Peripartum implications of caffeine intake in pregnancy: Is there cause for concern?

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Summary
Maternal use of “social drugs” such as caffeine, ethanol and tobacco in pregnancy is on increase worldwide. Caffeine is probably the most frequently ingested pharmacologically active substance in the world. It is found in common beverages (coffee, tea, soft drinks), in products containing cocoa or chocolate, and in medications. Because of its wide consumption at different levels by most segments of the population, the public and the scientific community have expressed interest in the potential for caffeine to produce adverse effects on human health. Reproductive-aged and pregnant women are ‘at risk’ subgroups of the population who may require specific advice on moderating their daily caffeine intake. This article highlights the implications of caffeine intake in pregnancy, reviews the latest evidence-based information available on this subject, and offers recommendations (practical advice) for anesthesiologists and obstetrician-gynecologists proving peripartum care to these potentially complicated pregnancies.

Implicaciones en el parto del uso de cafeína durante el embarazo: ¿existe una causa para preocuparse?

Resumen
El uso materno de “drogas sociales” tales como caféína, etanol y tabaco durante el embarazo se encuentra en aumento en todo el mundo. La cafeína es probablemente la sustancia farmacológicamente activa de uso más frecuente en todos los países. Se encuentra en bebidas comunes (café, té, refrescos), en productos que contienen cacao o chocolate, así como en medicaciones. Debido a su amplio consumo a diferentes niveles por la mayor parte de los segmentos de la población, la comunidad científica ha manifestado su interés en el potencial de la cafeína para producir efectos adversos en la salud humana. Las mujeres en edad reproductiva y las mujeres embarazadas son subgrupos de riesgo que pueden requerir consejos acerca de la moderación en la ingesta diaria de cafeína. Este artículo pone de manifiesto la implicación de la ingesta de cafeína durante el embarazo, revisa las últimas evidencias basadas en la información disponible sobre esta materia y ofrece recomendaciones (consejos prácticos) para anestesiólogos y ginecólogos-obstetras sobre los cuidados que hay que ofrecer en el transcurso del parto a estos embarazos potencialmente complicados.

Key words:

Palabras clave:

1. Social drug use in pregnancy: defining the problem
2. Caffeine in pregnancy: is there cause for concern?
3. Conclusion

1. Social drug use in pregnancy: defining the problem

The illicit drug abuse in pregnancy has received significant attention over the past three decades. However, far too little attention has been given to the consequences of the use of “social drugs” such as caffeine, ethanol and tobacco, which are by far the most commonly abused substances during pregnancy and significantly contribute to the perinatal complications. In addition, while the deleterious effects of cocaine, amphetamines or hallucinogens on the mother and the fetus are more pronounced and easier to detect, the addiction to caffeine, ethanol and tobacco is usually subtle and more difficult to diagnose. As a
result these forms of chemical dependency may continue undetected in pregnancy significantly impacting pregnancy outcome and peripartum management of these patients.

Caffeine is probably the most frequently ingested pharmacologically active substance in the world. It is found in common beverages (coffee, tea, soft drinks), in products containing cocoa or chocolate, and in medications. Because of its wide consumption at different levels by most segments of the population, the public and the scientific community have expressed interest in the potential for caffeine to produce adverse effects on human health. This article reviews the consequences of the social caffeine use in pregnancy and offers recommendation for peripartum management of these potentially complicated pregnancies.

2. Caffeine in pregnancy: is there cause for concern?

Pharmacology, epidemiology and pathophysiology

Caffeine is a methylxanthine found in a variety of products such as tea, coffee, cola and cocoa. Most Americans consume caffeine daily in one of its many forms. A cup of coffee, for example, contains 29 to 176 mg of caffeine depending on its strength. It has been reported that approximately 80% of women drink caffeine-containing beverages daily. Coffee is a complex mixture of chemicals that provides significant amounts of chlorogenic acid and caffeine. The results of epidemiological research suggest that coffee consumption may help prevent several chronic diseases, including type 2 diabetes mellitus, Parkinson’s disease and liver disease (cirrhosis and hepatocellular carcinoma). Most prospective cohort studies have not found coffee consumption to be associated with significantly increased cardiovascular disease risk. However, coffee consumption is associated with increases in several cardiovascular disease risk factors, including high blood pressure and plasma homocysteine. At present, there is little evidence that coffee consumption increases the risk of cancer. For adults consuming moderate amounts of coffee (3-4 cups/day providing 300-400 mg/day of caffeine), there is little evidence of health risks and some evidence of health benefits. However, some groups, including people with hypertension, children, adolescents, and the elderly, may be more vulnerable to the adverse effects of caffeine. In addition, currently available evidence suggests that it may be prudent for pregnant women to limit coffee consumption to 3 cups/day providing no more than 300 mg/d of caffeine to exclude any increased probability of spontaneous abortion or impaired fetal growth.

