European Journal of Obstetrics & Gynecology and Reproductive Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Associations between consumption of coffee and caffeinated soft drinks and late stillbirth—Findings from the Midland and North of England stillbirth case-control study

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ARTICLE INFO

Article history:
Received 18 June 2020
Received in revised form 5 October 2020
Accepted 8 October 2020
Available online xxx

Keywords:
Caffeine
Perinatal death
Stillbirth
Cola
Sweetened soft drinks

ABSTRACT

Objective: The consumption of caffeinated drinks and soft drinks is widespread in society, including by pregnant women. Data regarding the association of caffeine intake and stillbirth are varied. We aimed to investigate the degree of consumption of caffeinated drinks or soft drinks in the last four weeks of pregnancy in women who experienced a late stillbirth compared to women with ongoing live pregnancies at similar gestation. Influences on maternal caffeine intake and soft drink consumption during pregnancy were also investigated.

Study Design: A case-control study undertaken in 41 maternity units in the United Kingdom. Cases were women who had a singleton non-anomalous stillbirth ≥28 weeks' gestation (n = 290) and controls were women with an ongoing pregnancy at the time of interview (n = 729). Data were collected using an interviewer-administered questionnaire which included questions regarding consumption of a variety of caffeinated drinks and soft drinks in the last four weeks of pregnancy as well as other behaviours (e.g. cigarette smoking).

Results: Multivariable analysis adjusting for co-existing demographic and behavioural factors found the consumption of instant coffee, energy drinks and cola were associated with increased risk of stillbirth. There was an independent association between caffeine intake and late stillbirth (adjusted Odds Ratio 1.27, 95 % Confidence Interval (95 %CI) 1.14, 1.43 for each 100 mg increment/day). 15 % of cases and 8% of controls consumed more than the World Health Organisation (WHO) recommendation (>300 mg of caffeine/day; aOR 2.30, 95 % CI 1.40, 4.24). The population attributable risk for stillbirth associated with >300 mg of caffeine/day was 7.4 %. The majority of respondents reduced caffeine consumption in pregnancy. Midwives and internet resources were the most frequently used sources of information which influenced maternal behaviour with regard to soft drinks and caffeine, and this did not differ between cases and controls.

Conclusions: Women should be informed that consumption of caffeine during pregnancy is associated with increased risk of stillbirth, particularly at levels greater than recommended by the WHO (>300 mg/day). Recommendations from midwives and internet-based resources are likely to be the most effective means to influence maternal behaviour.

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https://doi.org/10.1016/j.ejogrb.2020.10.012
0301-2115/

Introduction

Stillbirth is an important public health problem with enduring impact not only in terms of lives lost but also with economic, psychological and social impacts upon affected families. [1,2] One approach to reducing stillbirth is to identify factors associated with increased risk so that their effects may be reduced. Epidemiological studies have identified risk factors for stillbirth, some of which are modifiable (e.g. cigarette smoking, drug misuse) and others which are not (e.g. maternal age, ethnicity) [3].

The Stillbirth Priority Setting Partnership identified a research need to ascertain modifiable risk factors for late stillbirth [4]. The Midland and North of England Stillbirth Study (MiNESS) was a case control study which aimed to identify modifiable risk factors for late stillbirth (≥28 weeks' gestation) [5]. Due to their ubiquitous consumption, 80 % of the UK population drinks instant coffee and on average 211.5 L of soft drinks (many of which contain high levels of caffeine) were consumed per capita per year [6]. Accordingly, this study included questions about intake of caffeinated drinks and soft drinks during pregnancy. To date, the evidence linking caffeine intake and stillbirth shows variable effect size and some studies focus on coffee consumption rather than consumption of any source of caffeine [7–9]. Presently, the World Health Organisation recommends that high caffeine intake (>300 mg/day) is decreased to reduce the risk of pregnancy loss and the UK National Health Service recommends caffeine intake is <200 mg/day during pregnancy [10]. Given that caffeinated drinks, are widely consumed we aimed to investigate whether there is a relationship between consumption of these beverages and the risk of late stillbirth.

Methods

MiNESS was a prospective case-control study undertaken in 41 secondary and tertiary maternity units in the UK [5]. The methodology has been described in detail previously and was conducted in accordance with the published protocol [5,11]. Following ethical approval (Ref 13/NW/0174) and study registration (NCT02025530) participants were recruited between April 2014 and March 2016. Cases were singleton stillbirths occurring ≥28 weeks' gestation with no evidence of congenital anomaly. Women who had a multiple pregnancy, who could not consent or who were <16 years of age were excluded. Controls were mothers who had an ongoing singleton pregnancy with no evidence of congenital anomaly. To achieve a similar distribution of gestational age between groups, controls were frequency matched to the distribution of stillbirths in the preceding four years at that maternity unit. Potential control participants were randomly selected from the booking lists and gestation for interview calculated; interviews for controls were contemporaneous with those for cases.

