Nutrición Hospitalaria

Nutr Hosp. 2015;32(6):2658-2664
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original/*Pediatría*

Perinatal outcomes of prematurity and birth weight according to maternal caffeine consumption

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Abstract

Objetive: **identify whether there is an increased risk of adverse perinatal outcomes, like prematurity or decreased weight in newborns, associated with caffeine consumption during the first half of pregnancy in pregnant women of our population.**

Methods: **transversal study carried out in 1175 patients from Virgen de las Nieves University Hospital of Granada (Spain). Information about caffeine consumption during first half of gestation and perinatal outcomes was obtained by personal interview, medical records and telephone call after delivery. The average caffeine intake was calculated from meals and drinks included in a validated questionnaire.**

Results: **there was no difference in caffeine consumption in pregnant women with birth weight ≥2500 g and <2500 g, or in pregnant women with newborns appropriate for gestational age and small for gestational age, or in pregnant women with term and preterm delivery. When studying the birth weight as a dependent variable, adjusted for confounding variables, a significant association (p <0.05) with decreased birth weight was found (-87.7; 95% CI -159.8, -15.6 g) for caffeine consumption in the fourth quartile (115.01-650 mg/day).**

Conclusions: **there is no relation between caffeine intake and low birth weight, small for gestational age or prematurity, but a decrease in birth weight of mothers who consume large amounts of caffeine is observed.**

(*Nutr Hosp*. 2015;32:2658-2664)

DOI:10.3305/nh.2015.32.6.9846

Key words: *Caffeine. Perinatal outcomes. Birth weight. Prematurity.*

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Recibido: 6-IX-2015.
Aceptado: 9-IX-2015.

RESULTADOS PERINATALES DE PREMATURIDAD Y PESO DEL RECIÉN NACIDO SEGÚN EL CONSUMO DE CAFEÍNA DE LA GESTANTE

Resumen

Objetivo: **identificar si existe un aumento del riesgo en resultados perinatales adversos de prematuridad y disminución del peso de los recién nacidos asociados al consumo de cafeína durante la primera mitad del embarazo en gestantes de nuestra población.**

Métodos: **estudio transversal llevado a cabo en 1.175 gestantes del Hospital Universitario Virgen de las Nieves de Granada (España). La información sobre el consumo de cafeína durante la primera mitad del embarazo y los resultados perinatales estudiados se obtuvieron mediante entrevista personal, consulta de la historia clínica y llamada telefónica tras el parto. La ingesta media de cafeína se calculó a partir de las comidas y bebidas incluidas en un cuestionario validado.**

Resultados: **no hubo diferencias en el consumo de cafeína en gestantes con recién nacidos de peso ≥2.500 g y <2.500 g ni en gestantes con recién nacidos adecuados a la edad gestacional y pequeños para la edad gestacional, ni en gestantes con parto a término y pretérmino. Al estudiar el peso del recién nacido como variable dependiente, ajustada por las variables de confusión, se encontró una asociación significativa (p <0,05) con la disminución del peso al nacer (-87,7; 95% CI -159,8, -15,6 g) para el consumo de cafeína en el cuarto cuartil (115,01-650 mg/día).**

Discusión: **no hay relación entre el consumo de cafeína y el nacimiento de recién nacidos de bajo peso, pequeños para la edad gestacional o prematuros, pero sí se observa una disminución del peso del recién nacido de madres que consumen mayores cantidades de cafeína.**

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Palabras clave: *Cafeína. Resultados perinatales. Peso al nacer. Prematuridad.*

Abbreviations:

SGA: small for gestational age.
Non-SGA: appropriate for gestational age.
IUGR: intrauterine growth restriction.