There is wide inter-individual variation in caffeine metabolism, primarily due to variations in CYP1A2 enzyme activity. Considerable evidence exists that maternal caffeine metabolism is influenced by a variety of endogenous and exogenous factors. There is substantial evidence that measurement of maternal, fetal, and neonatal caffeine metabolites may allow for a more precise measure of fetal caffeine exposure.

Diagnosis and clinical presentation

Studies on the effects of caffeine on human health, while numerous, have produced inconsistent results. One of the most uncertain and controversial effects is on pregnancy outcome. The major challenge is the accurate assessment of caffeine intake. Boylan et al. attempted to explore different methods of assessing caffeine exposure in pregnant women. Twenty-four healthy pregnant women completed both a detailed questionnaire, the caffeine assessment tool (CAT) designed specifically to assess caffeine intake and a prospective 3 day food and drink diary. The women also provided nine saliva samples over two consecutive days for estimation of caffeine and a metabolite (paraxanthine). Caffeine intakes from the CAT and diary showed adequate agreement (intra-class correlation coefficient of 0.5). For saliva caffeine and paraxanthine measures, the between-sample variation (within the same woman) was greater than between-woman and between-day variation. However, there was still adequate agreement between these measures and the CAT. The authors concluded that the CAT is a valuable tool that is now being used in a large prospective study investigating caffeine’s role in pregnancy outcome.

Clinical research indicates that withdrawal symptoms can occur when daily consumption of caffeine is abruptly interrupted. The caffeine physical dependence syndrome may lead to peripartum complications such as headache, nausea, vomiting and muscular aches. Most commonly, however, abrupt discontinuation of regular daily caffeine intake will lead to anxiety, mild to moderate headache and muscle aches.

Interactions with pregnancy

Caffeine is readily absorbed from the mucosa of the gastrointestinal tract. It crosses the human placenta rapidly reaching concentration in the fetus similar to maternal plasma levels. Caffeine has been implicated as a cause of spontaneous abortion, intrauterine
growth restriction (IUGR), low birth weight (LBW) and preterm delivery.

Boylan et al. conducted a prospective longitudinal observational study designed to examine the association of maternal caffeine intake with fetal growth restriction. The study included 2,635 low risk pregnant women recruited between 8-12 weeks of pregnancy. Investigations Quantification of total caffeine intake from 4 weeks before conception and throughout pregnancy was undertaken with a validated caffeine assessment tool. Caffeine half life (proxy for clearance) was determined by measuring caffeine in saliva after a caffeine challenge. Fetal growth restriction, as defined by custom birth weight centile, adjusted for alcohol intake and salivary cotinine concentrations.

Caffeine consumption throughout pregnancy was associated with an increased risk of fetal growth restriction (odds ratios 1.2 (95% CI 0.9 to 1.6) for 100-199 mg/day, 1.5 (1.1 to 2.1) for 200-299 mg/day, and 1.4 (1.0 to 2.0) for >300 mg/day compared with <100 mg/day; test for trend P<0.001). Mean caffeine consumption decreased in the first trimester and increased in the third. The association between caffeine and fetal growth restriction was stronger in women with a faster compared to a slower caffeine clearance (test for interaction, P=0.06). The authors concluded that caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction and this association continued throughout pregnancy. Sensible advice would be to reduce caffeine intake before conception and throughout pregnancy.

Bech et al. conducted randomized double blind controlled trial designed to estimate the effect of reducing caffeine intake during pregnancy on birth weight and length of gestation. The study included 1,207 pregnant women drinking at least three cups of coffee (caffeinated or decaffeinated instant coffee) a day, recruited before 20 weeks’ gestation. Data on birth weight were obtained for 1150 live born singletons and on length of gestation for 1153 live born singletons. No significant differences were found for mean birth weight or mean length of gestation between women in the decaffeinated coffee group (whose mean caffeine intake was 182 mg lower than that of the other group) and women in the caffeinated coffee group. After adjustment for length of gestation, parity, prepregnancy body mass index, and smoking at entry to the study the mean birth weight of babies born to women in the decaffeinated group was 16 g (95% confidence interval -40 to 73) higher than those born to women in the caffeinated group. The adjusted difference (decaffeinated group-caffeinated group) of length of gestation was -1.31 days (-2.87 to 0.25). The authors concluded that a moderate reduction in caffeine intake in the second half of pregnancy has no effect on birth weight or length of gestation.