Information was collected by an interviewer-administered questionnaire and extracted from the mother's medical records; interviewers were not blinded to participants' status. This questionnaire included a wide range of self-reported social and demographic characteristics as well as behaviours. This included the frequency of intake in the preceding four weeks for different drinks including servings of coffee, tea, chocolate, cola, energy drinks and also recorded the sugar added to drinks as a potential confounding factor. In addition, respondents were asked whether they had altered their consumption of drinks during their pregnancy and if so, whether this was due to any advice and the sources of advice. The median gestation at interview for controls was 36 weeks 3 days (Interquartile Range (IQR) 32 weeks 6 days to 38 weeks 5 days). The median gestation at diagnosis of stillbirth was 37 weeks 4 days (IQR 33 weeks 4 days to 39 weeks 5 days) and the median time between diagnosis of stillbirth and the interview was 25 days (IQR 17–35).

Exposure assessment

Total caffeine consumption per day was calculated based upon the reported frequency of consumption for instant coffee (81.5 mg/serving), brewed/filter coffee (120.8 mg/serving), decaffeinated coffee (3.5 mg/serving), tea (54.9 mg/serving), chai tea (100 mg/serving), green tea (27 mg/serving), drinking chocolate (5 mg/serving), eating chocolate (10 mg/serving), energy drinks (103.9 mg/serving) and cola (38.5 mg/serving). These values were derived from searching established sources of data and where possible a mean value taken. [12–14] Caffeine consumption was assessed as continuous variable and categorically defined as individual servings of each drink / source of caffeine.

Statistical methods

All statistical analyses were performed in R 3.6.2. Univariable logistic regression was initially carried out to determine the association between stillbirth and daily average consumption of each drink for which data were collected in the last month prior to stillbirth (cases) or interview (controls) as part of a univariable analysis. Drinks and sources of caffeine were included individually in the multivariable analysis to adjust for maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, fetal factors (gestation, birthweight centile) and maternal use of dietary supplements (folic acid, iron, multivitamins, multivitamins for pregnancy, vitamin D, omega 3 and others) in the last month prior to stillbirth (cases) or interview (controls). Chi-squared tests were used to analyse changes in maternal behaviour and influences on behaviour.

Results

During the recruitment period, 3490 women were identified as potentially eligible participants for MiNESS (660 cases and 2830 controls, Fig. 1), 760 women could not be contacted (77 cases (11 %), and 683 controls (24 %)) and 1700 women did not consent to participate (287 cases (43 %) and 1413 controls (50 %)). Six participants were excluded after data collection as five stillbirths had previously unidentified congenital abnormalities detected on post-mortem and one control participant had a stillbirth. Thus, there were 296 (44 %) cases and 734 (26 %) controls in the study population. Women who had a stillbirth were more likely to participate than controls ($p < 0.0001$). Data on soft drink consumption was available on 290 cases and 729 controls (99.7 % of cases and 99.4 % of participants included in analysis of the main study respectively; Fig. 1).

Detailed information about participants has been reported previously [12]. Briefly, the majority of participants, 80.4 % of cases and 81 % of controls, were of white ethnicity (Table 1), with a significant proportion of participants of South Asian (13.4 % of cases and 13.0 % controls) and Black ethnic groups (4.1 % of cases and 4.0 % of controls). Participants' ages were distributed from <20 years to over 40 years, with the largest group between 30−34 years of age in both groups (29.6 % cases, 36.6 % controls). The majority of women, 57.4 % of cases and 40.4 % of controls, were primiparous. There was no difference in mean body mass index (Cases 26.9 kg/m^2, Controls 26.0 kg/m^2). Stillbirth were most frequently associated with fetal growth restriction (45.2 % of cases), placental insufficiency (16.4 %), placental abruption (6.5 %) or acute infection (4.5 %).

The frequency of exposure to each type of drink, chocolate or sugar intake and their univariable odds ratios (OR) for their

