View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Via Medica Journals

Comparison of maternal and fetal blood levels of caffeine and its metabolite. A pilot study

Porównanie stężenia kofeiny i jej metabolitu we krwi matki i noworodka. Badanie pilotażowe

Regina Wierzejska[1], Mirosław Jarosz[1], Magdalena Siuba[1], Włodzimierz Sawicki[2]

[1] Department of Nutrition and Dietetics with Clinic of Metabolic Diseases and Gastroenterology, National Food and Nutrition Institute, Warsaw, Poland
[2] Clinic of Obstetrics, Gynecology and Oncology, 2nd Faculty of Medicine, Medical University of Warsaw, Poland

Abstract

Objective: *The aim of the study was to compare caffeine and paraxanthine concentrations in venous blood of pregnant women and in the umbilical cord blood of their newborns.*

Materials and Methods: *Pregnant women who gave birth at the Clinic of Obstetrics, Gynecology and Oncology, 2nd Faculty of Medicine, Medical University of Warsaw were included in the study. Caffeine and paraxanthine concentrations were analyzed in 30 samples of venous blood serum drawn from the women before delivery and 30 samples of umbilical cord blood serum of their newborns. Caffeine intake in the last 24 hours before delivery was estimated using a questionnaire. Statistical analysis employed a linear logistic regression model, Wilcoxon rank sum test and a non-parametric Spearman's rank correlation coefficient.*

Results: *No difference was found between caffeine concentration in maternal venous blood and neonatal umbilical cord blood. However, paraxanthine level in venous blood was higher than in umbilical cord blood ($p = 0.04$).*

Conclusions: *Caffeine consumed by a pregnant woman passes through the placenta to the fetus freely.*

Key words: **caffeine** / **paraxanthine** / **blood** / **pregnancy** / **newborn** /

Streszczenie

Cel: *Porównanie stężenia kofeiny i jej metabolitu (paraksantyny) we krwi żylnej kobiet ciężarnych i krwi pępowinowej noworodków.*

Corresponding author:
Regina Wierzejska
National Food and Nutrition Institute
Powsińska St. 61/63, 02-903 Warsaw, Poland
Tel. +48 22 550 97 47 Fax: +48 22 842 11 03
e-mail: rwierzejska@izz.waw.pl

Otrzymano: **11.12.2013**
Zaakceptowano do druku: **04.03.2014**

© Polskie Towarzystwo Ginekologiczne

Materiał i metody: *W badaniu wzięło udział 30 pacjentek rodzących w Klinice Położnictwa, Chorób Kobiecych i Ginekologii Onkologicznej II Wydziału Lekarskiego Warszawskiego Uniwersytetu Medycznego (analizie poddano 30 zestawów krwi „matka-dziecko"). Spożycie kofeiny przez kobiety ciężarne zostało oszacowane za pomocą wywiadu o spożyciu z ostatnich 24 godzin. W analizie statystycznej wykorzystano wieloczynnikowy model regresji logitowej, korelację liniową Spearmana, test sumy rangowych znaków Wilcoxona.*

Wyniki: *Nie stwierdzono różnicy w stężeniu kofeiny pomiędzy krwią żylną kobiet i pępowinową noworodków, natomiast stężenie paraksantyny we krwi matek było większe niż we krwi noworodków (p = 0,04).*

Wnioski: *Kofeina spożywana przez kobietę ciężarną swobodnie przenika przez łożysko do płodu.*

Słowa kluczowe: **kofeina/paraksantyna/krew/ciąża/noworodek** /

Introduction

Caffeine is the most common psychoactive substance in human diet and it is consumed by the majority of pregnant women [1, 2]. In the liver, caffeine is metabolized to paraxanthine, which is its primary metabolite and accounts for 72-80% of caffeine metabolism [3]. Maternal elimination of caffeine is notably decreased during pregnancy. The half-life of caffeine changes from 5 to 18 hours in the third trimester of pregnancy and is conditioned by numerous endogenous and exogenous factors [2,4]. Caffeine and its metabolites are transferred through the placenta to the fetus, the amniotic fluid and also to the breast milk [4-6]. The fetus, due to the immaturity of its liver, is unable to metabolize caffeine, so it remains in the fetal body much longer [3,7-9]. As the period of maternal and fetal exposure to caffeine is prolonged during pregnancy, pregnant women should limit its intake [4, 10, 11].

The influence of caffeine on pregnancy has not been definitely determined. While some studies show that high intake of caffeine may result in miscarriage, preterm birth, or deterioration of fetal growth [1, 2, 12], others do not prove that theory [10, 12-14]. In the opinion of some experts, fetal exposure to caffeine depends not only on the maternal intake, but also its metabolism in her body [3]. However, data about a relationship between concentration of caffeine and its metabolites in the maternal and umbilical cord blood and the outcome of pregnancy remain unclear [15-17].

