MOTHERISK UPDATE

Caffeine during pregnancy?

In moderation

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abstract

QUESTION Many of my female patients, those who plan pregnancy or have conceived, are afraid of any intake of caffeine. This often makes their lives miserable during pregnancy. Is this justified scientifically?

ANSWER Motherisk's recent meta-analysis suggests that the risks for miscarriage and fetal growth retardation increase only with daily doses of caffeine above 150 mg/d, equivalent to six typical cups of coffee a day. It is possible that some of this presumed risk is due to confounders, such as cigarette smoking.

résumé

QUESTION Plusieurs de mes patientes, celles qui planifient une grossesse ou sont enceintes, ont peur de consommer de la caféine. Cette privation leur cause souvent des désagréments durant la grossesse. Cette crainte est-elle justifiée sur le plan scientifique?

RÉPONSE Une récente méta-analyse réalisée par Motherisk fait ressortir que les risques de fausses couches et de retard de croissance fœtale augmentent seulement avec des doses quotidiennes de caféine dépassant 150mg/j, l'équivalent de six tasses normales de café par jour. Il est possible que ce présumé risque soit dû en partie à des facteurs confusionnels comme le tabagisme

In 1980, the United States Food and Drug Administration (FDA) issued a warning regarding use of caffeine during pregnancy.[1] Because conclusions about human teratogenicity could not be definite at that time, the FDA suggested that, as a precautionary measure, pregnant women should be advised to avoid or limit consumption of food or drugs containing caffeine. Due to the large worldwide consumption of caffeinated beverages (eg, coffee, tea, cola), it is important to know whether such a warning is actually warranted. If caffeine consumption during pregnancy were linked to adverse effects, such as spontaneous abortion or fetal growth retardation, those findings would have important implications for public health. Furthermore, the potential effect of such an association is underscored by the fact that low birth weight is associated with high mortality and morbidity among neonates.

Caffeine clearance from the body continues essentially unchanged during the first trimester of pregnancy, but is substantially delayed during the second and third trimesters, because the half-life of caffeine extends to 10.5 h from a normal of 2.5 h to 4.5 h.[2] Caffeine is known to cross the placenta readily; substantial quantities pass into the amniotic fluid and umbilical cord blood, and appear in the urine and plasma of neonates. In addition, human fetuses and neonates have low levels of the enzymes needed to metabolize caffeine.

Several mechanisms by which caffeine might produce adverse outcomes have been postulated. For example, caffeine increases cellular cyclic adenosine monophosphate (cAMP) through inhibition of phosphodiesterases. The rise in cAMP might interfere with fetal cell growth and development.[3]

Animal studies

Animal studies of caffeine and pregnancy outcomes have had varied results. Some studies have suggested a link between caffeine and teratogenesis, fetal resorption, and low fetal weight.[4,5] An increase in the rate of malformations, specifically cleft palate and ectrodactyly, was

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demonstrated in rats and mice given caffeine doses of 100 mg/kg/d or more.[5] This effect was not seen at doses of 50 mg/kg/d, and humans ingest caffeine at substantially lower doses of 1.7 to 4.5 mg/kg/d.[5]

Epidemiologic studies have produced incomplete or conflicting results concerning the effects of caffeine exposure during pregnancy. Motherisk recently conducted a meta-analysis to determine the association of moderate to heavy caffeine consumption during pregnancy with spontaneous abortion and fetal growth in humans.[6]

Motherisk's meta-analysis

For spontaneous abortion, five studies were included (three cohort and two case-control studies) involving a total of 42 889 patients. The combined odds ratio (OR) was 1.36 (95% confidence interval [CI] 1.29 to 1.45), indicating that mothers who consumed caffeine had a higher risk of spontaneous abortion than those who did not.

For fetal growth, five studies involving a total of 64 268 patients were included. Combined relative risk was 1.51 (1.39 to 1.63). Risk ratio for comparing moderate caffeine consumption with controls (0 to 150 mg of caffeine consumption) was 1.33 (95% CI 1.21 to 1.47) and for comparing heavy caffeine consumption with controls was 1.81 (95% CI 1.61 to 2.04). A risk ratio of 1.06 (95% CI 1.00 to 1.13) resulted from comparing our controls with "zero" caffeine consumption; because this risk ratio included unity, it validated our choice of control group.

