Maternal caffeine consumption and fetal death: a case–control study in Uruguay

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Summary

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The objective of this study was to examine the association between caffeine intake during pregnancy and fetal mortality in Montevideo, the capital city of Uruguay, taking into account several potential confounding factors. A population-based case–control study was conducted between 1 August 2002 and 31 December 2003. A total of 382 cases and 792 controls were recruited. Cases consisted of women hospitalised with a medically confirmed diagnosis of spontaneous antepartum fetal death, in all maternity hospitals during the study period. Antepartum fetal death was defined as a fetal death in which the attending doctor certified that the death occurred prior to the onset of labour. Fetal deaths were included if they were of at least 20 weeks' gestational age or weighed >350 g. Controls were women who had a live, vigorous and term adequate-for-gestational-age newborn. Multiple gestations and fetuses/newborns with evident congenital malformations were excluded.

Only a small proportion of the mothers (8.1% of the cases and 9.5% of the controls) did not consume caffeine during pregnancy. Among consumers, mate drinking was the most frequent source of caffeine in both cases and controls. After controlling for mother's and her partner's education, history of abortions and/or fetal deaths, vomiting/nausea during the first trimester of gestation and attendance for prenatal care, the category of mean caffeine intake of ≥300 mg/day showed a significantly increased risk of fetal death (OR 2.33 [1.23; 4.41]) compared with no caffeine consumption during pregnancy. The study also found that less-educated women, mothers who did not attend for prenatal care and women with a history of abortions and fetal death were at an increased risk of fetal death. As mate drinking is highly consumed among pregnant women in Uruguay, the association found with fetal death makes it a preventable risk factor.

Keywords: *antepartum fetal death, caffeine, mate, coffee.*

Introduction

Fetal deaths represent a large proportion of perinatal deaths, and are an important public health problem especially in developing countries.[1] There are many well-established risk factors for fetal deaths, but for a substantial proportion of them, an apparent cause of death cannot be found.[2,3] Lethal anomalies, prenatal infections, severe fetal growth retardation, chronic maternal disorders and pregnancy-related diseases have been associated with fetal mortality.[4] Some maternal characteristics like obesity/overweight,[5,6] advanced age,[7,8] low socio-economic status,[9] low maternal education,[10,11] reproductive history of fetal loss[12] and cigarette and alcohol consumption[13–16] have been related to fetal mortality in several studies.

Caffeine intake during pregnancy has also been suggested as a risk factor for fetal death.[17–20] Caffeine is a methylated xanthine widely present in many beverages, such as coffee, tea, mate (a hot infusion of the herb *Ilex paraguayensis*), soft drinks, in products con-

taining cocoa or chocolate, and in many medications.[21] Its main mechanism of action is the antagonism of adenosine receptors.[22] Following studies in animals, caffeine intake during pregnancy has been suggested as a risk factor for fetal mortality. Studies in monkeys after chronic caffeine exposure showed that those treated with caffeine in their drinking water had an increased rate of fetal death.[23] It is biologically plausible that caffeine could be harmful to fetal life, as caffeine ingested by the pregnant women is rapidly absorbed from the gastrointestinal tract, readily crosses the placenta and is distributed to all fetal tissues. The fetus may be exposed to high amounts of caffeine or its metabolites, because the half-life of caffeine is markedly increased in pregnant women due to a delay in its clearance and to the absence of the enzymes needed for metabolising caffeine in the fetus.[24–26] In humans, although epidemiological studies examining the relationship between caffeine consumption and fetal mortality are rarely comparable due to differences in the diagnosis of fetal death and in caffeine assessment, the available studies suggest an increased risk of fetal mortality among caffeine consumers.[17–20]

Although coffee is the main common source of caffeine in the studies so far available, in South American countries another relevant source of this substance, and sometimes the most important source, is the habit of drinking a local tea known as 'mate'.[27,28]

Uruguay is a South American country, with a population of 3.3 million inhabitants. It is highly urbanised, and there is universal access to health services. During the last 20 years, although infant mortality was reduced by 53%, fetal mortality rates showed only a slight decrease, from 12 fetal deaths per 1000 births in 1984 to 10 per 1000 in 2000. As mate drinking is the traditional 'national beverage' and is commonly consumed by women whether pregnant or not, it is important to evaluate whether this habit actually has harmful effects on the fetus.

