Clinical Digest

ONLINE EDITION

Women's Health

Caffeine and Birth Weight

How much caffeine during pregnancy is too much? Studies on the subject have put the limit of safe consumption at varying levels, say researchers from the CARE Study Group. They cite one study that found significant reduction in infant birth weight when women ingested more than 141 mg/day and others that concluded that, while more than 300 mg/day might be associated with such poor outcomes as low birth weight, the evidence was too scanty to make a definite judgment.

The CARE researchers suggest that possible reasons for the inconclusive findings could include inaccurate estimation of caffeine consumption—for instance, some women assume that tea and coffee are the only sources of caffeine. In addition, the mother's own caffeine metabolism often is not taken into consideration. The researchers say this is a critical measurement, since caffeine is absorbed rapidly and crosses the placenta easily and the placenta and fetus lack a main enzyme required to metabolize caffeine. In fact, they assert, variations in caffeine metabolic activity are more accurate predictors of fetal growth restriction than blood caffeine concentrations. Thus, the researchers wanted their prospective, longitudinal, observational study to reflect not only all potential sources of caffeine but also individual variations in metabolism.

Over a three-year period, more than 13,000 women aged 18 to 45 years, who were carrying a single fetus and had no concurrent medical conditions, were identified from two large teaching hospitals in Leeds and Leicester, Great Britain and were invited to participate in the study. The 2,635 who agreed completed a caffeine intake questionnaire at recruitment (that covered the period of four weeks before pregnancy to eight to 12 weeks gestation), at 28 weeks, and at 40 weeks. Within two weeks of recruitment, the women completed a caffeine challenge test at home and collected and mailed in a saliva sample, from which researchers determined individual caffeine half-life.

Prior to pregnancy, the mean caffeine intake for all study participants was 238 mg/day. Throughout the course of pregnancy, the mean intake was 159 mg/day, which broke down to 163, 147, and 153 mg/day during the first, second, and third trimesters, respectively. Notably, there was a sharp decline in mean caffeine intake to 139 mg/day between weeks five and 12 of pregnancy—roughly corresponding to the time when most participants would have learned they were pregnant. About 62% of the caffeine came from tea, 14% from coffee, 12% from cola drinks, and 8% from chocolate. Soft drinks, hot chocolate, energy drinks, alcoholic drinks, and over-the-counter medications each contributed 2% or less.

Appropriate fetal growth occurred in 2,292 babies, whereas fetal growth restriction occurred in 343. Using a reference caffeine intake of less than 100 mg/day, the odds ratio of having a growth-restricted baby was 1.2 for an intake of 100 to 199 mg/day, 1.5 for an intake of 200 to 299 mg/day, and 1.4 for an intake of 300 mg/day or more.

The researchers could find no amount of caffeine intake that was not associated with fetal growth restriction, and the estimated risk of growth restriction rose linearly in a dose-responsive relationship. After adjusting for smoking status and alcohol intake, the researchers found birth weight reductions of 34 to 59 g (P = .009), 24 to 74 g (P = .006), and 66 to 89 g (P = .004) associated with an average caffeine intake of greater than 100 mg/day in the first, second, and third trimesters, respectively.

The magnitude of fetal growth restriction's association with caffeine intake was similar to that of its association with alcohol intake in the study. The researchers say it's "sensible advice" for women contemplating pregnancy to reduce their caffeine intake from all sources before conception; once pregnancy is confirmed, they should "make every effort to stop or markedly reduce caffeine consumption."

Source: *BMJ.* 2008;337:a2332. doi:10.1136/bmj.a2332.

Gastroenterology

Diagnosing Acute Bacterial Diarrhea

Although bacteriologic culture is the gold standard for differentiating acute bacterial from acute noninfectious diarrhea, this method takes a minimum of 48 hours and costs around $1,000 per positive culture. The fecal occult blood test (FOBT) and fecal lactoferrin also have been used to differentiate the problems, but studies of their accuracy have had widely varying results. Could fecal calprotectin—a calcium binding cytosolic neutrophil protein that is the most accurate identifier of chronic diarrhea's inflammatory causes—offer a cheap, fast, and accurate alternative?

Researchers from Johann Wolfgang Goethe-University and Weindel und Colleagues, both in Frankfurt

am Main, Germany, and Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India, set out to answer this question through a prospective, case-control, multicenter study. Drawing from a sample of 2,383 consecutive patients with acute diarrhea whose stool samples were analyzed by bacteriologic culture, they found that 200 patients had a positive microbiological diagnosis. The researchers then randomly selected another 200 age- and sex-matched patients from the sample who had a negative microbiological diagnosis. Finally, they used FOBT, fecal lactoferrin, and fecal calprotectin to analyze the stool samples of patients in both the positive group and the negative group, and they compared the results of these tests with those of bacteriologic culture.

Fecal calprotectin was significantly more accurate than FOBT or fecal lactoferrin, the researchers found. While calprotectin had 83% sensitivity and 87% specificity, FOBT had 38% sensitivity and 85% specificity and lactoferrin had 78% sensitivity and 54% specificity. The researchers found that the most appropriate threshold value for calprotectin was 1.9 mg/L.

These results indicate that calprotectin "may potentially revolutionize management algorithms for patients with acute diarrhea," according to the researchers. They note that calprotectin is stable in stool samples for up to seven days at room temperature—"a big advantage" when it is impossible to process a sample immediately. A fecal calprotectin test currently takes a minimum of six hours, and an office-based version of the test that takes 10 minutes is being evaluated. These advantages suggest the utility of an algorithm for managing acute diarrhea in which patients with positive calprotectin results undergo a more definitive diagnostic test while those with negative calprotectin results continue with symptomatic treatment, according to the researchers.

They add that calprotectin testing does have some drawbacks, however. As fecal calprotectin levels are elevated in patients with systemic and gastrointestinal inflammatory conditions, calprotectin's value as a marker of acute bacterial diarrhea might be limited in these populations. In addition, the test's 83% sensitivity in the study suggests that it could have false negative results in about 17% of acute bacterial diarrhea cases. The researchers suggest, however, that the test's sensitivity might be improved by repeating it in patients who have negative results but continuing diarrhea.

Source: *Am J Med.* 2008;121(12):1099–1106. doi:10.1016/j.amjmed.2008.06.034.