Institution: University of Leeds

Unit of Assessment: 6

Title of case study: Case Study 1: Caffeine intake during pregnancy: impact on national guidance

1. Summary of the impact (indicative maximum 100 words)

Caffeine is widely consumed in pregnancy as has the potential to harm the developing fetus. Professor Janet **Cade** and colleagues at the University of Leeds designed a robust study to accurately quantify caffeine intake in 2635 pregnant women throughout pregnancy. The results showed caffeine intake is associated with an increased risk of fetal growth restriction, which is linked with perinatal mortality and morbidity and adverse effects in later life. As a result of this study, and a review of previous evidence, the Food Standards Agency issued new advice to pregnant women to limit their daily caffeine intake to below 200mg/day.

2. Underpinning research (indicative maximum 500 words)

Animal studies had suggested that consumption of caffeine during pregnancy could harm the developing fetus but research in humans had proven inconclusive, largely due to inconsistencies in study methodology and difficulties in accurately assessing caffeine intake or the effect of variation in caffeine metabolism.

In 2001, the UK Committee on Toxicity of Chemicals in Food (COT) reviewed the evidence and concluded that caffeine intake of more than 300mg/day might be associated with low birth weight and spontaneous miscarriage but that more rigorous work was needed.[1]

After an initial competitive round of submissions, a team at the University of Leeds (**Janet Cade**, Professor of Nutritional Epidemiology; **Alastair Hay**, Professor of Environmental Toxicity; **Darren Greenwood**, Senior Lecturer in Biostatistics) was commissioned in 2003 by the Food Standards Agency (FSA) to design and conduct the Caffeine and Reproductive Health (CARE) study – a multicentre prospective, longitudinal observational project based in two large maternity hospitals in Leeds and Leicester – to determine the safe upper limit of caffeine consumption in pregnancy.

To more accurately ascertain caffeine intake, **Cade** developed a validated caffeine assessment tool which was designed to record habitual caffeine consumption before and after pregnancy and from all potential dietary sources and over-the-counter drugs, not just from coffee or tea, as in many previous studies.[2] Specific brand names, portion sizes, preparation methods and quantity and frequency of intake at different periods of gestation were recorded. Precise caffeine intakes were then calculated using a program the Leeds group designed.[2]

Hay also developed a novel saliva test for determining the half-life of caffeine, which enabled the team to take into account individual variations in metabolism.

Together both centres recruited a total of 2635 low risk, pregnant women between 8-12 weeks of pregnancy who recorded total caffeine intake from four weeks before conception and throughout pregnancy as well as potential confounding factors such as alcohol and smoking, with nicotine concentrations confirmed with saliva cotinine tests.

The study showed that caffeine consumption throughout pregnancy was associated with a significantly increased risk of fetal growth restriction as defined by customised birthweight centile (taking account of factors such as maternal height, weight and ethnicity), and adjusted for alcohol intake and salivary cotinine concentrations (**Greenwood**).[3]

Women with caffeine intakes 300mg/day or more had a 40% increased risk of having a growth-restricted baby compared with those with intakes of less than100mg/day. Caffeine consumption of

200mg/day was associated with a reduction in birth weight of about 60-70g, a similar size of effect to that seen for alcohol intake in pregnancy.[3]

The study also found a strong association between caffeine intake in the first trimester and subsequent late miscarriage and stillbirth. Compared with those consuming less than 100 mg/day of caffeine, there was a 2.2 times higher risk for those consuming 100–199 mg/day, 1.7 times higher risk for 200–299 mg/day, and 5.1 times higher risk for 300mg/day or more.[4]

After further analysis, no evidence was found that the relationship between maternal caffeine intake and fetal growth restriction was modified by nausea and vomiting in pregnancy.[5]

3. References to the research (indicative maximum of six references)

1. Committee on Toxicity. COT statement on the reproductive effects of caffeine. London : Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2001.http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2001/caffeine

2. Boylan SM, **Cade** JE, Kirk SFL, Greenwood DC, White KLM, Shires S, Simpson NAB, Wild CP and Hay AWM. Assessing caffeine exposure in pregnant women. British Journal of Nutrition 2008 ; 100: 875-882. 10.1017/S0007114508939842 [doi]

3. CARE Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. BMJ 2008 ; 337: a2332. 10.1136/bmj.a2332 [doi]

4. Greenwood DC, Alwan N, Boylan S, **Cade** JE, Charvill J, Chipps KC, Cooke MS, Dolby VA, Hay AW, Kassam S, et al. Caffeine intake during pregnancy, late miscarriage and stillbirth. Eur J Epidemiol 2010; 25:275-80. 10.1007/s10654-010-9443-7 [doi]

5. Boylan SM, Greenwood DC, Alwan N, Cooke MS, Dolby VA, Hay AW, Kirk SF, Konje JC, Potdar N, Shires S, Simpson NA, Taub N, Thomas JD, Walker JJ, White KL, Wild CP, **Cade** JE. Does nausea and vomiting of pregnancy play a role in the association found between maternal caffeine intake and fetal growth restriction? Matern. Child Health J. 2013; 17: 601-608. 10.1007/s10995-012-1034-7 [doi]

4. Details of the impact (indicative maximum 750 words)

Most pregnant women in the UK and elsewhere consume caffeine from one or more sources yet before the current work the evidence of any harm to the fetus was inconclusive and a level at which harm may occur was unclear.

The CARE study overcame several limitations seen in previous studies. **Cade** developed a tool to accurately calculate an individual's caffeine intake from all potential dietary and over-the-counter sources, taking into account brands and preparation, rather than just a tally of coffee and tea consumption. The Leeds research also looked at the effects of caffeine consumption across all trimesters and prior to conception, rather than just a snapshot at one point in pregnancy.