Introduction

Caffeine is the most widely and accepted active substance used during pregnancy. It is present in foods and beverages such as coffee, cola drinks and chocolate. Its half-life increases during pregnancy and may reach 15 hours in the third trimester, due to a decrease in clearance time that results in elevated levels of circulating catecholamines, which may cause uteroplacental vasoconstriction and fetal hypoxia. In addition, caffeine goes through the placenta freely[1] and neither the fetus or placenta are able to metabolize it due to the cytochrome P450 1A2, a major enzyme in its metabolism, which is absent in both, so the fetus is exposed to caffeine and its metabolites for long periods during fetal life[2].

The first recommendation about consumption was made by the Food and Drug Administration of the United States, which recommended a maximum intake of 300 mg/day of caffeine during pregnancy, as currently recommend the World Health Organization[3]. However, this limit has been lowered in the last years by the American College of Obstetrics and Gynecology (ACOG) to 200 mg/day[4].

The results from studies about the caffeine effects on pregnancy are variable. While some found an increased risk of abortion, premature delivery and low birth weight[5-8], others do not find this association[9,10]. The inconsistency of these results is probably due to methodological flaws and confounders, such as tobacco, which are not considered in many studies.

The aim of this study is to evaluate if there is an increased risk of adverse perinatal outcomes like prematurity and birth weight loss associated with high caffeine consumption during the first half of pregnancy in pregnant women from our population.

Methods

We conducted a cross-sectional study in the catchment area of Virgen de las Nieves University Hospital (Granada, Spain). It provides medical coverage to the northern part of the province of Granada, with a population of 400,000 inhabitants, and approximately 4,000 births per year.

The reference population consists of healthy pregnant women living in this area and attending their 20th gestational week visit. According to the Integrated Healthcare Process "Pregnancy, Childbirth and Postpartum" of the Ministry of Health of the Government of Andalusia, all pregnant women should have an ultrasound examination at the hospital around the 20th week. Ethical approval was given to this study by the Ethic Committee of the University of Granada and the Ethic Committee of Virgen de las Nieves Hospital. Before participating, all women signed a written consent form.

The eligibility criteria were: singleton pregnancy, Spanish nationality, being over 18 years old, absence of complicated pregnancies that required rest, and absence of metabolic, chronic or acute diseases that might limit one´s daily activities. From the original set of potential women, one of every five women was systematically recruited, selecting one out of five according to the visit order of those coming to the hospital for their ultrasound visit. During the recruitment period, a total of 1,222 women were thus selected from the reference population. Finally, 1,175 of them fulfilled the selection criteria and wished to take part in the study.

All these pregnant women were contacted by two previously trained interviewers, right before the ultrasound examination. After agreeing to participate, each woman was interviewed face to face, and a structured questionnaire was used to collect the data. Pilot samples of 50 women (not included in the present study) were previously interviewed during a 2-month period of time so as to train the interviewers and check the consistency of the gathered information.

Some information about social-demographic, obstetric and lifestyles variables (tobacco, diet, alcohol and physical activity during the first half of the pregnancy and the previous year of the latter) were collected. The diet information was gathered by a Food Frequency Questionnaire previously translated, adapted and validated in a sample of Spanish women aged 18-64, and used in other studies among the Spanish population[11]. The eating frequency and the intake amount of 118 types of food and drinks were registered. Not only were participants asked about the frequency and the intake amount during the previous year and the first half of the pregnancy, they were also asked to report the intake frequency in terms of daily, weekly or monthly. For each category, there were provided several examples of the food quantity that is equivalent to one portion. The average intake was calculated for each food group.

Caffeine sources included in the questionnaire were: cola, diet caffeinated cola, coffee, decaffeinated coffee, chocolate, and chocolate biscuits. The amount of caffeine (mg/day) consumed by the pregnant women was calculated based on the table of contents of caffeine in foods by Harland[12].