The purpose of this study was to examine the association between caffeine intake during pregnancy and fetal mortality in Montevideo, the capital city of Uruguay, taking into account several potential confounding factors.

Methods

A population-based case–control study was conducted in Montevideo (pop. 1.5 million inhabitants). This city was chosen because more than 50% of the deliveries of the country occur there and 99% of all deliveries take place in hospitals. The study was conducted between 1 August 2002 and 31 December 2003.

The study was planned to have a power of 80% to detect an odds ratio (OR) of ≥1.8 as significant at the 5% level, taking into consideration that 10% of the controls have a mean caffeine consumption during pregnancy of ≥300 mg/day. With two controls per case and allowing 20% for confounding, losses or refusals, a sample size of 382 cases and 764 controls was deemed adequate.

Cases consisted of women hospitalised with a medically confirmed diagnosis of spontaneous antepartum fetal death, in the maternity hospitals (5 public and 11 private) of Montevideo during the study period. Antepartum fetal death was defined as a fetal death in which the attending doctor certified that the death occurred prior to the onset of labour. Fetal deaths were included if they were of at least 20 weeks' gestational age or weighed >350 g. Controls were women who had a live, vigorous (Apgar at the first and fifth minute of life >6) and term (≥37 completed weeks' gestation) adequate-for-gestational-age newborn (≥10th percentile birthweight for gestational age based on a recently studied Canadian population).[29] The proportion of controls to be studied in each maternity hospital followed the proportion of births that occurred in each of the city maternity hospitals in the year 2001, and were chosen by birth order. Multiple gestations and fetuses/newborns with evident congenital malformations during physical examination were excluded, for both cases and controls.

Structured interviews of mothers of cases and controls, most of them during the first 24 h after birth, were conducted by specially trained medical students.

Gestational age of cases and controls was assessed using the first day of the last normal menstrual period (LMP), or estimated by obstetric ultrasound obtained during the first trimester when LMP was not reliable (due to use of contraceptive pills or lactation) or not available. In the absence of both menstrual and ultrasound information, gestational age was estimated by physical examination (Capurro's method)[30] in 28 controls.

According to previous studies in the southern region of South America (Argentina, Uruguay and southern Brazil),[27,28,31,32] the main sources of caffeine in the region are coffee and mate drinking, thus caffeine intake was estimated from these sources. For coffee

and mate, the frequency of consumption per day was obtained separately for each trimester of pregnancy using a questionnaire tested in a previous study.[31] Mothers were considered as 'consumers' if they reported at least one weekly intake of one of these sources.

For coffee, information was collected on the usual method of preparation, the size of the serving and the reported strength of the preparation. According to previous research,[31] strong coffee has a caffeine content of 0.25 mg/mL, medium strength coffee 0.20 mg/mL and weak coffee a caffeine content of 0.11 mg/mL. The same source established for mate drinking an amount of 0.17 mg/mL. For instant coffee, information was collected about the size of spoon used (full coffee spoon, 2.6 g; level coffee spoon, 2.3 g; full small coffee spoon, 2.5 g; level small coffee spoon, 1.5 g; full dessert spoon, 7.5 g; and level desert spoon, 7.0 g) and the number of spoons used to serve it. For this kind of coffee, the manufacturer's information of an average of 3 mg of caffeine per gram of powder was used.

For each mother, daily maternal caffeine intake, by source, by trimester and throughout pregnancy (mean caffeine consumption taking into account the gestational age of the fetus/newborn) was calculated. For comparability with previous studies,[18,20] women who did not consume caffeine during pregnancy were regarded as the reference group. Because the majority of studies that reported an increased risk of adverse pregnancy outcomes with caffeine consumption showed association at levels of ≥300 mg/day,[33] women who had a mean consumption of caffeine ≥300 mg/day were chosen as the highest category.

The questionnaire also collected information on the following variables, some of which are potential confounders: maternal anthropometric measures, marital status, family income, crowding, level of education of the mother and her partner, mother's age, smoking during pregnancy, prenatal care attendance, obstetric history and morbidity during pregnancy. Information about birthweight, sex and causes of death were obtained from maternal and newborn hospital records.

