and McBride in Australia suggested that prenatal exposure to a drug, thalidomide, led to serious problems in fetal structural development. Based on increased awareness over the years of the potential danger of a variety of drugs on fetal development, the pendulum has now swung in the opposite direction. Today, most drugs are believed to be harmful to the developing fetus. As a result, during their pregnancy, women with certain chronic diseases that require specific medications often decrease or even discontinue taking a drug that is necessary for their own health, potentially leading to greater harm to the fetus than the drug itself. The purpose of this article is to outline what is known and what is not known about some of the more common pharmacologic agents that pregnant women come into contact with during pregnancy, and to suggest possible prevention strategies.

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PHARMACOLOGIC AGENTS COMMONLY TAKEN DURING PREGNANCY

There are many drugs that are used for the treatment of conditions that occur more frequently in women in their childbearing years or for the treatment of diseases that are limited to pregnancy. This article will focus on those medications.

Asthma During Pregnancy

Asthma is the most common chronic condition in pregnant women. Studies show increasing prevalence in the past decade, with estimates of up to 8% of women affected in the United States, and up to 12% affected globally.¹ Asthma control is critically important in helping to maintain a healthy pregnancy, and medications play a key role in treating and preventing exacerbations that can decrease oxygen levels reaching the fetus. Asthma may worsen in the second and third trimesters; consequently, monthly monitoring of asthma and the effectiveness of asthma medications is recommended. Pregnant women may be hesitant to take their asthma medications, but uncontrolled asthma increases risks for complications that affect the mother and child, including preterm delivery, cesarean section, low birth weight, preeclampsia, congenital malformations, gestational diabetes, placenta previa, placental abruption, premature rupture of membranes, neonatal hospitalization, and neonatal death.^{1–3} Therefore, adequate treatment of asthma improves pregnancy outcomes.

This section will describe the available data for some of the drugs used most commonly to treat asthma: systemic or oral corticosteroids, inhaled corticosteroids, short-acting beta-agonists (SABAs), such as albuterol, long-acting beta-agonists (LABA), and montelukast. As there are challenges to recruiting pregnant women into clinical trials, data are limited in pregnancy, although this is true for most medications used for any condition during gestation. Although more studies are needed, existing data for these more commonly used asthma medications are generally reassuring for the treatment of pregnant women.

Systemic Corticosteroids

Meta-analysis of studies of systemic corticosteroids such as prednisone have shown mixed results, with one showing no overall increased risk for major malformations, and another concluding there is a 3-fold increased risk for oral clefts.⁴ Yet no increased risk for oral clefts was seen in the most recent and largest case-control research from the US National Birth Defects Prevention Study (US NBDPS),⁵ leading to the conclusion that there may be a small increased risk for oral clefts with first trimester use of corticosteroids. Increased rates of pregnancy complications such as preterm delivery,⁶ low birth weight, preeclampsia, and gestational diabetes have been seen in pregnant women treated with systemic steroids, but these were reduced when studies controlled for maternal disease and disease severity. A recent study concluded that there is little evidence to show that use of systemic corticosteroids independently increases risks for preterm birth, low birth weight, or preeclampsia,⁷ although maternal disease is associated with increased risk.

Prednisone is excreted into human milk at very low levels and is thought to be compatible with lactation.⁸

Inhaled Corticosteroids

A meta-analysis did not find an increased risk for major malformations for inhaled corticosteroids in general; nor were risks seen for preterm delivery, low birth weight, or gestational hypertension.⁹ Furthermore, studies have not demonstrated an increased risk for gestational diabetes or gestational hypertension.¹⁰ For budesonide in

particular, one study of more than 2000 exposed women showed no increased risk for major birth defects overall or for oral clefts, and no increased risk in another study of nearly 3000 women for preterm birth, reduced birth weight or length, or stillbirth.¹¹ For fluticasone, similar results were seen, no increased risk for major malformations compared with women exposed to other inhaled corticosteroids¹² and stratified by severity.