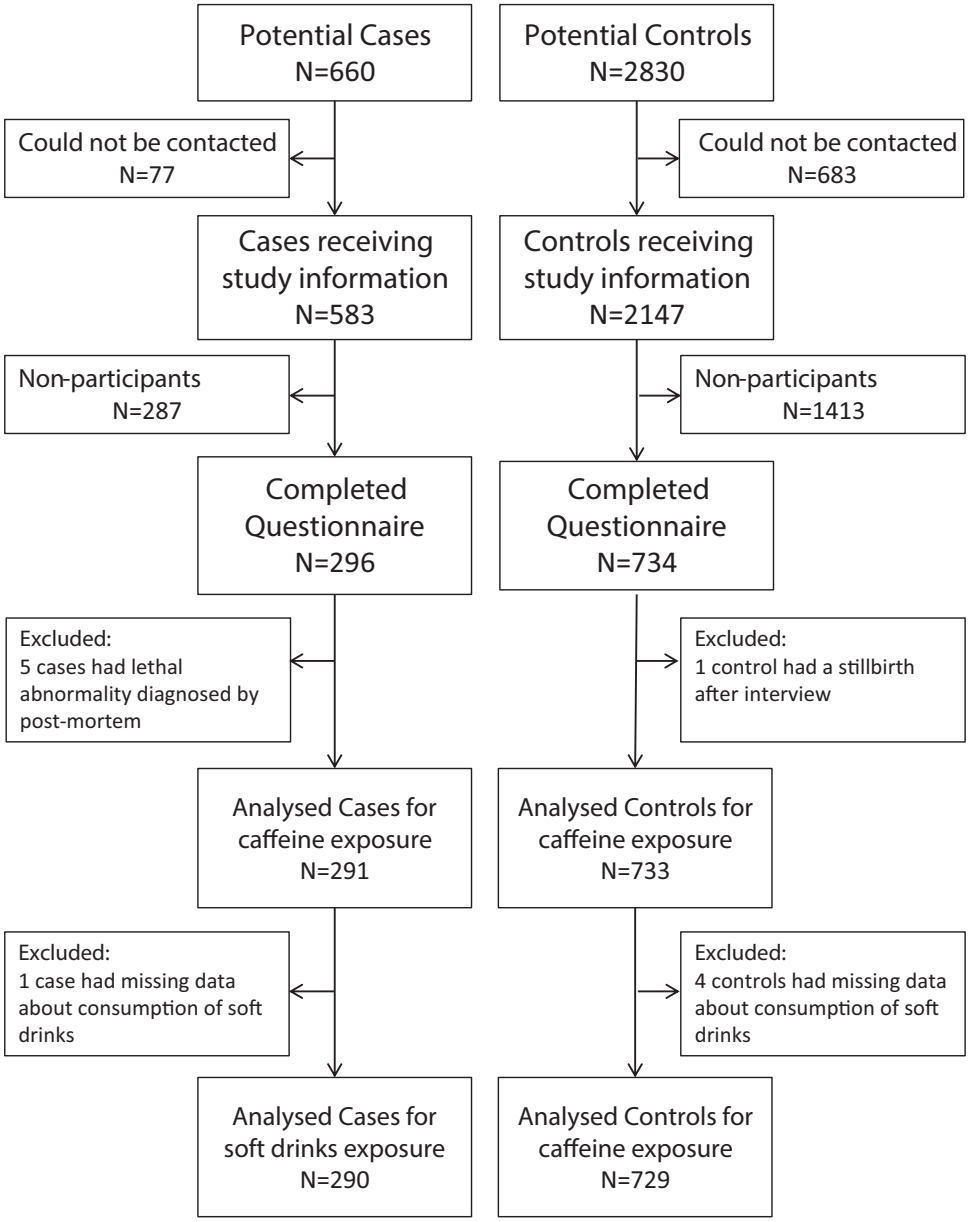

Fig. 1. Flow diagram reporting the numbers of women eligible for the study, women who did not participate and those included in the final analysis of caffeine and soft drink consumption.

association with stillbirth are presented in Table 2. In the univariable analysis, the following variables were associated with stillbirth: caffeine intake per 100 mg, cola, instant coffee, drinking chocolate, energy drinks and supplementary sugar in the preceding month. 62.8 % of cases and 56.3 % of controls had ≥100 mg of caffeine per day, and a smaller proportion, 15.1 % of cases and 8.3 % of controls reported intake in excess of the WHO recommendations (>300 mg per day). [10] When multivariable analysis was performed intake of cola (aOR 1.23, 95 % CI 1.03, 1.48), instant coffee (aOR 1.34, 95 % CI 1.09–1.71) and energy drinks (aOR 1.85, 95 % CI 1.11, 3.58) were all independently associated with increased risk of stillbirth. We fitted a generalized additive model (GAM) and found the relationship between caffeine intake and stillbirth to be of a linear nature, no threshold level of association was observed (Supplementary File 1). For each 100 mg caffeine intake the adjusted Odds Ratio (aOR) was 1.27 (95 % Confidence Interval (95 % CI) 1.14, 1.43). Caffeine intake greater than 300 mg/day was associated with stillbirth aOR 2.30 (95 % 1.40–4.24); the population attributable risk associated with this level of consumption was 7.4 %. There was no relationship between caffeine intake and sleep duration in the preceding month (R=-0.01, p = 0.78), but there was a weak negative relationship between caffeine intake and birthweight (R=-0.09, p = 0.003).

In total, 607 women reported making alterations to their consumption of caffeinated and/or soft drinks during their pregnancy, 166 who had a stillbirth and 441 controls. The proportion of women who altered their caffeine consumption did not differ between cases and controls (Table 3), in both groups the majority of women who altered their consumption reported either reducing consumption of coffee, tea or energy drinks or changing to decaffeinated drinks (Table 3, 51.3 % of cases, 56.1 % of controls). In contrast, 3.8 % of cases and 1.9 % of controls increased their caffeine intake during pregnancy. With regard to fizzy drinks such as cola or soda, 1.4 % of cases and 1.6 % of controls reduced their intake and a smaller group of 0.7 % of cases and 0.8 % of controls increased their intake of this type of drinks. Most women

Table 1
Demographic characteristics and sleep practices in 291 women who had a late stillbirth compared to 734 controls who participated in MiNESS. Data are presented as the number (percentage) or median (interquartile range).

