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**Over the Counter Cold Medications in Pregnancy**

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Cold season is upon us, and many pregnant women will have concerns about the teratogenic risk of over-the-counter cold medications. Most data on cold medication use during pregnancy comes from large, retrospective studies; little prospective data is available despite the common use of these medications in pregnancy. Many cold medications contain a combination of an antihistamine, a decongestant (sympathomimetic), an expectorant and/or an analgesic. This combination of medications makes determining the teratogenic risk of a specific agent more difficult. Rather than consuming a cold medication that treats all possible symptoms, pregnant women may want to limit medications to treat specific symptoms of nasal congestion, allergic rhinitis and/or malaise.

This RISK//NEWSLETTER will review the most common components of over-the-counter cold medications: antihistamines, sympathomimetics, expectorants and analgesics. We will also address less traditional cold treatments such as echinacea, zinc and vitamin C. The accompanying table lists the ingredients present in several common over-the-counter cold remedies.

## Antihistamines

The most common antihistamines in cold medications are chlorpheniramine, diphenhydramine, brompheniramine and clemastine. In the Kaiser-Permanente Prospective Study of Asthma During Pregnancy, there was no relationship between first trimester exposure to antihistamines and major malformations (Schatz et al., 1997).

Prospective study of 269 women with first trimester exposure to chlorpheniramine did not find any increase in malformations (Schatz et al, 1997). This finding is supported by two retrospective studies of 1070 and 61 women with first trimester exposure to chlorpheniramine (Heinonen et al., 1977; Briggs et al., 1994). Therefore, chlorpheniramine exposure in pregnancy does not appear to increase the risk for malformations above the general population frequency.

Most studies of diphenhydramine use during pregnancy have not found a significantly increased risk for malformations. Saxen (1974) examined 599 children with oral clefts and 590 controls and found a significant association between first trimester use and oral clefting. This finding has not been confirmed by retrospective studies which examined more than 2300 pregnancies exposed in the first trimester (Heinonen et al., 1977; Aselton et al., 1985; Briggs et al., 1994). As such, the risk for malformations, including clefts, is likely to be low. High doses of diphenhydramine (>50mg) may lead to “oxytocin-like” properties. Because of this, high doses of diphenhydramine should not be used late in pregnancy to avoid the theoretical risk of pre-term labor.

The Collaborative Perinatal Project found a slight increase in malformations, specifically syndactyly,

associated with first trimester exposure to brompheniramine (Heinonen et al., 1977). This study was too small (N=65 women), however, to draw causal conclusions about the risk of brompheniramine in pregnancy. Additionally, a larger retrospective study (N=270 women) did not find an association between exposure and an increased risk for malformations (Aselton et al., 1985).

Studies on clemastine are limited to a retrospective study of 1,617 women; no increased risk for malformations was noted (Briggs et al., 1994). Based on this, clemastine exposure does not appear to increase the risk for malformations above the general population frequency.

**Decongestants (Sympathomimetics)**

The most common decongestants include psuedoephedrine, phenylpropanolamine, phenylephrine, oxmetazoline and xylometazoline. As a group, decongestants (or sympathomimetics) mimic epinephrine and result in vasoconstriction; they also can produce maternal hypertension (Horowitz et al., 1980). Theoretically, this could impair blood flow to the fetus, leading to IUGR and/or fetal vasoconstriction. Several studies show an increased risk for gastroschisis after sympathomimetic exposure. Werler et al. (1992) reported that first trimester exposure to pseudoephedrine, but not to phenylpropanolamine, was more common among children born with gastroschisis (RR=3.2, 95% CI 1.3-7.7). Torfs et al. (1996) found the reverse, with significant associations between gastroschisis and exposure to all decongestants, particularly with phenylpropanolamine (OR 10.0; CI 1.2-85.6). A recent prospective study of 453 women using decongestants during the first trimester did not find a significantly increased risk for malformations, including gastroschisis (Schatz et al., 1997). However, due to the biological plausibility of vasoconstricting agents and gastroschisis, it has been suggested that use of decongestants in pregnancy be minimized.

Pseudoephedrine has been well studied in pregnancy. Schatz et al (1997) prospectively followed 714 women exposed to pseudoephedrine and found no increased risk for malformations. Retrospective studies of 940 women support this finding (Briggs et al., 1994), making it unlikely that first trimester exposure to pseudoephedrine poses an increased risk for malformations. Because pseudoephedrine has both alpha and beta agonist properties, single doses do not significantly alter blood flow velocities (Smith et al., 1990); pseudoephedrine, therefore, has the lowest theoretical risk of inducing maternal hypertension.

Phenylpropanolamine is a commonly used decongestant. The Collaborative Perinatal Project reported an association between first trimester exposure to phenylpropanolamine and an increased risk for minor malformations (N=726), but no pattern of malformations was observed, making a causal association unlikely (Heinonen et al., 1977). Another retrospective study of 82 women exposed to phenylpropanolamine in the first trimester found no increased risk for minor or major malformations (Aselton et al., 1985). Based on these results, the risk of malformations associated with phenylpropanolamine is considered low.

Two case-control studies involving approximately 700 women reported that first trimester use of phenylephrine was more common among children born with congenital heart disease (Rothman et al, 1979; Zierler & Rothman, 1985). The relationship between other exposures and maternal disease could not be ruled out as causes of the increased incidence of congenital heart disease in these women. The Collaborative Perinatal Project found a slight increase in the incidence of minor anomalies, mostly eye and ear malformations, in 1249 women exposed during the first trimester (Heinonen et al., 1977). Further studies are needed to clarify these associations.