Because the amounts of inhaled corticosteroids absorbed into the bloodstream and excreted into breastmilk are small, use by a nursing mother is not expected to cause adverse reactions in a breastfed infant.¹³

Albuterol and Other Short-Acting Beta-Agonists

In studies of albuterol-exposed pregnancies, no increased rate of birth defects was seen with first-trimester exposure,¹⁴ although modest increased risks (<2.0 or <3.0) for isolated oral clefts, any cardiac defect, gastroschisis, anorectal or esophageal atresia, or omphalocele^{15,16} have been noted in some studies. Additional study is required to discern if these findings are because of SABA exposure, maternal disease, disease severity, or another factor. Research on more than 1800 pregnancies exposed to any SABAs has not revealed increases in rates of preterm delivery, low birth weight, gestational hypertension, or small for gestational age infants.⁶

An expert panel concluded that use of albuterol is compatible with breastfeeding even in the absence of published studies, because of low bioavailability and low maternal serum levels.¹⁷

Long-Acting Beta-Agonists

First-trimester exposure to LABAs increased the risk for major cardiac defects and “other and unspecified” major malformations¹⁴ in a data linkage study. The authors suggest that this could be because of the medication, to an association with more severe and uncontrolled asthma that is found with LABA users, to chance, or to the fact that some of these malformations are common among preterm infants, and preterm birth occurs more often among LABA users than non-users. Other studies have not found an increased risk for major birth defects with LABA use.¹⁸ Studies conducted on salmeterol exposure in 126 pregnant women compared use with (1) pregnant women who took SABAs and (2) healthy controls, and found no increased risk for major birth defects, preterm birth, or low birth weight.¹⁹

Similar to albuterol, many experts consider inhaled bronchodilators such as salmeterol and formoterol compatible with breastfeeding because of the low bioavailability and low maternal serum levels after dosing.²⁰

Leukotriene Receptor Antagonists

No increased risk for major birth defects was seen in a claims study of 1164 first-trimester-exposed pregnancies,²¹ or in a study of 180 exposures reported to 7 teratogen information services.²² Similar results were seen in a Danish registry study of preconception and first-trimester-exposed pregnancies.²³ This study also showed a higher risk for preeclampsia and gestational diabetes, although these are associated with more severe asthma and likely not specific to montelukast. No increased risk for pregnancy loss, gestational diabetes, preeclampsia, low maternal weight gain, preterm delivery, low Apgar scores, or small size was seen in a study of 96 infants exposed to leukotriene receptor antagonists in pregnancy.²⁴ Further, no pattern of major anomalies could be identified, and malformation rates were not significantly higher among the infants of asthmatics who took leukotriene receptor antagonists or SABAs. Similarly, no increased risk has been shown for low

birth weight, shortened gestational age, preterm delivery, or preeclampsia in studies comparing exposed pregnancies with those of other asthmatic women not exposed to montelukast.²²

Montelukast is excreted into breastmilk in very low levels²⁵ and has been used in neonates at levels higher than would be found in milk. No adverse reactions are expected in the infant of a nursing mother taking montelukast.²⁶

Drugs Used for Treatment of Nausea and Vomiting of Pregnancy

Ondansetron

Nausea and vomiting of pregnancy (NVP) is the most common medical condition that occurs during pregnancy, with an estimated incidence of 85% of pregnant women.²⁷ Most of those women take antiemetic drugs to mitigate their symptoms. Based on a study of antiemetic use from an insured population of pregnant women in the United States who delivered live-born babies, Taylor and colleagues²⁷ observed a marked increase in the use of ondansetron for treatment of NVP from less than 1% of pregnancies in 2001 to 22.25% in 2014.

Ondansetron is a serotonin 5-HT₃ receptor antagonist. It was originally marketed for nausea and vomiting associated with chemotherapy, radiation therapy, and surgery. Its use in NVP is off-label. Studies evaluating the effect of ondansetron on fetal development are few and the data are conflicting.

Anderka and colleagues,²⁸ used data from the US NBDPS to determine if NVP or its treatment was associated with an increased risk for the most common non-cardiac defects including non-syndromic cleft lip with or without cleft palate, cleft palate alone, neural tube defects, and hypospadias. NVP was not associated with any of the 4 non-cardiac defects. However ondansetron was associated with an increased risk for cleft palate alone (adjusted odds ratio = 2.37; 95% CI: 1.18–4.76).