Characteristic	Case (n = 291)	Control (n = 734)
Age (years)		
<20	7 (2.4)	15 (2.0)
20–24	48 (16.5)	81 (11.1)
25–29	82 (28.2)	219 (29.9)
30–34	86 (29.6)	268 (36.6)
35–39	52 (17.9)	125 (17.1)
40+	16 (5.5)	25 (3.4)
Ethnicity		
White	234 (80.4)	594 (81.0)
Black	12 (4.1)	29 (4.0)
South Asian	39 (13.4)	95 (13.0)
Others	6 (2.1)	15 (2.0)
Parity		
0	167 (57.4)	296 (40.4)
1–2	92 (31.6)	386 (52.7)
3+	32 (11.0)	51 (7.0)
Level of Education		
Graduate Education	99 (34.0)	326 (31.8)
Further Education	112 (38.5)	278 (27.2)
Secondary education to 16 years	56 (19.2)	100 (9.8)
No formal educational qualification	23 (7.9)	29 (2.8)
Body Mass Index	Median 26.9 (15.4–47.9)	Median 26.0 (15.41–48.6)
Cause of Stillbirth		
Acute Infection	13 (4.5)	
Fetal-maternal haemorrhage	6 (2.1)	
Fetal Growth Restriction	132 (45.2)	
Umbilical Cord Prolapse	1 (0.3)	
Constricting loop or knot of cord	10 (3.4)	
Placental abruption	19 (6.5)	
Vasa Praevia	1 (0.3)	
Placental Insufficiency	48 (16.4)	
Chorioamnionitis	6 (2.1)	
Uterine rupture	1 (0.3)	
Diabetes	9 (3.1)	
Obstetric Cholestasis	1 (0.3)	
Intrapartum asphyxia	1 (0.3)	
No relevant condition identified	42 (14.4)	

made changes to their diet and caffeine intake following advice from a midwife (18.6 % of cases and 21.4 % of controls, Table 3). The next most frequently used source of information to change behaviour was the internet, pregnancy books and relatives, with a minority of women receiving advice from their family or hospital doctor (Table 4).

Discussion

This study found an association between caffeine intake and late stillbirth; this appears to be mediated through an increased intake of instant coffee, cola and energy drinks in cases compared to controls. Tea consumption, the most widely consumed caffeinated drink (1.44 servings/day in controls) did not differ between cases and controls. Although the majority of participants (54.5 %) reduced their caffeine intake during pregnancy, a small proportion (3%) increased it and over 15 % of cases and 8% of controls consumed more than the WHO recommended limit of 300 mg caffeine/day. Midwives and the internet were the most commonly used sources of information leading to change in maternal behaviour.

Strengths and limitations

This study was strengthened by obtaining information about all possible sources of caffeine intake, not just coffee. Nevertheless, other sources of caffeine e.g. headache medication were not included, meaning caffeine consumption may have been underestimated. As there is no standard calculation for the caffeine content of drinks average values were taken from different reliable sources. [12–14] The study was also strengthened by asking whether women's behaviour had changed during pregnancy; and if so, the sources of information that had driven this change. This study is limited by self-reported caffeine intake which may have led to errors in measurement of caffeine intake or recall bias, where women who had a stillbirth may recall exposures differently. However, there was no information about hypotheses regarding diet or caffeine intake in the study materials. There is also the potential for reverse causality i.e. caffeine consumption increased due to undetected fetal demise. However, this effect is likely small as the mean duration between diagnosis of stillbirth and presumed time of fetal death was always <7 days.

Significance of the association between caffeine consumption and stillbirth

To understand whether the association between caffeine intake and stillbirth is likely to be causal, we have applied the Bradford-Hill Criteria [15]. The association is only moderately strong, exceeding the WHO recommendation of <300 mg/day has an aOR 2.30. Critically, the findings of this study are in agreement with the majority of studies investigating the effect of caffeine on pregnancy; a review of found 32 out of 42 studies reported caffeine increased the risk of miscarriage, stillbirth or low birth weight and/or small for gestational age neonate, with 10 studies reporting no or inconclusive associations [16]. There appears to be a biological gradient, as each increment of 100 mg/day of caffeine was associated with a 27 % increase in the risk of stillbirth, which is consistent with an early UK study conducted in 2004–2006 which demonstrated increased risk of stillbirth with increasing intake of caffeine [17]. In our population, the association was linear, meaning that we were unable to generate a threshold value over which risk increases markedly. The temporal relationship between caffeine consumption is appropriate (i.e. exposure to caffeine precedes the outcome) and interestingly, the risk to fetal growth and increased risk of pregnancy loss may extend to high periconceptual caffeine consumption [18]. An association between caffeine consumption and stillbirth is analogous to the association of caffeine consumption with early miscarriage, neonatal death and sudden infant death syndrome [7,19], although the neonatal death also may relate to cigarette smoking, maternal age, education and parity [20].

The association between caffeine consumption is biologically plausible, caffeine readily crosses the placenta with poor fetal clearance (levels are 30 times greater in the fetus than the mother) [21,22]. Caffeine is metabolised by CYP1A2, the activity of which decreases by 65 % in the third trimester [23], resulting in an increase in the half-life of caffeine from 3 h in non-pregnant women to 10.5 h in the third trimester [22]. High maternal caffeine intake increases placental vasoconstriction and fetal catecholamine levels, potentially impairing fetal growth [24]. In agreement, we observed a weak negative correlation between caffeine intake and birthweight. However, another study of 100 women found no relationship between caffeine consumption and birthweight, although only 2 participants had daily caffeine intake >200 mg [25]. High consumption of caffeine, especially in energy drinks, is associated with cardiac arrhythmias which can be fatal [26]. In an animal model, in utero exposure to caffeine alters gene expression in cardiomyocytes and the embryonic response to hypoxia [27,28]. Furthermore, exposure to energy drinks during pregnancy induces oxidative damage in fetal liver, kidney and brain in a murine model [29]. These experimental observations suggest excessive caffeine could lead to adverse fetal outcome.