Caffeine and paraxanthine levels are easily measured in the serum [3]. Their concentration in the umbilical cord blood of a newborn reflects the actual fetal exposure to caffeine more precisely than the result established on the basis of maternal caffeine intake. The concentration of those markers in the umbilical cord blood shows the extent to which they are transferred through the placenta to the fetus [15]. Data from the literature demonstrate a balance between caffeine concentration in maternal and fetal blood, but research on that topic remains scant [18,19].

Objectives

The aim of the study was to compare the concentrations of caffeine and its major metabolite (paraxanthine) in venous blood of pregnant women and umbilical cord blood of their newborns and to analyze the factors which may influence their blood levels.

Material and methods

The study population consisted of women participating in a study concerning caffeine intake conducted at the Clinic of Obstetrics, Gynecology and Oncology, 2nd Faculty of Medicine, Medical University of Warsaw [20]. Our sample included 30 mothers of full-term singletons who volunteered for the study. Characteristics of some parameters of the participants are presented in Table I. The approval of the Ethics Committee of the National Food and Nutrition Institute was obtained.

Caffeine and paraxanthine content was analyzed in 30 samples of venous blood serum drawn from the women before delivery and 30 samples of umbilical cord blood serum of their newborns drawn at delivery (mother-child blood sample sets). Caffeine and paraxanthine content was determined by reversed phase high performance liquid chromatography (HPLC) using 2695 Waters liquid chromatograph with a PAD detector at the National Food and Nutrition Institute. Caffeine and paraxanthine detection threshold in this method is 0.01 μg/ml.

Table I. Characteristics of the pregnant women (Charakterystyka kobiet ciężarnych).

N=30	Range
Maternal age [years]	19 – 38
Caffeine intake in the last 24 hours [mg]	0 – 224
Caffeine concentration in venous blood [μg/ml]	0.02 –6.4
Caffeine concentration in umbilical cord blood [μg/ml]	0.05 – 7.22
Paraxanthine concentration in venous blood [μg/ml]	0.01 – 1.45
Paraxanthine concentration in umbilical cord blood [μg/ml]	0.01 – 1.19
Number of women smoking during pregnancy	6
Pregnancy length [weeks]	37 – 42
Neonatal body weight [g]	2550 – 4466
Apgar score	9-10

© Polskie Towarzystwo Ginekologiczne

Among the factors which may affect caffeine and paraxanthine concentration in blood, the following were analyzed: maternal caffeine intake in the last 24 hours and the time that elapsed between drawing venous blood and umbilical cord blood.

Caffeine intake was estimated on the basis of a questionnaire on the frequency of consumption of products containing caffeine in the last 24 hours before delivery. The questionnaire employed the face-to-face method. The caffeine content in the products which are main sources of caffeine was established through our own analyses [20], while for the products whose consumption was reported as 'low' the caffeine content was established according to the data in the literature [21-23]. Data on pregnancy length, birth weight and Apgar score of the newborns were derived from patient records.

Differences in caffeine and paraxanthine concentrations between venous blood and umbilical cord blood were analyzed using the Wilcoxon rank sum test. The non-parametric Spearman's rank correlation coefficient was used to assess the existence of a relationship between caffeine and paraxanthine concentration in venous and umbilical cord blood and between caffeine intake. Differences between paraxanthine concentration in venous blood and umbilical cord blood were analyzed using the linear regression model of the relationship with the time between drawing venous blood and umbilical cord blood.

The significance level was assumed at 5%, the tests were two-sided. Calculations were made using Stata v.10 [24].

Results

Our study did not reveal a difference between caffeine concentration in maternal venous blood and neonatal umbilical cord blood. However, it found the concentration of the major metabolite of caffeine (paraxanthine) to be higher in venous blood than in the umbilical cord blood. (Figure 1)

The differences in paraxanthine concentration between venous blood and umbilical cord blood did not depend on the time elapsed between drawing venous blood and umbilical cord blood (average 4.9 hours) ($p > 0.1$). Neither caffeine and paraxanthine concentration in venous blood of the women nor in the umbilical cord blood of their newborns was linearly dependent on caffeine intake in the last 24 hours of pregnancy.

Discussion

The absence of differences between caffeine concentrations in maternal venous blood and neonatal umbilical cord blood confirms that placenta does not constitute a barrier for caffeine, which is easily transmitted to the fetus. Data from the literature comparing the concentration of caffeine and its metabolites in maternal and fetal blood are scant. The balance between caffeine concentration in maternal and fetal blood serum as soon as at 7 –8 weeks of pregnancy was determined in the 1960s by Goldstein and Warren [18].