There was one additional study showing an increased risk for structural defects following prenatal exposure to ondansetron. Published by Danielsson and colleagues,²⁹ data from the Swedish Medical Birth Register combined with the Swedish Register of Prescribed Drugs were used to recruit 1349 infants whose mothers took ondansetron in early pregnancy. Although there was no statistically increased risk for major malformations, the risk for cardiovascular defects, particularly cardiac septal defects, was statistically significantly increased (odds ratio = 1.62, 95% CI: 1.04–2.14 and relative risk = 2.05, 95% CI: 1.19–3.28). No cases of cleft palate were reported in the offspring of exposed women in that study.

Three other studies have shown the opposite result.

Based on a study using data from the Medical Birth Registry and the National Patient Registry in Denmark, Pasternak and colleagues,³⁰ compared major birth defect outcomes among the offspring of 1233 women exposed to ondansetron in the first trimester compared with the offspring of 4932 unexposed women. Prenatal exposure to ondansetron was not associated with an increased risk when compared with the offspring of unexposed women for any major malformation (2.9% and 2.9%, respectively; prevalence odds ratio, 1.12; 95% CI: 0.69–1.82). Einarson and colleagues³¹ published data from a prospective comparison study involving 176 pregnancy outcomes in women taking ondansetron in the first trimester, 176 women taking another antiemetic, and 176 women with non-teratogenic exposures. There were no statistically significant differences in the prevalence of major malformations in the 3 groups.

Fejzo and colleagues³² reported pregnancy outcome in 1070 women who took ondansetron in pregnancy for the treatment of hyperemesis gravidarum

(HG) compared with pregnancy outcome in 771 pregnant women with a history of HG, but who reported no ondansetron exposure and 1555 pregnant women with no HG and no ondansetron exposure. There was no difference in major malformations in the HG/ondansetron group compared with the HG/No ondansetron group.

Based on the sparsity of studies and the lack of agreement between the studies that are available, it is not possible to state whether ondansetron is associated with a small risk for cleft palate or for cardiac defects. However, given the large number of women who are taking this drug during the first trimester of their pregnancy, more research into its prenatal effects is critical.

Drugs Used for the Treatment of Hyperthyroidism During Pregnancy

The presence of clinical hyperthyroidism in the childbearing years occurs in from 0.1% to 0.4%, and the most common cause is Graves' disease.³³ Graves' disease is an autoimmune disease in which an individual's own immune system makes thyrotropin receptor antibodies that bind to receptors on the surface of thyroid cells and cause them to overproduce and release thyroid hormone.³⁴ Methimazole (MMI)/carbimazole (CMZ), and propylthiouracil are the drugs of choice for hyperthyroidism in pregnancy.³⁵

Primarily case reports and a few epidemiologic studies have shown that MMI/CMZ is a human teratogen when taken during the first trimester of pregnancy, although the occurrences are rare. Milham and Elledge first suggested, in 1972, that MMI was a human teratogen based on the observation that 2 of 11 newborns with midline scalp defects were born to women treated with MMI for the treatment of hyperthyroidism during pregnancy.³⁶ Thereafter Clementi and colleagues³⁷ suggested that MMI was associated with a specific pattern of structural defects. Identical features have been associated with CMZ, which is converted to MMI after absorption. It has been suggested that the critical window for exposure is between the third and ninth gestational weeks. The pattern of malformations documented in 72 case reports comprise: ectodermal defects including scalp aplasia cutis congenita, aplasia/hypothelia, and hypoplastic/dystrophic nails; gastrointestinal defects including esophageal atresia, hypoplastic/absent gall bladder, and patent omphalomesenteric duct; *abdominal wall defects* including omphalocele and gastroschisis, as well as other anomalies including choanal atresia, coloboma, heart defects, renal anomalies, and intellectual disability in 60% of cases.³⁷

Propylthiouracil

Andersen and colleagues³⁸ evaluated the presence of birth defects in the offspring of women who redeemed a prescription for propylthiouracil (PTU) from a nationwide registry of all children born in Denmark from 1996 to 2008. Fourteen children with birth defects were identified following PTU exposure early in pregnancy. Of those 14 children, 7 had defects involving the face and neck and 7 had defects involving the urinary tract. Among those children the adjusted hazard ratio (HR) for children having a defect of the face and neck was 4.92 (95% CI: 2.04–11.86) and for the urinary system the adjusted HR was 2.73 (95% CI: 1.22–6.07).