Xylometazoline and oxymetazoline are decongestants found in nasal sprays. 5-10% of a medication delivered via nasal spray reaches maternal circulation; fetal exposure is, therefore, low. Because nasal congestion is common during pregnancy, women may use more than the recommended amount of nasal spray. Prospective data on 197 women exposed to intranasal oxymetazoline did not indicate an

increased risk for malformations (Schatz et al 1997); a retrospective study on 207 women exposed to xylometazoline had similar negative findings (Aselton et al., 1985). Based on this, combined with the low exposure level, the risk of adverse outcome after exposure to nasal spray is thought to be minimal.

In summary, there is no clear association between decongestant exposure during pregnancy and an increased risk for malformations. However, because of the theoretical risk of decongestant use leading to maternal/fetal vasoconstriction, they should be used conservatively during pregnancy.

**Expectorants**

An increased incidence of inguinal hernias was noted in a retrospective study of 197 women with first trimester exposure to guaifenesin (Heinonen et al., 1977). Other retrospective studies have not, however, found an increased incidence of malformations associated with guaifenesin exposure during the first trimester (Aselton et al., 1985; Briggs et al., 1994). Overall, the teratogenic risk of guaifenesin is thought to be low.

Dextromethorphan is the focus of a recent controversy, following a report that dextromethorphan induced miscarriage and malformations, such as open neural tube defects, in chick embryos injected with dextromethorphan (Andaloro et al., 1998). The results from this study remain controversial because it is unclear how relevant these observations are to human exposures. Retrospective data on dextromethorphan use during human pregnancy, totaling 300 women exposed in the first trimester, have not found any increase in malformations (Heinonen et al., 1977; Aselton et al, 1985).

There is no evidence that either of these two expectorants significantly increases the risk for birth defects in human pregnancy when taken therapeutically during the first trimester.

**Analgesics**

The most commonly used analgesics in cold medications are aspirin, acetaminophen and ibuprofen. These medications do not appear to increase the risk for birth defects when taken therapeutically in the first trimester of pregnancy. However, aspirin and non-steroidal anti-inflammatories are not recommended in the third trimester because their prostaglandin inhibition properties may lead to an increased risk of intracranial hemorrhage and premature closure of the ductus arteriosis in infants, especially in premature or low-birthweight infants.

**Non-traditional Cold Treatments**

For centuries, homeopathic remedies including echinachea have been used to treat cold symptoms. Because of echinachea's natural properties, many consumers assume that it is "safer" than other pharmacologic agents. However, little epidemiologic data exists on the use of any homeopathic remedy during gestation. Gallo et al. (1998) presented an abstract reviewing 66 women exposed to echinachea during the first trimester and compared them to disease matched controls. No increased risk for birth defects, miscarriage or low birth weight was noted. However, because this study involved a small number of women, the risks associated with using echinachea during pregnancy remain unclear.

Many patients consume large quantities of vitamin C to lessen cold symptoms, often at significantly higher levels than the recommended daily allowance (RDA 60 - 70 mg for pregnant women). Vitamin C is water soluble, and while deficiency leads to scurvy, excessive doses are usually not associated with clinical symptoms (Goodman and Gilman, 1996). While vitamin C exposure at or near the RDA has not been associated with adverse outcome, there is little data on possible risks associated with high doses. It also appears that Vitamin C is concentrated in the fetus at levels higher than those seen in the mother. In animals, some offspring exposed to high doses of vitamin C showed symptoms of scurvy (Cochrane, 1965). Human reports are limited to two infants who developed scurvy after exposure to greater than 400 mg/day (Cochrane, 1965) and a woman with an anencephalic infant after taking multiple vitamins

at elevated doses (Averback, 1976).

In recent years, cold preparations and cough drops containing zinc (usually 13mg) have been marketed to reduce the severity of cold symptoms. The RDA of zinc is 12-15 mg per day. Animal studies showed an increased risk for malformations, particularly skeletal defects, with extremely high exposures to zinc during gestation; these findings may be related to maternal toxicity from elevated zinc levels.

In humans, the question whether zinc levels play a role in the occurrence of neural tube defects is unresolved. Two reports showed elevated zinc levels in the blood or amniotic fluid, respectively, in a total of 24 infants with anencephaly or spina bifida (Zimmerman, 1984; Parkinson et al, 1982). Another study found elevated maternal serum zinc levels in 69 women carrying a pregnancy with a neural tube defect as compared to 592 control pregnancies (McMichael et al, 1994). In contrast, other studies have shown decreased levels of maternal serum zinc in women who had a pregnancy affected with a neural tube defect (Cadver et al 1980; Hinks et al 1980). Finally, it appears that maternal zinc levels are related proportionately to infant birth weight and head circumference (Neggars et al 1990; Goldenberg et al 1995).

**Miscellaneous Cold Remedies**

Menthol is a common ingredient of many throat lozenges and sprays. There are no human studies on the use of menthol during pregnancy, so its risk is undetermined. The concentration of menthol in throat lozenges and sprays is low, and because of this the risk for malformations is believed to be small. Camphor (VapoRub) is also used to treat cold symptoms. Retrospective studies have not shown any developmental toxicity associated with in utero camphor exposures (Heinonen et al, 1975). Topical exposure generally delivers a low level of medication, therefore the risk to the fetus is thought to be small.

**Summary:**

Over-the-counter cold medications contain many different ingredients, most of which are not associated with an increased risk for birth defects. There is some theoretical risk of vasoconstriction with decongestant use in pregnancy, and for that reason, use should be minimized. During pregnancy, cold medications that specifically address a pregnant woman’s symptoms should be used to minimize theoretical risks in pregnancy.

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