We confirmed such a balance on the day of delivery. In our study, average caffeine levels in maternal venous blood were comparable to average concentrations reported by Klebanoff et al. [6]. As far as caffeine and paraxanthine concentrations in the umbilical cord blood are concerned, our findings are similar to the results obtained by Grosso et al. [9]. Higher concentration of paraxanthine in venous blood of the mother is conditioned by their metabolism of caffeine.

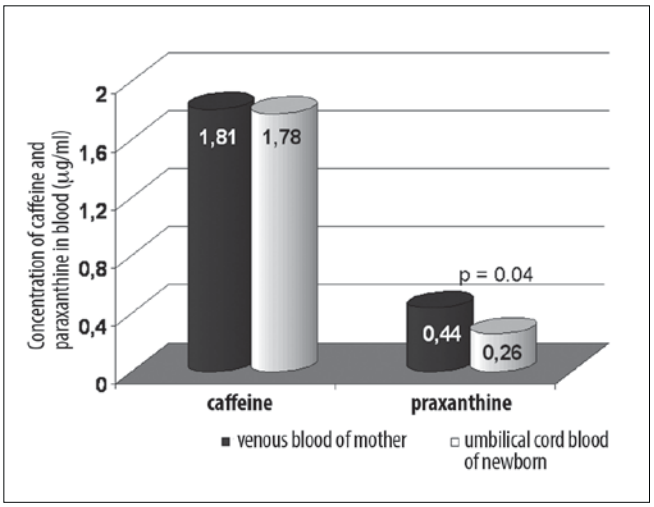

Figure 1. Average caffeine and paraxanthine concentration in blood.

In our study, caffeine intake declared by pregnant women in the last 24 hours before delivery did not affect caffeine and paraxanthine concentrations in venous blood of the mothers and umbilical cord blood of their newborns. These results are contrary to the findings of Klebanoff et al., and Grosso et al., who reported that increased caffeine intake resulted in an elevated concentration of caffeine and paraxanthine in maternal blood serum or, accordingly, fetal umbilical cord blood [6,9]. Lack of clear relationship between caffeine intake and its level in blood in our study may have resulted from the fact that the majority of women consumed small amounts of caffeine. At such consumption as in case of our study population the differences in caffeine concentrations may be less visible as compared to other studies. Moreover, some reports in the literature indicate that concentrations of caffeine and its metabolites in body fluids may differ from the expected findings, which are based on the data reported in the questionnaire. In the study by Klebanoff et al., caffeine was present in the serum of 7 out of 10 women who reported no caffeine intake in their diet. These authors also stressed that caffeine is not perfectly correlated with the declared intake due to considerable individual differences in caffeine metabolism in humans [6]. It should be also underlined that caffeine concentration in the blood of adults reaches its maximum level in the initial hours after consumption and subsequently decreases at a fast pace. Thus, its concentration in blood largely depends on the time that elapses between caffeine intake and drawing blood. Moreover, towards the end of pregnancy caffeine metabolism of pregnant women is much slower. Thus, its concentration in blood may not reveal a direct relationship between caffeine intake. We should also consider that caffeine metabolism depends on individual characteristics and environmental conditions, which may interfere with the relationships between caffeine intake and its concentration in body fluids.

A sample size was the main limitation of our study. Therefore, the conclusions are preliminary in nature and require further confirmation.

The strength of the study lies in estimating maternal caffeine intake on the basis of analytically determined caffeine content in

© Polskie Towarzystwo Ginekologiczne

products available on the local market. Also, in case of coffee and tea, analyses were conducted on infusions prepared with the use of the same methods as those reported by the respondents. The brewing method is largely the factor behind caffeine content.

Conclusions

Placenta does not constitute a barrier for caffeine and allows for it to be freely transmitted from the mother body to the fetus, confirming that the mother and the fetus alike are exposed to the effect of caffeine.

Oświadczenie autorów

1. Regina Wierzejska – autor koncepcji i założeń pracy, zebranie materiału, analiza i interpretacja wyników, przygotowanie manuskryptu i piśmiennictwa – autor zgłaszający i odpowiedzialny za manuskrypt.
2. Mirosław Jarosz – autor koncepcji i założeń pracy, współautor tekstu pracy.
3. Magdalena Siuba – analiza i interpretacja wyników, przygotowanie manuskryptu, przechowywanie dokumentacji.
4. Włodzimierz Sawicki – ostateczna weryfikacja i akceptacja manuskryptu.