Anthropometric variables included maternal height and pre-pregnancy weight, both obtained from prenatal records or in its absence by recall, in centimetres and kilograms, respectively, and were used to calculate the pre-pregnancy body mass index [BMI, weight (kg)/height $(m)^2$]. Pre-pregnancy BMI was categorised according to the World Health Organisation in <18.5 kg/m^2 (lean weight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight) and ≥30 k/m^2 (obesity).[34]

Marital status: women who were widowed, divorced or lived without a partner were classified as single mothers, while women who lived with a partner, married or not, were classified as living in 'stable union'.

Family income was defined as the income earned by the family group to acquire goods and services and quantified by the Brazil's Economic Classification Criteria.[35] According to these criteria, families were classified into seven categories and regrouped for the analysis in three categories: higher income (groups A1, A2, B1, B2), medium income (group C) and lower income (groups D and E).

Crowding was defined as more than two people per room.

The education of the mother and her partner was categorised as: ≤6, 7–11 and ≥12 years of formal education.

Maternal age was categorised as: <20, 20–34 and ≥35 completed years at the moment of delivery.

Smoking at each trimester of gestation was based on maternal self-report. Mothers were defined as smokers if they smoked at least one cigarette per day, and the consumption during pregnancy was summarised in two categories (yes or no).

Attendance for prenatal care was categorised as no prenatal care and ≥1 visit for prenatal care.

Reproductive history included: parity (defined as number of viable previous pregnancies, categorised as: 0, 1, 2–3 and ≥4), previous abortions (defined as number of previous pregnancies which ended at <20 weeks' gestational age) and previous fetal deaths (defined as number of previous pregnancies which ended at ≥20 weeks' gestational age). Previous abortions and previous fetal deaths were categorised in two categories (0 and ≥1).

Morbidity during pregnancy: information was collected through maternal self-report and confirmed by the review of prenatal and/or delivery hospital records. Vomiting and nausea were categorised as no and yes (at least one episode of vomiting and/or nausea during the first trimester of gestation). Information about diseases was analysed and classified by a physician (A.M.) according to the International Classification of Diseases, Tenth Revision (ICD-10).[36] Premature labour (code O60) was defined as labour that starts before 37 weeks' gestational age. Premature rupture of membranes (code O42) was defined as a spontaneous rupture that occurs before the onset of labour, but it

was not possible to know whether the cases were alive at the time of rupture of membranes. Bleeding included placenta praevia with haemorrhage (code O44.1) and placental abruption (code O45). Gestational hypertension included pre-eclampsia (code O14) and eclampsia (code O15). Gestational diabetes mellitus and anaemia were codes O24.4 and O99.0 respectively. Anaemia was defined as haemoglobin concentration <11.0 g/dL at any time during pregnancy or at birth for those pregnancies with no antenatal information.

Statistical analysis

Associations between fetal death and the independent variables were explored using the chi-squared test, with statistical significance defined as a two-tailed *P*-value below 0.05. Bivariable and multivariable analysis were carried out using logistic regression. Only potential confounders of the association between caffeine intake and fetal death were entered in the multivariable analysis taking into account the hierarchical relationship[37] between them, and were retained in the model if they reached at least 0.2 level of significance. Potential confounders were the variables associated with both fetal death and caffeine intake, and not an intermediate step in the causal link between caffeine intake and fetal death.[38] In the first level, we included family income, marital status, and maternal and partner's education; in the second level, maternal history of abortion and/or fetal death; in the third level, smoking and caffeine intake during pregnancy, vomiting/nausea during the first trimester of gestation and attendance for prenatal care.

The following variables were found not to act as confounders and were omitted from the adjusted analyses: crowding, maternal age, pre-gestational BMI, parity and morbidity during pregnancy (gestational hypertension, gestational diabetes, anaemia, premature labour, bleeding and premature rupture of membranes). Interaction terms between caffeine intake and both smoking and vomiting/nausea were introduced into the multivariable analysis to assess the potential effect modification. The linear effects of increasing levels of ordinal variables, such as caffeine intake and education on the risk of fetal death were examined using the chi-squared tests for trend.

All analyses were performed using STATA 8.0 for Windows (Stata Corporation, College Station, TX, USA) statistical software. This study was approved by the local authorities and the ethical committees of the institutions. Interviewers obtained informed consent from the mothers to complete the questionnaire and to obtain access to medical records. No data are available for women who refused to participate.