Of the 7 children with a birth defect of the face and neck, most had a preauricular or branchial fistula/cyst, and of the 7 children with urinary tract defects most had a single cyst of the kidney or hydronephrosis.

This study is in contrast to 3 previous studies that showed no increase in the risk of birth defects in offspring of women using PTU in pregnancy.^{39–41}

Treatment of Pain and Fever During Pregnancy

Acetaminophen (paracetamol)

Acetaminophen is the most common drug used in pregnancy for the treatment of pain and fever. Various studies have shown that the drug is used by up to 60% of women at some time during their pregnancy.⁴² Several studies have recently evaluated neurobehavioral outcome in children prenatally exposed to acetaminophen. Although the results of these studies have varied, there is clearly reason that the effect of prenatal exposure to this drug on neurodevelopment needs to be more fully studied.

A study published in 2013 used data from the Norwegian Mother and Child Cohort Study, which included 2919 same-sex sibling pairs who were used to adjust for familial and genetic factors.⁴³ A total of 134 (4.6%) were discordant for prenatal exposure to acetaminophen for ≥ 28 days during the pregnancy and 805 were discordant for prenatal exposure for less than 28 days. Those children prenatally exposed for ≥ 28 days had poorer gross motor development, poorer communication skills, externalizing and internalizing behavioral problems, and higher activity levels. Those prenatally exposed for less than 28 days had poorer gross motor functioning.

Another study evaluated neurobehavioral development using 64,322 live-born children and their mothers enrolled in the Danish National Birth Cohort.⁴⁴ Children prenatally exposed to acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of hyperkinetic disorder (HR = 1.37; 95% CI: 1.15–1.59); having attention-deficit/hyperactivity disorder-like behaviors at age 7 years (relative risk = 1.13; 95% CI: 1.01–1.27); and use of attention-deficit/hyperactivity disorder medications (HR = 1.29; CI: 1.15–1.44). There was a stronger association observed with use of the drug in more than one trimester of pregnancy.

Language development at 30 months of age was evaluated in the offspring of 754 women who enrolled in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy study.⁴⁵ Language delay in girls but not in boys at 30 months of age was noted to be associated with prenatal exposure to acetaminophen in the first trimester of pregnancy. Similarly, first-trimester exposure to acetaminophen was associated with poorer overall attention scores in childhood and parent-rated subnormal executive function. The risk was increased with longer duration of exposure during pregnancy.

A study of the prenatal use of acetaminophen on child IQ provides further reason to suggest that a study to more appropriately evaluate the effect of this drug on neurodevelopment needs to be done. Data from the Danish National Birth Cohort was used to assess the prenatal effect of maternal fever and acetaminophen on the IQ of the child.⁴⁶ Children born to mothers who took acetaminophen without fever had on average a 3.4 lower performance IQ compared with those born to women who neither took acetaminophen nor had fever during their pregnancy. In addition, women who experienced fever, but did use acetaminophen during pregnancy, scored lower on verbal and performance IQ. However, for women with fever who took acetaminophen during pregnancy, there was no effect on IQ score suggesting that by decreasing the fever its effect on child IQ was lessened.

In summary, although the prenatal effect of this drug on fetal neurodevelopment may be small, the large number of women taking this drug during pregnancy raises concern that its impact may be great.

Depression During Pregnancy

Depression is one of the most common conditions occurring in pregnancy, with a prevalence of greater than 10%. The most common drugs used for the treatment of

depression during pregnancy are the selective serotonin reuptake inhibitors (SSRIs). A study conducted by the US NBDPS evaluated pregnancy outcome following maternal exposure to 5 SSRIs including fluoxetine, paroxetine, citalopram, escitalopram, and sertraline from 1 month before conception through the third month of pregnancy.⁴⁷ A Bayesian analysis was used in that study to interpret new data in the context of previous reports. The authors reviewed the medical literature to find previous reports of specific birth defects noted in association with prenatal exposure to an SSRI that was included in the US NBDPS. They found no association with prenatal exposure to citalopram or escitalopram monotherapy for any or the 5 birth defects seen in previous reports, including anencephaly, cardiac septal defects, anal atresia, any limb reduction defect, or omphalocele. However, for the 7 previously reported birth defects associated with prenatal exposure to paroxetine, significant associations were seen in 5 of them, including anencephaly, atrial septal defect, right ventricular outflow tract obstruction, gastroschisis, and omphalocele. No association was seen for cleft palate or hypospadias. It was concluded from that study that the various SSRIs need to be evaluated separately as opposed to as a group with respect to pregnancy outcome, and that, although the data were reassuring relative to pregnancy outcome for some of the SSRIs, there was concern for others.