Źródło finansowania:

Badania statutowe Instytutu Żywności i Żywienia – C3/K.

Konflikt interesów:

Autorzy nie zgłaszają konfliktu interesów oraz nie otrzymali żadnego wynagrodzenia związanego z powstawaniem pracy.

References

1. Care Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. doi: 10.1136/bmj.c2331.
2. Bakker R, Steegers E, Obradov A, [et al.]. Maternal caffeine intake from coffee and tea, fetal growth, and the risks of adverse birth outcomes: the Generation R Study. *Am J Clin Nutr.* 2010, 91, 1691-1698.
3. Grosso L, Bracken M. Caffeine metabolism, genetics and perinatal outcomes: a review of exposure assessment considerations during pregnancy. *Ann Epidemiol.* 2005, 15, 460-466.
4. Nawrot P, Jordan S, Eastwood J, [et al.]. Effects of caffeine on human health. *Food Addit Contam.* 2003, 20, 1-3.
5. Higdon J, Frei B. Coffee and health: A review of recent human research. *Crit Rev Food Sci Nutr.* 2006, 46, 101-123.
6. Klebanoff M, Levine R, DerSimonian R, [et al.]. Serum caffeine and paraxanthine as markers for reported caffeine intake in pregnancy. *Ann Epidemiol.* 1998, 8, 107-111.
7. Hinds T, West W, Knight E, Harland B. The effect of caffeine on pregnancy outcome variables. *Nutr Rev.* 1996, 54, 203-207.
8. Kirkinen P, Jouppila P, Koivula J, [et al.]. The effect of caffeine on placental and fetal blood flow in human pregnancy. *Am J Obstet Gynecol.* 1983, 147, 939-942.
9. Grosso L, Triche E, Benowitz N, Bracken M. Prenatal caffeine assessment: fetal and maternal biomarkers or self-reported intake? *Ann Epidemiol.* 2008, 18, 172-178.
10. Maslowa E, Bhattacharya S, Lin S, Michels K. Caffeine consumption during pregnancy and risk of preterm birth: a meta-analysis. *Am J Clin Nutr.* 2010, 92, 1120-1130.
11. Karowicz-Bilińska A, Nowak-Markwitz E, Kędzia W, [et al.]. W odpowiedzi na artykuł „Potrzeba działań z zakresu prenatalnego zdrowia publicznego w Polsce." *Ginekol Pol.* 2012, 83, 953-955.
12. Bracken M, Triche E, Belanger K, [et al.]. Association of maternal caffeine consumption with decrements in fetal growth. *Am J Epidemiol.* 2003, 157, 5, 456-466.
13. Mills J, Holmes L, Aarons J, [et al.]. Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993, 269, 5, 593-957.
14. Clausson B, Granath F, Ekbom A, [et al.]. Effect of caffeine exposure during pregnancy on birth weight and gestational age. *Am J Epidemiol.* 2002, 155, 5, 429-436.
15. Grosso L, Triche E, Belanger K, [et al.]. Caffeine metabolites in umbilical cord blood, cytochrome P-450 1A2 activity and intrauterine growth restriction. *Am J Epidemiol.* 2006, 163, 7, 1035-1041.
16. Klebanoff M, Levine R, Clemens J, Wilkins D. Maternal serum caffeine metabolites and small-for-gestational age birth. *Am J Epidemiol.* 2002, 155, 1, 32-37.
17. Cook D, Peacock J, Feyerabend C. Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. *BMJ.* 1996, 313, 1358-1362
18. Goldstein A, Warren R. Passage of caffeine into human gonadal and fetal tissue. *Biochem Pharmacol.* 1962, 11, 166-168.
19. Kuczkowski K. Caffeine in pregnancy. *Arch Gynecol Obstet.* 2009, 280, 695-968.
20. Jarosz M, Wierzejska R, Siuba M. Maternal caffeine intake and its effect on pregnancy outcomes. *Eur J Obstet Gynecol Reprod Biol.* 2012, 160, 156-160.
21. Białas M, Łuczak H, Przygoński K. Zawartość kofeiny w wybranych napojach kawowych w proszku. *Bromat Chem Toksykol.* 2009, 3, 426-430.
22. Mandel H. Update on caffeine consumption, disposition and action. *Food Chem Toxicol.* 2002, 40, 1231-1234.
23. Camargo M, Toledo M, Farah H. Caffeine daily intake from dietary sources in Brazil. *Food Addit Contam.* 1999, 16, 2, 79-87.
24. Stata Statistical Software: Release 10, College Station, TX, Stata Corporation.

© Polskie Towarzystwo Ginekologiczne