Results

A total of 382 cases and 792 controls were recruited in the study. For both cases and controls, the interviews were conducted in the first 24 h after birth. Due to early hospital discharge in the immediate postpartum period, mothers of four cases and three controls were interviewed at home, and for four cases and five controls, the interview was carried out by phone. Both home and phone interviews were performed in the first week after discharge. The study had 18 losses, 13 among the cases (6 refusals, 2 maternal deaths, 4 discharged before the interview and not found at the home address, and 1 could not answer due to severe psychiatric illness), and 5 among the controls (1 refusal, 4 discharged before the interview and not found at the home address).

Table 1 presents data on maternal characteristics, habits, pregnancy symptoms and complications. None of the variables had more than 2% of missing values. More cases than controls were single mothers, had lower family income, lower educational level, and their partners were less educated. Cases were slightly younger and had a more frequent history of adverse pregnancy outcomes than controls. More controls than cases had at least one prenatal consultation during pregnancy. The distribution of pre-gestational BMI and number of previous pregnancies were similar between cases and controls. The proportion of mothers who smoked during pregnancy was higher among cases. More cases than controls had vomiting/nausea during the first trimester, premature labour, bleeding and premature rupture of membranes. Anaemia was found more frequently in controls.

Mean caffeine intake from each source and from all sources together was highly correlated in the three trimesters of pregnancy ($P < 0.001$). Because of this, the results are based on the mean caffeine intake throughout pregnancy. Caffeine intake during pregnancy was significantly associated with fetal mortality ($P < 0.001$), and a dose–response effect of an increased risk of fetal death with higher caffeine intakes during pregnancy was observed (P for trend 0.001). Among cases, the proportion of women who did not consume caffeine during pregnancy was lower and the proportion of

Table 1 Characteristics of study subjects, Montevideo, Uruguay 2002–03

Variable	Cases ($N = 382$) *n* (%)	Controls ($N = 792$) *n* (%)	Unadjusted OR [95% CI]
Mean caffeine consumption during pregnancy (mg/day)***			
0	31 (8.1)	75 (9.5)	1.00 Reference
1–59	88 (23.0)	280 (35.4)	0.77 [0.47, 1.25]
60–149	73 (19.1)	168 (21.1)	1.06 [0.64, 1.75]
150–299	124 (32.5)	190 (24.0)	1.59 [0.98, 2.58]
≥300	66 (17.3)	79 (10.0)	2.06 [1.20, 3.51]
Family income***			
High	31 (8.2)	153 (19.4)	1.00 Reference
Medium	124 (32.6)	282 (35.7)	2.19 [1.40, 3.42]
Low	225 (59.2)	355 (44.9)	3.17 [2.07, 4.86]
Crowding[a]			
No	240 (63.2)	519 (65.7)	1.00 Reference
Yes	140 (36.8)	271 (34.3)	1.12 [0.86, 1.44]
Marital status[a]			
Stable union	303 (79.3)	666 (84.1)	1.00 Reference
Single mother	79 (20.7)	126 (15.9)	1.38 [1.00, 1.88]
Maternal education (years)***			
≤6	132 (34.6)	206 (26.0)	2.78 [1.93, 4.01]
7–11	194 (50.7)	342 (43.2)	2.45 [1.74, 3.45]
≥12	56 (14.7)	244 (30.8)	1.00 Reference
Partner's education (years)***			
≤6	110 (36.3)	165 (24.8)	3.09 [2.06, 4.65]
7–11	149 (49.2)	291 (43.7)	2.45 [1.67, 3.60]
≥12	44 (14.5)	210 (31.5)	1.00 Reference
Age (years)*			
<20	72 (18.8)	104 (13.1)	1.53 [1.09, 2.14]
20–34	253 (67.8)	575 (72.6)	1.00 Reference
≥35	50 (13.4)	113 (14.3)	1.01 [0.70, 1.45]
Pre-gestational BMI (kg/m^2)[a]			
<18.5	29 (7.7)	59 (7.5)	1.05 [0.66, 1.70]
18.5–24.9	235 (62.2)	511 (64.6)	1.00 Reference
25.0–29.9	83 (22.0)	160 (20.2)	1.12 [0.83, 1.53]
≥30	31 (8.1)	61 (7.7)	1.09 [0.69, 1.74]
Parity[a]			
0	137 (35.9)	324 (40.9)	1.00 Reference
1	85 (22.2)	182 (23.0)	1.10 [0.79, 1.53]
2–3	105 (28.3)	202 (25.5)	1.26 [0.92, 1.71]
≥4	51 (13.6)	84 (10.6)	1.47 [0.98, 2.19]
Previous abortions*			
0	150 (62.2)	335 (71.6)	1.00 Reference
≥1	91 (37.8)	133 (28.4)	1.52 [1.09, 2.12]
Previous fetal deaths**			
0	204 (84.6)	432 (92.3)	1.00 Reference
≥1	37 (15.4)	36 (7.7)	2.20 [1.35, 3.58]
Smoking during pregnancy*			
No	269 (70.6)	611 (77.2)	1.00 Reference
Yes	112 (29.4)	181 (22.8)	1.41 [1.07, 1.86]
Vomiting/nausea during the 1st trimester*			
No	146 (38.2)	358 (45.2)	1.00 Reference
Yes	236 (61.8)	434 (54.8)	1.34 [1.04, 1.73]
Gestational hypertension[a]			
No	292 (76.4)	636 (80.3)	1.00 Reference
Yes	90 (23.6)	156 (19.7)	1.26 [0.94, 1.69]