Table 2
Association between caffeinated and soft drink consumption and late stillbirth. Multivariate analysis adjusted for maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, fetal factors (gestation, birthweight centile) and maternal use of dietary supplements (folic acid, iron, multivitamins, multivitamins for pregnancy, vitamin D, omega 3 and others) in the last month prior to stillbirth (cases) or interview (controls).

	Stillbirth (Average number of servings/day) or n (%)	Control (Average number of servings/day) or n(%)	Odds Ratio (95 % Confidence Interval)	Adjusted Odds Ratio (95 % Confidence Interval)	P value
Tea (Number of servings/day) *Mean 54.9 mg/serving*	1.66 (0–14)	1.44 (0–15)	1.07 (0.99, 1.15)	0.96 (0.85, 1.08)	0.53
Diet Soft Drinks (Number of servings/day) *Mean 38.5 mg/serving*	>1	>1	0.51 (0.10, 3.69)	0.17 (0.02, 1.68)	0.104
Chocolate (Number of servings/day) *Mean 10 mg/serving*	0.49 (0–6)	0.50 (0–16)	1.00 (0.85, 1.15)	0.94 (0.73, 1.16)	0.62
Cola (330 ml **serving / day)** *Mean 38.5 mg/serving*	0.53 (0–8)	0.37 (0–12)	**1.13 (1.01, 1.28)**	**1.23 (1.03, 1.48)**	**0.025**
Instant Coffee (Number of servings/day) *Mean 81.5 mg/serving*	0.41 (0–10)	0.26 (0–10)	**1.18 (1.02, 1.36)**	**1.34 (1.09, 1.71)**	**0.009**
Decaffeinated Coffee (Number of servings/day) *Mean 3.5 mg/serving*	0.18 (0–5)	0.23 (0–7.5)	0.95 (0.88, 1.00)	0.94 (0.63, 1.28)	0.72
Drinking chocolate (Number of servings/day) *Mean 5.0 mg/serving*	0.11 (0–4)	0.07 (0–2)	**1.54 (1.00, 2.37)**	1.97 (0.92, 4.03)	0.07
Green Tea (Number of servings/day) *Mean 27 mg/serving*	0.09 (0–3)	0.07 (0–5)	1.10 (0.80, 1.50)	1.03 (0.64, 1.79)	0.93
Filter Coffee (Number of servings/day) *Mean 120.8 mg/serving*	0.08 (0–3)	0.05 (0–5)	1.29 (0.85,1.96)	1.54 (0.83, 1.17)	0.21
Energy drinks (Number of servings/day) *Mean 103.9 mg/serving*	0.09 (0–8)	0.02 (0–3)	**2.06 (1.26, 3.96)**	**1.85 (1.11, 3.58)**	**0.037**
Chai Tea (Number of servings/day) *Mean 100 mg/serving*	0.04 (0–2)	0.02 (0–2.5)	1.31 (0.70, 2.38)	1.45 (0.50, 3.25)	0.47
Teaspoons of sugar (Number of servings/day)	2.1 (0–30)	1.47 (0–24)	**1.07 (1.02, 1.12)**	1.00 (0.93, 1.08)	0.94
Caffeine intake (increments of 100 mg/day)	1.74 (0–10.75)	1.33 (0–9.62)	**1.21 (1.10, 1.33)**	**1.27 (1.14, 1.43)**	**0.004**
Exceeded WHO guidelines (300 mg Caffeine/day)	44 (15.1 %)	60 (8.3 %)	**1.96 (1.30, 2.99)**	**2.30 (1.40, 4.24)**	**0.008**
Participant reports changing their caffeine intake during pregnancy	216 (74.0 %)	582 (79.4 %)	1.4 (0.97, 1.83)	1.11 (0.66, 1.51)	0.70

Table 3
Changes to maternal behaviour regarding consumption of drinks in pregnancy.

Behaviour	Case (n = 290) N (%)	Control (n = 729) N (%)	Total (n = 1019) N (%)	P value
Reduced caffeine / switched to decaffeinated drinks	149 (51.3)	409 (56.1)	558 (54.8)	0.12
Increased intake caffeinated drinks	11 (3.8)	14 (1.9)	25 (2.5)	
No change to caffeinated drinks	130 (44.8)	306 (42.0)	436 (42.8)	
Reduced fizzy drinks (e.g. Cola, Soda)	4 (1.4)	12 (1.6)	16 (1.6)	0.93
Increased fizzy drinks (e.g. Cola, Soda)	2 (0.7)	6 (0.8)	8 (0.8)	
No change to fizzy drinks	284 (97.9)	711 (97.5)	995 (97.6)	

Table 4
Sources of information reported to have led to altered behaviour regarding consumption of drinks in pregnancy.