At least three cases of acute fetal arrhythmias secondary to excessive maternal intake of caffeine have been reported. Fernandez et al. found a small but statistically significant increase in the risk of spontaneous abortion and LBW infants in women consuming more than 150 mg of caffeine daily. Caffeine induced disturbances in the development of central nervous system such as neural tube closure in animal models (mouse) have been reported.

Weng et al. conducted a population-based prospective cohort study designed to examine whether the risk of miscarriage is associated with caffeine consumption during pregnancy after controlling for pregnancy-related symptoms. An increasing dose of daily caffeine intake during pregnancy was associated with an increased risk of miscarriage, compared with no caffeine intake, with an adjusted hazard ratio (aHR) of 1.42 (95% confidence interval 0.93 to 2.15) for caffeine intake of less than 200 mg/day, and aHR of 2.23 (1.34 to 3.69) for intake of 200 or more mg/day, respectively. Nausea or vomiting during pregnancy did not materially affect this observed association, nor did the change in intake pattern of caffeine during pregnancy. In addition, the magnitude of the association appeared to be stronger among women without a history of miscarriage (aHR 2.33, 1.48 to 3.67) than that among women with such a history (aHR 0.81, 0.34 to 1.94). The authors concluded that high doses of caffeine intake during pregnancy increase the risk of miscarriage, independent of pregnancy-related symptoms.

The physiologic effects and common use of caffeine during pregnancy call for examination of maternal caffeine consumption and risk of birth defects. Epidemiologic studies have so far yielded mixed results. Browne et al. studied consumption of caffeinated coffee, tea, soda, and chocolate to estimate total caffeine intake and separately examined exposure to each caffeinated beverage. Smoking, alcohol, vasoactive medications, folic acid supplement use, and infant gender were evaluated for effect modification. Maternal interview reports for 4,196 cardiovascular malformation (CVM) case infants overall and 3,957 control infants were analyzed. The study did not identify any significant positive associations between maternal caffeine consumption and CVMs. For tetralogy of Fallot, non-significant elevations in risk were observed for moderate (but not high) caffeine intake overall and among nonsmokers (ORs of 1.3 to 1.5). Risk estimates for both smoking and consuming caffeine were less than the sum of the excess risks for each exposure. The authors observed an inverse trend between coffee intake and risk of atrial septal defect; however, this single
significant pattern of association might have been a chance finding. In summary the study found no evidence for an appreciable teratogenic effect of caffeine with regard to CVMs.\textsuperscript{16}

\textit{Peripartum concerns}

Symptoms of caffeine withdrawal may occur during labor or in the parturient fasting before or after abdominal delivery. A significant relationship exists between daily caffeine intake prior to surgery and the incidence of postoperative headache.\textsuperscript{5} If regional anesthetic technique is selected, differentiation between post-dural puncture headache (PDPH) and caffeine withdrawal headache should be considered in all patients reporting postpartum headache.

3. Conclusion

Caffeine is probably the most frequently ingested pharmacologically active substance in the world. Maternal use of caffeine in pregnancy continues to increase worldwide. Nawrot et al.\textsuperscript{6} investigated the possibility that caffeine ingestion adversely affects human health. Based on the data reviewed, the authors concluded that for the healthy adult population, modest daily caffeine intake at a dose level up to 400 mg day\textsuperscript{-1} (equivalent to 6 mg kg\textsuperscript{-1} body weight day\textsuperscript{-1} in a 65-kg person) is not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance (with consumption of adequate calcium), changes in adult behavior, increased incidence of cancer and effects on fertility. The data also show that reproductive-aged women and children are ‘at risk’ subgroups who may require specific advice on moderating their caffeine intake. Based on available evidence, it is suggested that reproductive-aged women should consume \( \leq 300 \text{ mg caffeine per day (equivalent to } 4.6 \text{ mg kg}\textsuperscript{-1} \text{ bw day}\textsuperscript{-1} \text{ for a 65-kg person}) \) while children should consume \( \leq 2.5 \text{ mg kg}\textsuperscript{-1} \text{ bw day}\textsuperscript{-1} \).

\textbf{BIBLIOGRAFÍA}