A recent study[7] where levels of the caffeine metabolite paraxanthine were correlated with risk of spontaneous abortion corroborated our analysis. It showed that only very excessive coffee consumption is associated with increased risk.

Limitations of studies

When combining studies addressing the reproductive risks of caffeine, we have to acknowledge the limitations inherent in this research. All studies accepted into the meta-analysis depended on mothers' or expectant mothers' recall of their level and sources of caffeine consumption. The ability to accurately recall and report the amount of caffeine ingested partly depends on whether subjects are questioned prospectively or retrospectively.

A second possible error introduced involves caffeine measurement. How did subjects estimate the amount of caffeine contained in specific servings? Most studies used an educated "guess" by taking the averages of various samples obtained from their study population and analyzed for content.

A third potential error in estimating caffeine intake involves not identifying all sources of caffeine consumed. Although coffee is the most common source of caffeine, failure to include other sources, such as chocolate and cola, would lead to a degree of underestimation of caffeine use. It is assumed that this underestimation would occur to the same extent in control and study groups.

Wilcox and associates[8] showed that approximately 25% of biochemically detected pregnancies ended before being clinically detected. We might assume that early spontaneous abortion would follow the patterns of late spontaneous abortion among the various stratifications of caffeine consumption. The extent to which this assumption is valid determines the amount of error introduced into the meta-analysis.

Various confounding factors were identified in the articles Motherisk accepted. The most important common confounders appear to be concurrent smoking, alcohol use, maternal age over 35, and previous spontaneous abortion. Most other confounding factors would be equally distributed among the various stratifications of caffeine consumption. Levels of smoking, alcohol use, and maternal age, however, have been shown to be positively correlated with levels of caffeine consumption.[9]

Risk of spontaneous abortion increases as the quantity of cigarettes smoked per day increases.[9] In most of the five studies in the main analysis for spontaneous abortion, the ORs did not change significantly even after researchers adjusted for smoking and other confounders (as reported in each study).

Our results suggest a small but statistically significant increase in risk of spontaneous abortion and low birth weight babies in pregnant women consuming more than 150 mg of caffeine per day. Pregnant women should be encouraged to be aware of dietary caffeine intake and to consume less than 150 mg of caffeine a day from all sources throughout pregnancy.

References

1. Caffeine and pregnancy. *US Food and Drug Administration Drug Bull* 1980;10(3):19-20.
2. Knutti R, Rothweiler H, Schlatter C. The effect of pregnancy on the pharmacokinetics of caffeine. *Arch Toxicol Suppl* 1982;5(Suppl):187-92.
3. Weathersbee PS, Lodge R. Caffeine: its direct and indirect influence on reproduction. *J Reprod Med* 1977;19:55-63.
4. Thayer PS, Palm PE. A current assessment of the mutagenic and teratogenic effects of caffeine. *CRC Crit Rev Toxicol* 1975;3:345-69.
5. Wilson JG, Scott WJ. The teratogenic potential of caffeine in laboratory animals. In: Dews PB, editor. *Caffeine: perspectives from recent research*. Berlin, Ger: Springer-Verlag; 1984. p. 165-87.
6. Fernandes O, Shabarwal M, Smiley T,

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Pastuszak A, Koren G, Einarson T. Moderate to heavy caffeine consumption and relationship to spontaneous abortion and abnormal fetal growth: a meta-analysis. *Reprod Toxicol* 1998;12:435-44.

7. Klebanoff MA, Levine RJ, Der Sinonian R, Clemens JD, Wilkins DG. Maternal serum paraxantine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med* 1999;34:1639-44.
8. Wilcox AJ, Weinberg CR, Baird DD. Risk factors for early pregnancy loss. *Epidemiology* 1990;1:382-5.
9. Golding J. Reproduction and caffeine consumption—a literature review. *Early Hum Dev* 1995;43:1-14.

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