Source of Information	Case (n = 290) N (%)	Control (n = 729) N (%)	Total (n = 1,019)	P value
Midwife	54 (18.6)	156 (21.4)	210 (20.1)	0.78
General Practitioner / Family doctor	9 (3.1)	15 (2.1)	24 (2.4)	
Hospital doctor	7 (2.4)	16 (2.2)	23 (2.3)	
Relative	21 (7.2)	61 (8.4)	82 (8.0)	
Internet	42 (14.5)	96 (13.2)	138 (13.5)	
Magazine	6 (2.1)	28 (3.8)	34 (3.3)	
Pregnancy book	23 (7.9)	53 (7.3)	76 (7.5)	
Television	4 (1.4)	11 (1.5)	15 (1.5)	
None given	124 (42.8)	293 (40.2)	417 (40.9)	

It is important to note that other constituents of beverages may also be responsible for the observed associations with stillbirth. Sugar-sweetened soft drinks (such as cola) have been previously reported to be associated with poorer maternal diet quality [30] and increased risk of maternal obesity [31], gestational diabetes [32], preterm birth [33], pre-eclampsia [34] and congenital heart defects [35]. Energy drinks are often supplemented with taurine, which is positively correlated with fetal size, and could augment the effect of sugar on fetal macrosomia [36]. Conversely, taurine supplementation is associated with reduced birthweight and increased neonatal mortality in rats [37,38]. Finally, the effects of sugar substitutes used in soft drinks are largely unknown; aspartame decreases placental weight, impairs normal placental structure and increases rates of fetal growth restriction [39,40]. As

soft drinks are frequently consumed by pregnant women, further studies are needed to determine whether caffeine, taurine or sweeteners exert direct negative effects on the placenta and/or fetus.

Clinical implications

Our findings suggest that women should be advised to reduce their caffeine consumption during pregnancy. Women are likely already receiving some messaging; as in common with earlier studies we found the majority of participants reduced their caffeine consumption [41,42]. Although, WHO recommend limiting caffeine consumption, this is not reflected in the UK antenatal guidelines for uncomplicated pregnancies [43] and caffeine consumption is infrequently mentioned in antenatal consultations [44].

Based on our findings, midwives may be best placed to deliver information about safe caffeine consumption and to signpost women to further online resources. This agrees with prior studies of maternal diet which found advice from healthcare professionals and the internet were the most widely used sources of information [45,46]. Thus, combining these two approaches may enhance communication and information provision which may increase adherence to recommendations. In addition, when delivering information to women about caffeine consumption, it is important to ensure that underpinning reasons for the recommendations are adequately explained, as messages about associated risks are often not communicated effectively [47,48]. Perceiving a low level of associated risk may act as a barrier to carrying out the target behaviour [47], therefore training midwives and other health care professionals in effectively communicating information about the risks of caffeine consumption during pregnancy may improve women's adherence to advice.

Conclusions

This study demonstrates an independent association between caffeine consumption and stillbirth after 28 weeks' gestation. As there is also an increased risk of early pregnancy loss and neonatal deaths reported with excessive caffeine consumption, clinicians should be aware of these associations and women should be informed about the benefits of reducing caffeine consumption in pregnancy. The most effective means is likely to be via interaction with midwives accompanied by signposting to internet-based resources.

Funding

The Midland and North of England Stillbirth Study was funded by grant GN2156 from Action Medical Research, Cure Kids and Sands. AH receives salary support from Tommy's. EM and JT were supported by Cure Kids.

Declaration of Competing Interest

All authors declare that they have no competing interests.

Contribution to authorship

AH, TS, BM, DR, EM & LM contributed to all aspects of the study design and obtained funding. AH had overall responsibility for the study. JB coordinated the running of the study. KT and LR analysed the data with input from AH. All authors were responsible for the drafting of the manuscript. All authors gave approval for the final version of the manuscript.

Details of ethical approval

This study was reviewed by NRES Committee North West - Greater Manchester Central Reference (13/NW/0874) on 24th January 2014.

Data sharing statement

No additional data from the MiNESS study are available from a repository. Anonymised data is available on request to the corresponding author.