Current smokers were defined as those who smoked at least one cigarette per day, and ex-smoker those who had stopped the habit before or at the start of pregnancy. Academic level women were registered as: primary academic level (eight years or less of basic education), secondary (four years of secondary education) and university (graduate or postgraduate studies). Social status was classified from lowest (V) to highest (I). The social level I consists on managers of public

administration and companies with 10 or more employees, as well as professions associated with second and third university cycle. Company managers with fewer than 10 employees**,** professionals associated with a junior college degree, senior technicians, artists and sportswomen form the social level II. Social level III consists on administrative employees and management professionals. Social level IV consists on skilled manual workers and social level V is formed by unskilled workers. Previous pregnancies and miscarriages were also taken into consideration. Body mass index (BMI) was calculated as weight (in kg) just before the pregnancy divided by height (in m^2). Both, weight and height were obtained from the women medical records. Cut-off points set by the World Health Organization were used to determine overweight and obese women. Women with BMI ≥30 kg/m^2 were classified as obese, and those with BMI ≥25 kg/m^2 but ≤30 kg/m^2 were classified as overweight.

Pregnant women were then classified in view of caffeine intake, as <200 mg/day or ≥200 mg/day, the latter being the maximum amount recommended by expert groups during gestation[4] and as their daily consumption by quartile. They were classified according to newborns weight being greater or less than 2,500 g. Spanish tables for birth weight for gestational age were used, developed by the Spanish Society of Gynecology and Obstetrics[13], and the 10th percentile was the cut-off point for small fetuses for gestational age (SGA) and appropriate ones for gestational age (Non-SGA). Preterm birth was considered as happened before the 37th week.

Perinatal outcomes were collected from the patients' medical records and, if necessary, completed by telephone interview with the woman.

A descriptive analysis of the sample was performed. The distributions were calculated in order to get qualitative variables, absolute and relative frequencies. The arithmetic mean, standard deviation (SD) and range were calculated in order to get quantitative variables.

To compare the average caffeine consumption in the case of categorical variables, the ANOVA test was used. When significant differences among groups were identified, the Bonferroni correction was applied to identify differences among categories. The significance was set at $p < 0.05$. The crude and adjusted odds ratios and confidence intervals (95% CI) were calculated using a polytomous regression model to identify factors associated with consumption equal to or greater than 200 mg/day. Epidemiological and statistical criteria such as model selection variables were used. Analyses were performed using the statistical package SPSS.15.

Results

During the first half of the gestation, 1,120 of 1,175 pregnant women consumed caffeine (95.3%), and the consumption mean was 72.57 mg/day (SD 92.7; range 0.1-650 mg/day), being the average intake before pregnancy of 150.05 mg/day (SD 141.1; range 0.1-872 mg/day). The average birth weight was 3,218.8 g (SD 496.6) and the mean gestational age was 39.3 weeks (SD 1.8).

Table I shows the relation between the variables studied, excluding caffeine, and SGA newborns, being significant ($p < 0.05$) only the consumption of tobacco during pregnancy.

There was no significant difference in caffeine consumption in pregnant women with birthweight newborns >2,500 g (72.49 mg, SD 92.45) and <2,500 g (80.55 mg, SD 91.02),even by adjusting the weight for gestational age. Caffeine intake in pregnant women with Non-SGA newborns was 72.63 mg (SD 92.92 mg) and in pregnant women with SGA newborns was 80.38 mg (SD 87.42).

Regarding gestational age birth, no significant differences between caffeine intake of pregnant women with term delivery (72.64 mg, SD 92.10) and preterm delivery (73.72 mg, SD 94.40) were found.

When considering whether caffeine intake of pregnant women was <200 or ≥ 200 mg/day, there were no significant differences among perinatal outcomes of gestational age and birth weight (Table II).

No significant differences between daily caffeine intake of pregnant divided by quartiles and perinatal outcomes of gestational age and birth weight were found (Table III).

No relation between daily consumption of caffeine divided by quartiles and SGA infants, in crude nor in the adjusted analysis, was found (Table IV).

When studying the birth weight as the dependent variable, adjusted for confounding variables, a significant association ($p < 0.05$) with decreased birth weight (-87.7; 95% CI -159.8, -15.6 g) was found with caffeine consumption in the fourth quartile (115.01-650 mg/day) (Table V).