Table 1 *Continued*

Variable	Cases ($N = 382$) n (%)	Controls ($N = 792$) n (%)	Unadjusted OR [95% CI]
Gestational diabetes[a]			
No	369 (96.6)	762 (96.2)	1.00 Reference
Yes	13 (3.4)	30 (3.8)	0.92 [0.47, 1.78]
Anaemia*			
No	309 (80.9)	593 (74.9)	1.00 Reference
Yes	73 (19.1)	199 (25.1)	0.70 [0.52, 0.95]
Premature labour[a]			
No	309 (80.9)	664 (83.8)	1.00 Reference
Yes	73 (19.1)	128 (16.2)	1.22 [0.89, 1.68]
Bleeding**			
No	302 (79.1)	685 (86.5)	1.00 Reference
Yes	80 (20.9)	107 (13.5)	1.69 [1.23, 2.34]
Premature rupture of membranes***			
No	282 (73.8)	756 (95.5)	1.00 Reference
Yes	100 (26.2)	36 (4.5)	7.50 [5.0, 11.2]
Prenatal care***			
Yes	303 (79.5)	724 (91.4)	1.00 Reference
No	78 (20.5)	68 (8.6)	2.73 [1.92, 3.89]

[a]Variables not significant at 5% level.
BMI, body mass index.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

those who consumed ≥300 mg/day was higher than among controls. Among consumers of caffeine, mean caffeine intake did not change significantly during pregnancy, either among cases or among controls.

Table 2 shows the source and mean caffeine intake among cases and controls. Only a small proportion of the mothers (8.1% of the cases and 9.5% of the controls) did not consume caffeine during pregnancy. Among consumers, mate drinking was the most frequent source of caffeine both in cases and in controls. In women who consumed only coffee, the amount of caffeine consumed did not differ significantly between cases and controls, but in women who consumed only mate or both mate and coffee, mean caffeine intake was higher in cases than in controls. The amount of decaffeinated coffee consumed was negligible in both groups.

Coffee intake was associated with higher family income and education, whereas the habit of consuming mate was associated with lower income and fewer years of education in both cases and controls. Heavy caffeine consumers (≥300 mg/day throughout pregnancy) were more likely to have lower family income, to have fewer years of education, to be smokers and more often multiparae both in cases and in controls (data not shown).

Table 2 Type of source and mean caffeine intake in cases ($n = 382$) and controls ($n = 792$), Montevideo, Uruguay, 2002–03

	Cases			Controls		
Type of source of caffeine	n	%	Caffeine (mg/day)[a]	n	%	Caffeine (mg/day)[a]
No caffeine intake	31	8.1	–	75	9.5	–
Only coffee[b]	39	10.2	41.7	119	15.0	38.1
Only mate***	139	36.4	192.0	229	28.9	143.6
Both coffee and mate**	173	45.3	183.9	369	46.6	145.1
Total***	382	100	156.5	792	100	113.6

[a]Mean caffeine intake throughout pregnancy.
[b]Not significant at 5% level.
**Student's t-test $P < 0.01$, ***Student's t-test $P < 0.001$.