In addition, a study by Chambers and colleagues⁴⁸ has documented the risk for persistent pulmonary hypertension of the newborn (PPHN) following late third-trimester exposure to fluoxetine. In that study, 377 infants with PPHN and 836 control infants were ascertained through the Slone Epidemiology Center. Fourteen of the infants had been exposed to an SSRI after completion of the 20th week of gestation as opposed to 6 control infants (adjusted odds ratio, 6.1; 95% CI: 2.2–16.8). None of the infants with SSRI exposure before the 20th week of gestation developed PPHN. These observations have some biologic plausibility. It is known that SSRIs accumulate in the lung and have vasoconstrictive capabilities. Secondly SSRIs are known to inhibit the synthesis of nitric oxide, which is a vasodilator that regulates vascular tone.

Finally, it is important to realize that increased risk with regard to pregnancy outcome in women taking antidepressants must always take into consideration the extent of untreated maternal depression on pregnancy outcome. A study documenting relapse of major depression during pregnancy in women who maintained or discontinued antidepressant treatment is particularly relevant.⁴⁹ Of the 82 women in that study who continued to take their antidepressant medication during pregnancy, 21 (26%) of them relapsed, as opposed to 44 (68%) of the 65 women who discontinued their medication during pregnancy, a statistically significant difference.

POSSIBLE PREVENTION STRATEGIES

The U.S. Food and Drug Administration has the responsibility for protection of and promotion of public health through the control and supervision of, among other things, medications (prescription and over-the-counter pharmaceutical drugs). The safety of medication use during pregnancy represents a unique situation. Giving a woman a medication during pregnancy to test whether the drug causes birth defects or other adverse pregnancy outcomes is impossible to justify. Therefore, it becomes necessary to resort to post-marketing surveillance studies to determine the safety of medications during pregnancy.

In 1985, a multicenter prospective cohort methodology using the Organization of Teratology Services (OTIS) for the identification of human teratogens was established.⁵⁰ Twenty Teratology Information Services were established through the United States and Canada with the purpose of providing information about the

risk of adverse pregnancy outcome to women contemplating pregnancy, pregnant and breastfeeding women and their physicians, as well as to gain new information about the effect of medications about which pregnancy outcome data are unknown. The formation of this organization has facilitated communication among individual programs, has allowed for access to common database information, has increased public visibility of the individual services and has provided a forum for utilizing prospective pregnancy outcome data in a scientific manner that can be provided to the public. With respect to the latter, this cohort study design allows for documentation of a wide range of adverse pregnancy outcomes including spontaneous abortion, intrauterine growth retardation, prematurity, intellectual disability, and birth defects. Although the sample size of the studies limits in most cases the identification of an increased risk for single major malformations, the capability to do careful dysmorphism examinations, blind to prenatal exposure of the child, provides the ability to identify a specific pattern of minor anomalies. This is particularly important in that most of the known human teratogens are associated with a pattern of 3 or more minor anomalies, not a single major malformation. Through the use of this methodology OTIS studies have been used to document the risk or lack of risk of a number of agents. Clearly there are many limitations of this methodology including the use of volunteer subjects; the bias that could occur as a result of prenatal diagnosis (this has been dealt with by excluding women who have already had prenatal diagnosis before recruitment); the assessment of spontaneous abortion. (Most women who enroll in the study do so after pregnancy recognition. Therefore the relative risk for spontaneous abortion is confined to late first- or early second-trimester occurrences.)

There are some very important advantages about the OTIS methodology, particularly when it comes to counseling women contemplating pregnancy who have a concern about a particular medication they are taking. An increasing number of women are contacting OTIS services in the preconception period. Communicating with those women gives Teratology Information Specialists the opportunity to provide women information that can have a major impact on their risk of having a child with birth defects and other adverse pregnancy outcomes.

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