Discussion

Several studies have attempted to establish the association between caffeine consumption and adverse perinatal effects with variable results. Caffeine goes through the placenta and its life expectancy is increased during pregnancy. By increasing catecholamine levels, it may cause uteroplacental vasoconstriction and fetal hypoxia, which would result in fetal growth restriction. Restricting birth weight is associated with increased mortality and neonatal morbidity and other adverse outcomes such as metabolic and cardiovascular diseases in adults[14]. Therefore, it is important to know the impact of caffeine on fetal development and its effects on weight and gestational age.

In this work the effects of caffeine consumption during the first half of gestation in fetal weight and gestational age are analyzed. It was observed a de-

Table I
Selected maternal and infant characteristics of the study population with small for gestational age newborns

	SGA		*Non-SGA*		
	n	*%*	*n*	*%*	*p*
Maternal age (y)					
<25	16	9.9	146	90.1	
25-29	36	11.3	282	88.7	
30-34	47	11.9	346	88.1	ns
35-39	27	15.1	152	84.9	
≥40	1	6.7	14	93.3	
Educational level					
University	31	10.2	274	89.8	
Secondary	43	13.7	271	86.3	ns
Primary	53	11.8	395	88.2	
BMI					
18-24.9	91	12.7	626	87.1	
25-29.9	26	10.7	217	89.3	ns
≥30	10	9.4	97	90.6	
Smoking					
No	52	11.2	413	88.8	
Ex-smoker	41	10.3	357	89.7	<0.05
Yes	34	16.7	170	83.3	
Infant sex					
Female	70	12.4	495	87.6	ns
Male	57	11.4	444	88.6	
Parity					
0	78	13.5	501	86.5	
1	41	10.9	334	89.1	ns
2	7	7.3	89	92.7	
≥3	1	5.9	16	94.1	
Alcohol					
No	120	11.9	889	88.1	ns
Yes	7	12.1	51	87.9	
Total	127	11.9	940	88.1	

n = number; % = percentage.

Table II
Perinatal outcomes depending on the caffeine intake lower than 200 or ≥ 200 mg/day

	Birth weight infant		*Birth weight infant*		*Weeks of gestation*		*p*
	≥2500 g	*<2500 g*	*Non-SGA*	*SGA*	*≥37*	*<37*	
< 200 mg/day n (%)	915 (94.3)	55 (5.7)	845 (87.9)	116 (12.1)	911 (94.2)	56 (5.8)	ns
≥ 200 mg/day n (%)	99 (94.3)	6 (5.7)	95 (89.6)	11 (10.4)	98 (92.4)	8 (7.6)	ns
Total n (%)	1014 (94.3)	61 (5.7)	940 (88.1)	127 (11.9)	1009 (94)	64 (6)	
	1075		1067		1073		

n (%) = number (percentage).

Table III
Perinatal outcomes as caffeine intake (mg/ day) divided by quartiles

	Birth weight infant		*Birth weight infant*		*Weeks of gestation*	
	≥2500 g n (%)	*<2500 g n (%)*	*Non-SGA n (%)*	*SGA n (%)*	*≥37 n (%)*	*<37 n (%)*
0-7	259 (95.9)	11 (4.1)	236 (89.4)	28 (10.6)	252 (94)	16 (6)
7.01-29	248 (93.9)	16 (6.1)	242 (90.9)	24 (9.1)	249 (93.3)	18 (6.7)
29.01-115	258 (93.5)	18 (6.5)	236 (86.1)	38 (13.9)	257 (93.5)	18 (6.5)
115.01-650	249 (93.9)	16 (6.1)	226 (85.9)	37 (14.1)	251 (95.4)	12 (4.6)
Total	1014 (94.3)	62 (5.7)	940 (88.1)	127 (11.9)	1009 (94)	64 (6)
	1075		1067		1073	

n (%) = number (percentage).

