

Is guaifenesin safe during pregnancy?

Evidence-based answer

It's not clear; little evidence supports or refutes the safety of guaifenesin, a common expectorant, in pregnancy. A small number of observational and case-control studies suggest a weak association between guaifenesin use and inguinal hernias and neural tube

defects in newborns. However, substantial methodological flaws, the absence of statistical significance, and low rates of prevalence cast a shadow of a doubt over the data (strength of recommendation [SOR]: **B**, based on observational and case-control studies).

Clinical commentary

Always take a conservative approach to obstetrics

In my practice as a family physician, a conservative approach to obstetrical care has been the rule. It seems prudent to avoid guaifenesin during the first trimester. Although the evidence is inconclusive on potential harm to the fetus, the marginal benefit gained seems insufficient to justify treatment early in pregnancy when the fetus is most vulnerable to teratogenic effects in general.

As with most other Category C medications (except those with clear clinical benefit and no safer alternative), I typically avoid guaifenesin throughout pregnancy. However, it may be reasonable to prescribe it in the latter half of pregnancy when the potential risk is lower; particularly in light of the lack of any clear evidence demonstrating harmful effects.

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"In my practice, a conservative approach to obstetrical care has been the rule"

Evidence summary

Guaifenesin, available in numerous preparations (eg, Mucinex, Robitussin), is one of the most commonly used over-the-counter medications in pregnancy. The National Birth Defects Prevention Study surveyed 2970 pregnant women from 1997 to 2001; 6.2% reported taking guaifenesin during pregnancy.¹ A second survey evaluated 7563 mothers from 1998 to 2004; 9.2% of the mothers reported that they took it during pregnancy.¹

A weak link to inguinal hernias

Guaifenesin use in pregnancy has been associated with inguinal hernias in newborns. From 1958 to 1965, the Collaborative Perinatal Project recruited 132,500 women to participate in a multicenter study; however, selection and exclusion criteria were not consistent. From this initial group, only 50,282 mother-child pairs were studied. Trained examiners interviewed the women at the child's 4, 8, 12, and 24-month visits, and then annu-

ally thereafter to 8 years of age.

The examiners identified 7 children with inguinal hernias among 197 mothers who had used guaifenesin during their first trimester (standardized relative risk [RR] of 2.6; no CI or *P* value reported). Twenty children had inguinal hernias among the 1337 mothers who had used guaifenesin during any trimester of their pregnancy (RR=1.1; no confidence interval [CI] or *P* value reported).² The authors acknowledged that reporting bias among the participating centers prevented them from drawing any conclusions from the data.

A possible trend toward neural tube defects?

Guaifenesin use in pregnancy may also be associated with neural tube defects. In a case-control study, researchers identified 538 fetuses and live-born infants with neural tube defects between 1989 and 1991.³ Twelve patients with neural tube defects were exposed to guaifenesin during gestation; 6 in the control group reported exposure.

The authors reported a trend towards increased risk of neural tube defects in offspring of guaifenesin-exposed mothers (odds ratio=2.04; 95% CI, 0.79–5.28).³ However, since the results were not statistically significant, the authors concluded that guaifenesin had not contributed to the occurrence of neural tube defects.

In a study evaluating 6509 women whose pregnancies resulted in live births, 241 women reported first-trimester exposure to guaifenesin.⁴ Five of the guaifenesin-exposed infants (2.1%) had 1 of the birth defects studied (types of disorders not reported). The calculated RR of birth defect after in utero guaifenesin exposure was 1.3 (no CIs or *P* values reported); the authors concluded that there was no strong association between guaifenesin and the malformations studied.⁴

Interpret results with caution

Because of the significant potential for recall bias, interpret the findings of these case-control studies with caution.⁵ The

mother of a child with a birth defect may search her memory more aggressively for potential causes than a mother of a healthy infant, leading to different rates of recalled, rather than actual, exposures. In the absence of confirmatory prospective data, such as medication diaries or pharmacy databases, recall bias accounts for many spurious positive findings in case control studies.

Recommendations from others

Food and Drug Administration. The FDA assigned guaifenesin to category C—that is, its risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. Guaifenesin is recommended if the benefit to the pregnant woman warrants the risk to the fetus.⁶

ACOG. The American College of Obstetricians and Gynecologists (ACOG) makes no recommendation.⁷ The textbook *Drugs in Pregnancy and Lactation* reports that guaifenesin use during pregnancy exhibits very low risk to the fetus.⁶ The National Collaborating Centre for Women's and Children's Health suggests that guaifenesin be used sparingly during pregnancy.⁸ ■

References

1. Werler MM, Mitchel AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol* 2005; 193:771–777.
2. Heinonen OP, Sione D, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Littleton, Mass: Publishing Sciences Group, 1977.
3. Shaw GM, Todoroff K, Velie EM, Lammer, EJ. Maternal illness, including fever, and medication use as risk factors for neural tube defects. *Teratology* 1998; 57:1–7.
4. Aseton P, Jick H, Milunsky A, Hunter JR, Stergachis A. First-trimester drug use and congenital disorders. *Obstet Gynecol* 1985; 65:451–455.
5. Chouinard E, Walter S. Title recall bias in case-control studies: an empirical analysis and theoretical framework. *J Clin Epidemiology* 1995; 48:245–254.
6. Briggs GG, Freeman RK, Yaffe, SJ. *Drugs in Pregnancy and Lactation*. 7th ed. Baltimore, Md: Lippincott Williams & Wilkins; 2005.
7. The use of newer asthma and allergy medications during pregnancy. *Ann Allergy Asthma Immunol* 2000; 84:475–480.
8. National Collaborating Centre for Women's and Children's Health. *Antenatal Care: Routine Care for the Healthy Pregnant Woman*. London: RCOG Press; 2003.

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Despite the weak evidence, it seems prudent to avoid guaifenesin in the first trimester