Acknowledgements

The authors thank all the participants who participated in interviews in order to help us better understand stillbirth. The authors would also like to thank the Principal Investigators, Research Midwives and Nurses at the following institutions for their hard work and dedication to this study: Airedale NHS Foundation Trust, Birmingham Women's NHS Trust, Blackpool Teaching Hospitals NHS Foundation Trust, Bradford Teaching Hospitals NHS Foundation Trust, Buckinghamshire Healthcare NHS Trust, Burton Hospitals NHS Foundation Trust, Calderdale and Huddersfield NHS Foundation Trust, Central Manchester Hospitals NHS Foundation Trust, Countess of Chester Hospitals NHS Foundation Trust, County Durham and Darlington NHS Foundation Trust, East Lancashire Hospitals NHS Trust, Harrogate and District NHS Foundation Trust, Heart of England NHS Foundation Trust, Hull & East Yorkshire Hospitals NHS Trust, Lancashire Teaching Hospitals NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, Liverpool Women's NHS Foundation Trust, Mid Cheshire Hospitals NHS Foundation Trust, Mid-Yorkshire Hospitals NHS Trust, Northern Lincolnshire and Goole NHS Foundation Trust, Portsmouth Hospitals NHS Trust, Royal Wolverhampton Hospitals NHS Trust, Sandwell and West Birmingham NHS Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Sherwood Forest Hospitals NHS Foundation Trust, St Helens and Knowsley Teaching Hospitals NHS Trust, Stockport NHS Foundation Trust, Southport and Ormskirk Hospitals NHS Trust, South Warwickshire NHS Foundation Trust, The Dudley Group NHS Foundation Trust, United Lincolnshire Hospitals NHS Trust, University Hospitals of Coventry and Warwickshire NHS Trust, University Hospitals of North Midlands NHS Trust, University of Morecambe Bay NHS Foundation Trust, Walsall Healthcare NHS Trust, Warrington and Halton Hospitals NHS Foundation Trust, Western Sussex Hospitals NHS Foundation Trust, Wirral University Teaching Hospitals NHS Foundation Trust, York Teaching Hospitals NHS Foundation Trust.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.10.012.

References

[1] Flenady V, Wojcieszek AM, Middleton P, et al. Stillbirths: recall to action in high-income countries. Lancet 2016;387(10019):691–702.
[2] Heazell AE, Siassakos D, Blencowe H, et al. Stillbirths: economic and psychosocial consequences. Lancet 2016;387(10018):604–16.
[3] Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011;377(9774):1331–40.
[4] Heazell AE, Whitworth MK, Whitcombe J, et al. Research priorities for stillbirth: process overview and results from UK stillbirth priority setting partnership. Ultrasound Obstet Gynecol 2015;46(6):641–7.
[5] Platts J, Mitchell EA, Stacey T, et al. The Midland and North of England stillbirth study (MiNESS). BMC Pregnancy Childbirth 2014;14:171.
[6] British Coffee Association. Coffee Facts. 2020. www.britishcoffeeassociation.org/coffee-in-the-uk/coffee-facts.