Tabla IV
Crude and adjusted associations between caffeine consumption divided by quartiles, and low birth weight

	Odds ratio crude	*95% CI*	*Odds ratio adjusted*	*95% CI*
Quartile 1 0-7 mg/day	1	Reference	1	Reference
Quartile 2 7.01-29 mg/day	0.84	0.47-1.48	0.93	0.52-1.69
Quartile 3 29.01-115 mg/day	1.36	0.81-2.28	1.63	0.94-2.82
Quartile 4 115.01-650 mg/day	1.38	0.82-2.33	1.71	0.96-3.05

Tabla V
Difference in birth weight as caffeine intake by quartiles

	Crude coefficient	*95% CI*	*Adjusted coefficient*	*95% CI*
Quartile 1 0-7 mg/día	1	Reference	1	Reference
Quartile 2 7.01-29 mg/día	-5.84	-90.08; 78.41	-18.18	-86.51; 50.14
Quartile 3 29.01-115 mg/día	-26.98	-110.37; 56.42	-59.09	-127.57; 9.39
Quartile 4 115.01-650 mg/día	-44.48	-128.80; 39.84	-87.73*	-159.82; -15.65

* $p<0.05$.

creased fetal weight in pregnant women who consume this substance, which gets even lower as the amount of caffeine intake increases. Pregnant women with a higher caffeine intake than 115 mg/day have decreased fetal weight of 87.7 g compared to pregnant women who do not consume, which is significant and adjusted for confounding factors such as tobacco and alcohol. However, although significant, this result does not seem to be clinically relevant.

This finding would be comparable to the results of Bracken et al.[8] who also reported a decrease in fetal weight of 28 g per cup of coffee daily in pregnant women, although statistically significant, it did not appear to have clinical significance. Except in women who ingest more than 600 mg of caffeine daily, amount equivalent to 10 cups of coffee, which would mean a total loss of 170 g, similar to what occurs when smoking 10 cigarettes a day. Similarly, the CARE study group[6] found that caffeine consumption above 200 mg/day produced a decrease in fetal weight of 60-70 g. This weight loss increases with high consumption of this substance, which would be comparable to the findings of our study in Spanish population.

Other studies found a clear association between the intake of this substance and adverse outcomes. Bakker et al.[7] conclude that consuming more than 6 cups of coffee a day (540 mg) is associated with impaired fetal length growth (first-trimester crown-rump length and second- and third-trimester femur length and birth length) and weight of newborn. Sengpiel et al.[15] conclude that caffeine intake is associated with lower birth weight, with clinical implications when the recommended amount during this period (200 mg/day) is exceeded. Just as Hoyt et al.[16], who observed an increase in SGA infants in mothers with greater than 300 mg/day caffeine intake. Vic et al.[17] conclude that there is an increased risk of SGA in male fetuses associated with a high caffeine intake, due to a higher growth rate in males during the third trimester, which would make them more vulnerable to it.

However, there are studies that have not found this association between caffeine intake and decreased fetal weight[8,10,18-20]. Bech et al.[21] found no association between caffeine and low birth weight, although they found a slight decrease in the weight of newborns of mothers who smoke and consume caffeine. This effect could be due to paraxanthine, metabolite of caffeine, which is elevated in smokers, due to an increase in its metabolism. Similarly, Grosso et al.[22] demonstrated an association between high levels of paraxanthine with increased risk of intrauterine growth restriction (IUGR), while caffeine seems to have a protective effect. These findings may suggest that the metabolic activity of cytochrome P450 1A2 (CYP1A2) may be associated with IUGR.

Furthermore, maternal exposure to caffeine appears to play a role in the activity of an important placental enzyme, 11β- hydroxysteroid dehydrogenase-2 (11-β-HSD-2), involved in the regulation of fetal growth[23,24]. In a study conducted in pregnant rats that were administered caffeine intragastrically, corticosterone concentration increased in fetal and maternal blood and decreased the expression of 11-β-HSD-2 placental[25]. This decrease in the activity of 11-β-HSD-2 has been associated with decreased fetal growth in humans, although further studies are needed to clarify the mechanism by which may occur.

