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Serum fatty acids are positively associated with changes in systemic blood pressure throughout pregnancy

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ABSTRACT

Objectives: To assess whether serum concentrations of saturated (SFAs), polyunsaturated (PUFAs), and monounsaturated (MUFAs) fatty acids are associated with changes in blood pressure (BP) throughout pregnancy.
Study design: Prospective cohort.
Main outcome measures: Longitudinal measurements of systolic (SBP) and diastolic (DBP) BP.
Methods: Two hundred twenty-three healthy pregnant women were recruited in a public health center in Rio de Janeiro, Brazil between 2009 and 2011. Fasting blood samples and BP measurements were obtained at the 1st (5th–13th weeks), 2nd (20th–26th) and 3rd trimester (30th–36th). Crude and adjusted (maternal age, education, energy intake, gestational body weight change, leptin concentrations, early pre-pregnancy BMI, leisure time physical activity prior to pregnancy and linear and quadratic gestational weeks) longitudinal linear mixed-effects models were employed.
Results: SBP and DBP decreased from the 1st to the 2nd trimester and slightly increased from the 2nd to the 3rd trimester ($P < 0.001$). In the adjusted model (ß and 95% CI), total SFAs [0.005 (0.001–0.008); $P = 0.008$], total MUFAs [0.005 (0.001–0.009); $P = 0.019$] and total n-6 PUFAs [0.005 (0.001–0.009); $P = 0.025$] were positively associated with SBP throughout pregnancy.
Conclusions: Maternal serum concentrations of total SFAs, MUFAs and n-6 PUFAs were positively associated with BP levels in normotensive pregnant women.

1. Introduction

Physiological hemodynamic changes occur in the mother's body during pregnancy to accommodate maternal and fetal demands. Adaptations of the cardiovascular system include decreased vascular resistance and increased blood volume and systolic (SBP) and diastolic (DBP) blood pressure (BP) [1,2]. Studies have reported that maternal SBP and DBP tend to decrease from the 1st to the 2nd trimester and later increase progressively until delivery in uncomplicated pregnancies [2,3].

Although these physiological adaptations are expected, BP levels are inversely associated with birth weight and gestational age at birth, even in normotensive women [4,5]. Given the importance of BP to the pregnancy outcome, efforts have been undertaken to elucidate factors that may influence changes in BP during pregnancy. There is a growing body of evidence supporting the hypothesis that poor placenta implantation, mediated by systemic inflammatory response and endothelial cells dysfunctions, accounts for hypertension during pregnancy [6].

Thus, maternal biomarkers associated with endothelial cell function and the inflammatory response has the potential to be related to BP changes during pregnancy [7]. Fatty acids (FAs) are important endocrine mediators that play a major role in the inflammatory process [8] and vascular function in the offspring [9] and may have different bioactive properties and functions depending on the number of unsaturated bonds [10]. Greater intakes and levels of saturated fatty acids (SFAs) have also been related with increased levels of low-density lipoproteins (LDL-cholesterol) [11], thereby potentially contributing to

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an increased risk of developing cardiovascular disease [12]. However, the results of a large randomized clinical trial (RCT) has cast doubt on this finding [13]. In addition, observational trials and RCTs have reported that higher intake of monounsaturated fatty acids (MUFAs) and n-3 polyunsaturated fatty acids (PUFAs) may contribute to a decrease in BP in adult populations [14,15].

It is well-known that serum concentrations of FAs are increased during pregnancy [16]. Furthermore, studies have shown a high FA requirement to ensure adequate embryo implantation and placenta development [6]. Recent studies have also shown differences in n-3 PUFA concentrations in different regions of the placenta among both normotensive pregnancies and women with preeclampsia [17,18]. An RCT that provided n-3 PUFAs as fish oils or fish meals have unequivocally demonstrated a reduction in BP [19]. Lim et al. (2015) observed an inverse association between maternal plasma concentrations of total n-3 PUFAs and peripheral SBP in a study with 751 Chinese, Malay and Indian pregnant women [20]. Intake of n-6 PUFAs has been associated with increased pro-inflammatory eicosanoid levels in the general population [21]. However, in vitro studies suggest that n-6 PUFA intake may facilitate the early placentation process by stimulating angiogenesis in 1st trimester placental trophoblast cells [22,23,24].

Although there is previous evidence regarding the association between serum FAs and BP in the general population [14,15], we identified only one study that has investigated this association during pregnancy [20]. We aimed to investigate whether concentrations of various types of FAs during pregnancy were associated with BP throughout gestation in normotensive pregnant women. We hypothesized that during pregnancy, higher serum concentrations of MUFAs and n-3 PUFAs would be associated with lower SBP and DBP, while higher concentrations of SFAs and n-6 PUFAs would be associated with higher SBP and DBP values.

2. Methods

This report describes a prospective cohort study of pregnant women attending a prenatal care service offered by a public health center in Rio de Janeiro, Brazil. The enrollment of women occurred from November 2009 until October 2011, and the follow-up lasted until July 2012. The study consisted of three follow-up visits, which occurred during the 5th–13th (1st trimester), 20th–26th (2nd trimester), and 30th–36th (3rd trimester) gestational weeks.