[7] Greenwood DC, Thatcher NJ, Ye J, et al. Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis. Eur J Epidemiol 2014;29(10):725–34.
[8] Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. Am J Epidemiol 2005;162(10):983–90.
[9] Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr 2016;19(7):1233–44.
[10] Tuncalp O, Pena-Rosas JP, Lawrie T, et al. WHO recommendations on antenatal care for a positive pregnancy experience-going beyond survival. BJOG 2017;124(6):860–2.
[11] Heazell AE, Li M, Budd J, et al. Going to sleep supine is a modifiable risk factor for late stillbirth – findings from the Midland and North of England stillbirth case-control study *Bjog*. 2017 Submitted.
[12] New Zealand Nutrition Foundation. Caffiene. 2018. . (accessed 29th March 2018) https://nutritionfoundation.org.nz/nutrition-facts/nutrition-a-z/Caffeine.
[13] Mayo Clinic. Caffeine content for coffee, tea, soda and more. 2020. . (accessed 25th March 2020) https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20049372.
[14] National Health Service. Foods to avoid in pregnancy. 2017. . (accessed 19th March 2018) https://www.nhs.uk/conditions/pregnancy-and-baby/foods-to-avoid-pregnant/.
[15] Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol 2015;12:14.
[16] James JE. Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be. BMJ Evid Based Med 2020.
[17] Greenwood DC, Alwan N, Boylan S, et al. Caffeine intake during pregnancy, late miscarriage and stillbirth. Eur J Epidemiol 2010;25(4):275–80.
[18] Gaskins AJ, Rich-Edwards JW, Williams PL, Toth TL, Missmer SA, Chavarro JE. Pre-pregnancy caffeine and caffeinated beverage intake and risk of spontaneous abortion. Eur J Nutr 2018;57(1):107–17.
[19] Ford RP, Schluter PJ, Mitchell EA, Taylor BJ, Scragg R, Stewart AW. Heavy caffeine intake in pregnancy and sudden infant death syndrome. New Zealand cot death study group. Arch Dis Child 1998;78(1):9–13.
[20] Alm B, Wennergren G, Norvenius G, et al. Caffeine and alcohol as risk factors for sudden infant death syndrome. Nordic epidemiological SIDS study. Arch Dis Child 1999;81(2):107–11.
[21] Modzelewska D, Bellocco R, Elfvin A, et al. Caffeine exposure during pregnancy, small for gestational age birth and neonatal outcome - results from the Norwegian mother and child cohort study. BMC Pregnancy Childbirth 2019;19(1):80.
[22] Knutti R, Rothweiler H, Schlatter C. The effect of pregnancy on the pharmacokinetics of caffeine. Arch Toxicol Suppl 1982;5:187–92.
[23] Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem 2008;392(6):1093–108.
[24] Kirkinen P, Jouppila P, Koivula A, Vuori J, Puukka M. The effect of caffeine on placental and fetal blood flow in human pregnancy. Am J Obstet Gynecol 1983;147(8):939–42.
[25] Wierzejska R, Jarosz M, Wojda B. Caffeine intake during pregnancy and neonatal anthropometric parameters. Nutrients 2019;11(4).
[26] Levy S, Santini L, Capucci A, et al. European cardiac arrhythmia society statement on the cardiovascular events associated with the use or abuse of energy drinks. J Interv Card Electrophysiol 2019;56(1):99–115.
[27] Fang X, Mei W, Barbazuk WB, Rivkees SA, Wendler CC. Caffeine exposure alters cardiac gene expression in embryonic cardiomyocytes. Am J Physiol Regul Integr Comp Physiol 2014;307(12):R1471–87.
[28] Buscariollo DL, Breuer GA, Wendler CC, Rivkees SA. Caffeine acts via A1 adenosine receptors to disrupt embryonic cardiac function. PLoS One 2011;6(12)e28296.
[29] Al-Basher GI, Aljabal H, Almeer RS, Allam AA, Mahmoud AM. Perinatal exposure to energy drink induces oxidative damage in the liver, kidney and brain, and behavioral alterations in mice offspring. Biomed Pharmacother 2018;102:798–811.
[30] Gamba RJ, Leung CW, Petito L, Abrams B, Laraia BA. Sugar sweetened beverage consumption during pregnancy is associated with lower diet quality and greater total energy intake. PLoS One 2019;14(4)e0215686.
[31] Goran MI, Plows JF, Ventura EE. Effects of consuming sugars and alternative sweeteners during pregnancy on maternal and child health: evidence for a secondhand sugar effect. Proc Nutr Soc 2019;78(3):262–71.
[32] Chen L, Hu FB, Yeung E, Willett W, Zhang C. Prospective study of pre-gravid sugar-sweetened beverage consumption and the risk of gestational diabetes mellitus. Diabetes Care 2009;32(12):2236–41.
[33] Petherick ES, Goran MI, Wright J. Relationship between artificially sweetened and sugar-sweetened cola beverage consumption during pregnancy and preterm delivery in a multi-ethnic cohort: analysis of the born in Bradford cohort study. Eur J Clin Nutr 2014;68(3):404–7.
[34] Clausen T, Slott M, Solvoll K, Drevon CA, Vollset SE, Henriksen T. High intake of energy, sucrose, and polyunsaturated fatty acids is associated with increased risk of preeclampsia. Am J Obstet Gynecol 2001;185(2):451–8.
[35] Dale MTG, Magnus P, Leirgul E, et al. Intake of sucrose-sweetened soft beverages during pregnancy and risk of congenital heart defects (CHD) in offspring: a Norwegian pregnancy cohort study. Eur J Epidemiol 2019;34(4):383–96.
[36] Jung YM, Choi MJ. Relation of taurine intake during pregnancy and newborns' growth. Adv Exp Med Biol 2019;1155:283–92.
[37] Boujendar S, Reusens B, Merezak S, et al. Taurine supplementation to a low protein diet during foetal and early postnatal life restores a normal proliferation and apoptosis of rat pancreatic islets. Diabetologia 2002;45(6):856–66.
[38] Li M, Reynolds CM, Sloboda DM, Gray C, Vickers MH. Effects of taurine supplementation on hepatic markers of inflammation and lipid metabolism in mothers and offspring in the setting of maternal obesity. PLoS One 2013;8(10)e76961.
[39] Shalaby AM, Ibrahim M, Aboregela AM. Effect of aspartame on the placenta of adult albino rat. A histological and immunohistochemical study. Ann Anat 2019;224:133–41.
[40] Al-Qudsi FM, Al-Hasan MM. In utero exposure to commercial artificial sweeteners affects mice development and mammary gland structure. Environ Sci Pollut Res Int 2019;26(5):5054–64.
[41] Crozier SR, Robinson SM, Borland SE, et al. Do women change their health behaviours in pregnancy? Findings from the Southampton women's survey. Paediatr Perinat Epidemiol 2009;23(5):446–53.
[42] Peacock A, Hutchinson D, Wilson J, et al. Adherence to the caffeine intake guideline during pregnancy and birth outcomes: a prospective cohort study. Nutrients 2018;10(3).
[43] National Collaboration Centre for Women's and Children's Health. Antenatal care: routine care for the healthy pregnant woman. London: RCOG Press; 2008.
[44] Baron R, Martin L, Gitsels-van der Wal JT, et al. Health behaviour information provided to clients during midwife-led prenatal booking visits: findings from video analyses. Midwifery 2017;54:7–17.
[45] Funnell G, Naicker K, Chang J, Hill N, Kayyali R. A cross-sectional survey investigating women's information sources, behaviour, expectations, knowledge and level of satisfaction on advice received about diet and supplements before and during pregnancy. BMC pregnancy and childbirth 2018;18(1):182.
[46] Grimes HA, Forster DA, Newton MS. Sources of information used by women during pregnancy to meet their information needs. Midwifery 2014;30(1):e26–33.
[47] Athearn PN, Kendall PA, Hillers VV, et al. Awareness and acceptance of current food safety recommendations during pregnancy. Matern Child Health J 2004;8(3):149–62.
[48] Keely A, Gunning M, Denison F. Maternal obesity in pregnancy: women's understanding of risks. Br J Midwifery 2013;19(9):364–9.