Women who smoked during pregnancy had higher intake of caffeine. Among controls, mean caffeine consumption per day throughout pregnancy was significantly higher among smokers (168.0 mg/day) than non-smokers (97.5 mg/day) ($P < 0.001$). Among cases, mean caffeine consumption per day was also significantly higher among smokers (216.1 mg/day) than non-smokers (131.6 mg/day) ($P < 0.001$). Potential effect modification by smoking on the association between caffeine intake and fetal death was investigated, and the interaction was included in the adjusted analysis.

Among cases, but not among controls, women who had vomiting/nausea during the first trimester of gestation had lower mean caffeine consumption throughout pregnancy (139.3 mg/day) than those who did not have this problem (184.5 mg/day) ($P = 0.005$). An interaction term between caffeine intake and vomiting/nausea was included in the adjusted analysis.

In the adjusted analysis (Table 3), among variables included in the first level of analysis, family income ($P = 0.6$) and marital status ($P = 0.9$) showed no association with fetal death. Higher ORs for fetal death were observed for less-educated mothers and/or partners, and a negative and significant trend was also detected ($P = 0.003$ for maternal education and $P = 0.004$ for the partner's education).

Among variables included in the second level of analysis, mothers with previous abortions and/or fetal deaths had a higher risk of fetal death than mothers without a history of these adverse pregnancy outcomes.

After controlling for all potential confounders, caffeine intake remained significantly associated with fetal death (P for trend <0.001). No interaction was found between caffeine intake and smoking ($P = 0.8$), and between caffeine intake and vomiting/nausea ($P = 0.3$).

Among preterm fetuses ($n = 319$), high consumption of caffeine during pregnancy (≥300 mg/day) was associated with fetal death (OR 2.13 [1.21, 3.75]), whereas among term fetuses ($n = 63$), this association was not significant (OR 1.71 [0.55, 5.33]).

Smoking during pregnancy, which was associated with fetal death in the crude analysis, showed no association after adjustment ($P = 0.5$). The risk of fetal death associated with caffeine intake ≥300 mg/day was similar in smokers (OR 2.28 [1.00, 5.98]) and non-smokers (OR 2.27 [1.08, 4.79]). Vomiting/nausea was not statistically significant ($P = 0.1$) after adjustment.

Table 3 Adjusted analysis for fetal death, Montevideo, Uruguay 2002–03

Variable	Adjusted OR [95% CI]
Mean caffeine consumption during pregnancy (mg/day)[a]	***
0	1.00 Reference
1–59	0.74 [0.42, 1.31]
60–149	0.93 [0.51, 1.67]
150–299	1.22 [0.69, 2.17]
≥300	2.33 [1.23, 4.41]
Maternal education (years)[b]	**
≤6	2.08 [1.28, 3.38]
7–11	1.86 [1.21, 2.85]
≥12	1.00 Reference
Partner's education (years)[b]	**
≤6	1.99 [1.21, 3.28]
7–11	1.70 [1.09, 2.65]
≥12	1.00 Reference
Previous abortions[c]	**
0	1.00 Reference
≥1	1.54 [1.07, 2.23]
Previous fetal deaths[c]	**
0	1.00 Reference
≥1	[1.28, 3.77]
Prenatal care[d]	***
Yes	1.00 Reference
No	2.38 [1.46, 3.90]

[a]Adjusted for maternal and partner's education, history of abortions and/or fetal deaths, vomiting/nausea during the first trimester and attendance for prenatal care.
[b]Adjusted for maternal and partner's education.
[c]Adjusted for maternal and partner's education, history of abortions/fetal deaths.
[d]Adjusted for maternal and partner's education, history of abortions and/or fetal deaths, vomiting/nausea during the first trimester and mean caffeine consumption during pregnancy.
**$P < 0.01$; ***$P < 0.001$.

Mothers who did not attend for prenatal care showed a higher risk of fetal death than mothers with at least one antenatal visit.