A total of 322 women met the eligibility criteria [< 13 gestational weeks; 20–40 years old; no chronic diseases (aside from obesity)] and were invited to participate. From those 322 women, 23 women chose not to participate, and 76 women were excluded after enrolment for the following reasons: were diagnosed with chronic diseases (n = 12) or with infectious diseases (n = 9), had advanced pregnancy (≥14 weeks of gestation) (n = 15), had multiple pregnancies (n = 4), missed the baseline interview (n = 5) or the baseline blood collection (n = 6) or suffered early miscarriages (n = 25). The baseline sample consisted of 223 pregnant women. From the baseline to the 2nd trimester visit, 19 additional exclusions occurred, and 15 follow-up losses occurred, with 189 women remaining at the 2nd trimester visit. Two women dropped out between the 2nd and 3rd visits. In addition, an RCT was nested within the cohort starting after the 2nd trimester and lasting until delivery. The RCT aimed to investigate the effect of n-3 PUFA supplementation on postpartum depression (ClinicalTrials.gov: NCT01660165). Forty-one out of 189 women were randomized and received six gelatin capsules per day containing fish oil (n = 20) or placebo (soybean oil, n = 21). Six women out of 41 did not adhere to the RCT and were analyzed at the 3rd trimester visit, while 35 women who adhered to the RCT were excluded from the 3rd trimester analysis with a final remaining sample of 152 women in the 3rd trimester (Fig. 1) [25].

2.1. Blood samples

Blood samples were obtained at the 1st (5th-13th weeks), 2nd (20th-26th) and 3rd trimester (30th–36th) after 12 h of fasting, and were collected in vacutainer tubes and immediately centrifuged (5,031*g* for 5 min) within 1 h. Aliquots of serum (prepared from blood collected into tubes with a gel separator) were stored at −80 °C until analyses. Serum samples were used to determine the FA compositions.

2.2. Fatty acid concentrations

Analyses of serum FA composition were performed in the Section of Nutritional Neuroscience, Laboratory of Membrane Biochemistry and Biophysics of the National Institute of Health (NIH/USA). Serum samples were shipped from Brazil to the NIH/USA in boxes with dry ice.

High-throughput robotic direct methylation, coupled with fast gas-liquid chromatography, was used to identify the serum FAs. This technique was developed and validated by the NIH to allow analysis on a large scale [26]. The analyses were performed using a chromatograph HP 6890 Plus gas LAN equipped with three flame ionization detectors (Agilent Technologies, Santa Clara, CA, USA) coupled to a fused silica capillary column (Agilent 127-32H2 15 m × 0.1 mm × 0.1 mm).

Twenty-two FAs were measured: 14:0, 16:0, 16:1n-7, 18:0, 18:1n-9, 18:1n-7, 18:2n-6, 18:3n-6, 18:3n-3, 20:0, 20:1n-9, 20:2n-6, 20:3n-6, 20:4n-6, 20:5n-3, 22:0, 22:4n-6, 22:3n-3, 22:5n-3, 24:0, 22:6n-3, and 24:1n-9. Although we measured 22 FAs, we opted to present only n-3 and n-6 fractions plus totals for MUFAs, SFAs, and PUFAs, considering the representativeness of these fractions [27]. FAs were presented in absolute values (μg/mL).

2.3. Blood pressure

BP was measured twice at all follow-up visits (5th–13th, 20th–26th, and 30th–36th gestational weeks) with approximately 30-min intervals between measurements. The mean values obtained from each follow-up visit were calculated and considered in the analysis. Measurements were performed using an automated oscillometric BP monitoring system (Omron HEM-742, São Paulo, Brazil), which was previously validated [28] using an adequate cutoff that fit the upper arm's circumference. Prior to measuring BP, women were asked to rest for at least five minutes and to be seated comfortably with their backs supported, legs uncrossed, and feet flat on the floor, remaining silent during the procedure. The arm with the cuff was supported at the heart level, with the palm facing up and the elbow slightly flexed.

2.4. Covariates assessment

A structured questionnaire was administered by trained interviewers at each pregnancy trimester to determine the women's sociodemographic and lifestyle characteristics, including age (years), education (years), and practice of leisure time physical activity prior to pregnancy (yes/no). Total energy intake (kcal/d) was obtained using a validated food frequency questionnaire (FFQ), which used the previous six months' pregnancy as the time frame. The FFQ was administered at baseline [29].

Weight was measured in each visit using an electronic scale (Filizzola Ltd., São Paulo, Brazil), calibrated to the nearest gram. Height was measured in duplicate using a portable stadiometer (Seca Ltd., Hamburg, Germany) at baseline. Early pregnancy body mass index (BMI) [weight (kg)/height $(m)^2$] was determined based on the weight and height measured before the 13th gestational week. Women were classified according to early pregnancy BMI as either normal weight ($18.5 < BMI \leq 24.9\ kg/m^2$), overweight ($25 \leq BMI \leq 29.9\ kg/m^2$), or obese ($BMI \geq 30\ kg/m^2$). Trained staff performed anthropometric measures using standardized procedures [30].

Gestational age was estimated by ultrasound if performed prior to