In summary, this small effect found in decreased fetal weight in pregnant women who consume large amounts of caffeine during the first half of pregnancy, may explain why some studies find significant effects of caffeine intake while others do not.

As for preterm labor, in our study no relation associated with caffeine was found consumption. Maslova et al.[9] in a meta-analysis of 22 studies (15 cohort and 7 case-control) found no association, the same as Bech et al.[21] and Clausson et al.[10]. Eskenazi et al[26] report an increase in preterm labor in pregnant women who drank coffee, both caffeinated and decaffeinated, suggesting that this increase could be due to other coffee agents unrelated with caffeine. Furthermore, Sengpiel et al.[15] also found an association between coffee intake, not caffeine, and a slight increase in gestation time.

Jahanfar and Jaafar[27], in the latest Cochrane revision, claim that there is not sufficient evidence to confirm or refute the effectiveness of removing caffeine during pregnancy on birth weight or other perinatal outcomes evidence.

Regarding methodological considerations of this study, it should be noted that although there is no clear evidence of the effects of a high intake of caffeine, the limit of 200 mg/day established by the ACOG[4] was followed. The results were adjusted for confounding factors such as tobacco, which has a known effect on decreased fetal weight. Furthermore, both habits are associated in pregnant women and it has been found that in smoking pregnant patients who smoke, the CYP1A2 enzyme activity is altered. This increases the caffeine clearance and due to this the paraxanthine levels are increased. Paraxanthine is the active substance, so higher rates of adverse effects would be found in the fetus when levels are increased[2].

On the other hand, we must consider the difficulty of assessing fetal exposure to caffeine, due to the heterogeneity of maternal caffeine intake. This is due to the wide variation in caffeine content and the differences in the serving sizes and the different sources. The caffeine content may vary depending on the method of preparation of coffee, grain type or brand of cola[8]. In addition, caffeine intake estimated from sources consumed by the mother cannot accurately predict fetal exposure because it doesn't predicts how much caffeine or its metabolites are actually in the fetal circulation[2]. Therefore, fetal exposure depends not only on maternal consumption, but also on the rate of metabolism in the pregnant woman and substance clearance of fetal circulation. Many endogenous and exogenous factors affect the metabolism of caffeine, such as tobacco, liver disease or certain drugs, as well as pregnancy, that decreases its metabolism due to reduced activity of cytochrome P-450-1A2[28].

This sample is representative of all healthy women in reference to the area of Virgen de las Nieves University Hospital (Granada, Spain). Therefore, these results can be extrapolated to this population. All the information was collected by personal interviewers and the average caffeine intake was calculated from meals and drinks included in the questionnaire of Martin Moreno et al.[11], previously validated in Spanish population. Herbal supplements, tea, energy drinks and drugs were excluded because it was found in the pilot phase that their contribution to caffeine consumption was very low in Spanish population. The study was conducted in Spanish pregnant women due to the different sociocultural characteristics, however the results are consistent with those found in other observational studies in other countries with different sociocultural characteristics.

On the other hand, in this study only the caffeine consumption during the first half of gestation is eva-

luated because, after that moment, the dietary habits are usually kept[29], and the time to make the consumption records is lower and there is no interference with pregnancy outcomes, as when it is done at the end of it.

Although the results of the different studies are not conclusive, in general there seems to be a tendency to birth weight decrease in the fetuses of mothers who consume large amounts of caffeine. While these results are significant in some studies they do not seem to have important clinical implications, but pregnant women should be informed of the risks of caffeine consumption, especially in large amounts.

Acknowledgements

This research was funded by FIS Scientific Research Project PI 03/1207 and Junta de Andalucía Excellence Project CTS 05/942.

Authors' contributions

All the authors have seen and approved the content and contributed to the production of this piece of work.

Interest conflict

We declare that there are no conflicts of interest to disclose.

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