Discussion

Some methodological limitations of this study require discussion. Even though almost all cases and controls were interviewed in the first 24 h after delivery, and the time that elapsed between delivery and the interview did not differ between cases and controls, recall bias could have affected the study if cases tended to recall past exposure more accurately than controls. Due to specific warnings regarding cigarette smoking during pregnancy, mothers could have under-reported

their consumption. Despite this, the frequency of the habit found among controls was very close to the prevalence of cigarette smoking in pregnancy reported by mothers in Uruguay in 2000 (22.8% in the study vs. 25% in national data). On the other hand, in the absence of warnings about caffeine intake during pregnancy in Uruguay and 'mate drinking' being a national cultural habit, it is unlikely that mothers had underreported their caffeine consumption. Although we had to rely on reported caffeine consumption during pregnancy, attention was paid to reducing information error by carefully enquiring about the size of cup or drink, method of preparation and possible variations in consumption within each trimester of gestation.

The study found significant associations with previously reported and well-established risk factors for fetal death. As pointed out by other investigators,[10,11,18,39] less-educated women were at an increased risk of fetal death. Lack of knowledge about medical care and medical conditions and reduced comprehension of medical information are some of the mechanisms that may put these women at a higher risk.[40] Therefore, improving health workers' communication skills may improve women's understanding and their compliance with behaviour that promotes a safe pregnancy.[41]

In accordance with previous studies,[11,39,42] mothers with a history of abortions and fetal deaths and those who did not attend for prenatal care were at an increased risk of fetal death. Adequate antenatal care in an organised healthcare system potentially enables identification of high-risk patients during pregnancy. It may be possible to identify women at a particularly high risk (especially women after two fetal losses) at a time when an appropriate management of the gestation would allow opportunities for prevention in the current pregnancy. There are suggestions that using a combination of different methods of fetal surveillance, such as fetal heart rate monitoring, ultrasound biometry, amniotic fluid assessment, Doppler blood flow studies of fetal and uteroplacental circulation, and evaluation of biophysical fetal parameters lead to improvements in fetal morbidity and mortality.[43]

Our study found that high maternal caffeine consumption (≥300 mg/day) during pregnancy was associated with an increased risk of fetal death. Compared with the results from the crude analyses, there were no substantial changes of the caffeine-related estimates, suggesting that none of the adjustment variables acted as a strong confounder.

In spite of the faster metabolism of caffeine and its higher intake among smokers,[44] the risk of stillbirth associated with caffeine intake after adjustment was similar in smokers and non-smokers. This finding was also seen in a previous study.[20]

When the association between caffeine intake and fetal death was analysed separately for preterm and term antepartum fetal deaths, caffeine intake did not show a statistically significant association with term antepartum fetal death. However, due to the low number of term antepartum fetal deaths, it is possible that the study did not have sufficient power to study this association among these subgroups.

As occurs in any observational study, the possibility that some of the effects of caffeine on fetal death could be due to residual confounding, especially socio-economic, cannot be fully discarded. Nevertheless, the finding of a dose–response effect in our population, as well as of similar findings in other populations[17–20] with lower overall risks for fetal death and different patterns of caffeine consumption, suggests a real effect.

Mate drinking was the main source of caffeine in our population; this fact distinguishes our pattern of caffeine consumption from the countries where coffee and tea are the major sources of caffeine in the adult diet.[33] Mate drinking has long been a part of the Uruguayan culture. The fact that mate consumers differ from coffee consumers can be explained by the cost of each product (mate herb is cheaper than coffee). When we analysed separately the risk of fetal death in women who consumed only coffee, we did not find a significant risk of fetal death between cases and controls. But due to the low number of women who consumed only coffee and even lower proportion of high consumers from this source, the study did not have sufficient power to investigate this association alone.

One recent publication criticises the assumption that the effects observed after the ingestion of coffee must be due to caffeine, as there are many other substances in the beverage.[26] The mate herb, *Ilex paraguayensis*, as well as coffee, contains several other components besides caffeine, and it may be that these other components provide additional effects potentially harmful to the fetuses. Further studies should be carried out with mate and coffee contents before attributing the results to just one constituent.

To our knowledge, this is the first report of mate drinking as a source of caffeine being investigated in relation to fetal death. As mate drinking is widely distributed in Uruguay with high frequencies of con-

sumption among pregnant women, the association found with fetal death makes it a preventable risk factor in this population.

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