



Adverse effects of long-term and habitual caffeine consumption on pregnancy outcomes

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PREGNANCY OUTCOMES

Adverse outcomes investigated in relation to:

1. Length of gestation, e.g., pre-term delivery (PTD)
2. Birth weight, e.g., fetal growth restriction (FGR), small for gestational age (SGA)
3. Fetal death, e.g. miscarriage or spontaneous abortion, stillbirth
4. Infant death



MECHANISMS

Caffeine is rapidly absorbed, passes freely across the placenta, and it is poorly metabolised by the foetus

Caffeine consumption during pregnancy could adversely affect fetal development by:

1. \uparrow circulating catecholamines \Rightarrow \uparrow uteroplacental vasoconstriction, \uparrow fetal hypoxia
2. \uparrow cellular cAMP \Rightarrow impairment of normal cell development



INTERVENTION STUDY

Bech et al., 2007

- 1 207 women, < 20 weeks pregnant, ≥ 3 cups per day, Denmark
- Randomised to receive caffeinated coffee ($n = 568$) or decaffeinated coffee ($n = 629$)
- No advice on other caffeine sources
- Caffeine intake (all sources) assessed at 20, 25, and 34 weeks of gestation and 4 weeks after delivery
- Median caffeine intake = 317 mg/day vs 117 mg/day in the caffeinated and decaffeinated coffee groups, respectively

Decreasing caffeine from 300 to 100 mg/day in the last 4 months of pregnancy: no effects on length of gestation or birth weight



PROSPECTIVE COHORT STUDIES

5 prospective cohort studies on maternal caffeine intake from beverages and pregnancy outcomes:

- Potentially confounding variables adjusted for: e.g. alcohol, smoking, parity, socio-economical status
- Also generally considered for birth weight and related outcomes: maternal age, height and weight, maternal education, baby's sex, length of gestation, outcome of previous pregnancies and occasionally pregnancy-related symptoms (e.g. nausea, vomiting)



PROSPECTIVE COHORT STUDIES (1)

Care study group, 2008, Greenwood et al., 2010; Boylan et al., 2013

- 2 635 low risk pregnant women, 18-45 years, UK
- Recruited at 8-12 weeks of pregnancy
- Habitual caffeine intake estimated by FFQ
- Main sources = tea (62%), coffee (14%) and cola drinks (12%)
- Caffeine intake:
 - 238 mg/day before pregnancy
 - 139 mg/day between weeks 5 and 12
 - unchanged in second trimester
 - 153 mg/day in third trimester



PROSPECTIVE COHORT STUDIES (1)

Care study group, 2008, Greenwood et al., 2010; Boylan et al., 2013

Caffeine intake associated with:

- *Greater risk of fetal growth restriction (FGR) (P trend = 0.02)*
- *Greater reduction in birth weight (P trend = 0.004)*
- *Greater risk of late miscarriage or stillbirth (P trend = 0.004)*
- *When analysed as categorical variable = Reference < 100 mg/day; risk increases significantly for FGR at > 200 mg per day, and for late miscarriage or stillbirth at > 300 mg per day*
- *When analysed as a continuous variable = no threshold for FGR*



PROSPECTIVE COHORT STUDIES (2)

Sengpiel et al., 2013

- 59 123 women with uncomplicated pregnancies, Norway
- Habitual caffeine intake estimated by FFQ
- Main sources = coffee (56 %), black tea (22%) and soft drinks (14%)
- Caffeine intake:
 - 126 mg/day before pregnancy
 - 44 mg/day at week 17
 - 62 mg/day at week 30
- small for gestational age (SGA) diagnosed using 3 different growth curves and definitions



PROSPECTIVE COHORT STUDIES (2)

Sengpiel et al., 2013

- *No association between total caffeine intake and early or late, or overall spontaneous preterm delivery*
- *Conflicting data on gestational length (depending on caffeine source)*
- *Total caffeine and caffeine from the individual sources associated with lower birth weight*
- *Total caffeine intake dose-dependently associated with small for gestational age in all 3 models; significant at > 50 mg/day but increases notably at > 200 mg/day*



PROSPECTIVE COHORT STUDIES (3)

Bech et al., 2005

- 88 482 pregnant women at 16 weeks of gestation, Denmark
- Habitual caffeine intake from beverages (mostly coffee)
- Fetal death = miscarriage (age < 196 days) or stillbirth (age ≥ 196 days)

- *Dose-dependent association between caffeine intake at week 16 of pregnancy and fetal death-related outcomes (caffeine intake as continuous variable)*
- *Risk significant at caffeine intakes of about ≥ 400 mg/day (caffeine intake as categorical variable)*



PROSPECTIVE COHORT STUDIES (4)

Weng et al., 2008

- 1 063 women, early pregnancy, USA
- Habitual caffeine intake from beverages pre-pregnancy and during pregnancy
- Risk of miscarriage (abortion at ≤ 20 weeks of pregnancy)
 - *Dose-dependent association between caffeine intake at week 16 of pregnancy and miscarriage*
 - *Increased risk of miscarriage associated with caffeine intake at doses > 200 mg/day in early pregnancy, regardless of the source (caffeine intake as categorical variable)*



PROSPECTIVE COHORT STUDIES (5)

Fenster et al., 1997

- 5 144 women, early pregnancy, USA
- Habitual caffeine intake from beverages pre-pregnancy and in the first trimester of pregnancy
- Risk of miscarriage (≤ 20 weeks of pregnancy) and stillbirth (> 20 weeks of pregnancy)

➤ *Caffeine consumption and consumption of any type of caffeinated beverages were not associated with miscarriage*

➤ *Data on stillbirth not reported*



CASE CONTROL STUDIES

- 2008: thoroughly reviewed by the UK Committee on Toxicity of Chemicals (COT) in Food, Consumer Products and the Environment
- Overall, a positive association between caffeine intake during pregnancy and risk of adverse birth weight-related outcomes, whereas the relationship with other pregnancy-related outcomes is less consistent
- Conflicting results for association between caffeine intake and adverse pregnancy outcomes i.r.t. differences in the activity of enzymes involved in the metabolism of caffeine
- (No prospective studies on whether genetic polymorphisms may affect the risk of adverse pregnancy outcomes)



CONCLUSIONS ON PREGNANCY (1)

- Habitual caffeine intake is spontaneously reduced during pregnancy, mostly in the first and second trimesters
- Major sources of caffeine: coffee and tea, followed by soft drinks and chocolate; “energy drinks” about 2 % of caffeine intake
- Reducing caffeine intake from 300 → 100 mg/day in the third trimester does not decrease the risk (**Bech et al., 2007**)



CONCLUSIONS ON PREGNANCY (2)

- Prospective cohort studies (***CARE study group, 2008; Sengpiel et al., 2013***): dose-dependent positive association between caffeine intake during pregnancy and risk of adverse birth weight-related outcomes (i.e. FGR, SGA).
- Relationship observed at all levels of intake (no threshold)
- It becomes clinically significant at about 200 mg/day
- Relationship between caffeine consumption during pregnancy and other pregnancy outcomes (e.g., in relation to length of gestation or fetal death) less consistent.
- If present, it is observed at > 200-400 mg/day



CAFFEINE INTAKE AND PREGNANCY OUTCOMES

OPEN FOR DISCUSSION