In addition, the study took into account individual variations in caffeine metabolism that can show marked differences due to genetics, but also environmental factors such as nicotine.

Impact on public awareness of health risk

This robust study design showed that caffeine consumption during pregnancy is associated with an increased risk of fetal growth restriction at levels of 200mg/day and maybe even lower and that the association continues throughout the whole of pregnancy.[3]

Fetal growth restriction is an important outcome as it is associated with an increased risk of perinatal mortality and morbidity.[A] In addition, there is epidemiological evidence that it correlates with adverse effects in adult life. For example, affected individuals have an increased incidence of metabolic syndrome, manifesting as obesity, hypertension, hypercholesterolemia, cardiovascular disease, and type 2 diabetes.

Clearly, reducing the risk of perinatal morbidity and mortality through impact on birthweight is important for the long-term health and survival of every child.[B]

These results meant that for the first time women could be provided with clear evidence and advice to reduce their caffeine intake before conception and during the whole of pregnancy.

Further analysis led by Greenwood and published in 2010 showed a strong link between caffeine consumption in the first trimester and late miscarriage and stillbirth, further proving the harm associated with caffeine in pregnancy.[4]

Impact on public policy and services

In 2008, the team presented their results to COT who, in light of the evidence, decided to review their guidance and publish new recommendations to coincide with the publication of the CARE study.

A statement (in 2008) from COT, explicitly referring to the research at Leeds, concluded that while it seems likely that risk of fetal growth restriction is increased in association with caffeine intakes in the order of 200 mg/day and perhaps even lower, the absolute increase in incidence of fetal growth restriction from intakes less than this is likely to be less than 2% of infants.[C]

The FSA issued (in 2008) updated guidelines to women to limit their daily caffeine intake to below 200mg/day, the equivalent to two mugs of coffee, although caffeine is also present in tea, chocolate, some soft drinks, and certain medicines.[D] The previous advice had set a maximum daily intake of 300mg.

This new advice, along with results from the CARE study, was featured in national news reports in both the print and broadcast media, including BBC News Online, The Times, Daily Mail and The Daily Telegraph.[E] Professor **Cade** briefed key stakeholders prior to publication of the study and the FSA guidance.

The revised guidelines were taken up by the NHS[F] and included in the Pregnancy Book, which is a highly trusted source of advice handed out to all pregnant women (ca. 700,000 per year) England.[G] The NHS Choices website also contains these recommendations.[H]

Through the direct impact of this work - on the advice given to pregnant women - all families have the potential to benefit from this research. Moreover, healthcare providers including, GPs, obstetricians and midwives have clearer guidance for delivering appropriate prenatal care. The Royal College of Obstetricians and Gynaecologists issued a statement to highlight the updated advice.[I]

Data on the potential impact of the advice on caffeine intake in pregnant women for the relevant time period is not yet available. However, it is known that two thirds of infants who die have a low birth weight. Data from the Office for National Statistics show that for 2008-2010 the drop in infant mortality in England and Wales was significantly steeper than for the previous years at 4.5/1000 live births compared with4.8/1000 live births in 2006-2008.[J] While this reduction in the infant mortality rate cannot solely be attributed to changing patterns of behaviour during pregnancy in relation to caffeine, we are not aware of other guidance directed at pregnant women during this time, that would have contributed to this steeper rate of decline.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] Bryant AS, Worjoloh A, Caughey AB, Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. Am. J. Obstet. Gynecol. 2010 Apr;202(4):335-43. doi: 10.1016/j.ajog.2009.10.864 [doi]

[B] Saigal, S and Doyle, LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood, The Lancet, 2008, 371: 261-269.

[C] Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Statement on Reproductive Effects of Caffeine. 2008 http://cot.food.gov.uk/pdfs/cotstatementcaffeine200804.pdf

[D] Food Standards Agency press release on new caffeine advice for pregnant women. 2008 http://tna.europarchive.org/20111116080332/http://www.food.gov.uk/news/pressreleases/2008/nov/caffeineadvice

[E] The Times, 03/11/2008, Pregnant women told to drink no more than two cups of coffee a day. BBC News Online, 03/11/2008 Cut caffeine, pregnant women told. Daily Mail, 03/11/2008 Two cups of coffee a day can lead to underweight babies, experts claim.The Daily Telegraph 03/11/2008Caffeine link to under-weight babies prompts cut to government coffee guidelines.

[F] NHS Choices. Advice on caffeine during pregnancy.http://www.nhs.uk/chq/Pages/limit-caffeine-during-pregnancy.aspx

[G] Department of Health. The Pregnancy Book, 2009. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107302

[H] NHS Choices. Foods to avoid in pregnancy. http://www.nhs.uk/conditions/pregnancy-and-baby/pages/foods-to-avoid-pregnant.aspx#Caffeine

[I] Royal College of Obstetricians and Gynaecologists. RCOG statement on FSA guidance on caffeine consumption during pregnancy (3/11/2008). http://www.rcog.org.uk/what-we-do/campaigning-and-opinions/statement/rcog-statement-fsa-guidance-caffeine-consumption-durin

[J] Office for National Statistics. Data on infant mortality http://neighbourhood.statistics.gov.uk/dissemination/hierarchySelection.do?step=3&datasetFamilyId=1700&instanceSelection=026920&hierarchyId=2&rightPaneBoxHeight=497&JSAllowed=true&browserHeight=674&browserWidth=1206&%24ph=60_61_62&CurrentPageId=62&Back.x=10&Back.y=9