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Gestational Variables Correlate with Cardiometabolic Risk Factors in A Sex-Dependent Way in Adolescence

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Abstract

Background: Exposure to adverse conditions during the period of intrauterine development can lead to lifelong consequences. In this sense, evidence has pointed to an important influence of maternal variables, such as pre-gestational body mass index (BMI) and gestational weight gain (GWG), on the health of the offspring in adolescence, increasing the risk of obesity and damage to the cardiometabolic profile.

Methods and Findings: This is a cross-sectional study in a cohort of 49 adolescents. The following variables were collected with adolescents in a scheduled consultation: sociodemographic (sex and age), clinical (diastolic and systolic blood pressure), anthropometric (weight, height, BMI and waist circumference [WC]), biochemical (glucose, total cholesterol, LDL-c, HDL-c, triglycerides and leptin) and birth (birth weight and gestational age). In addition, gestational variables (pre-gestational weight and height, pre-gestational BMI, GWG, and type of delivery) were collected in an interview with the mothers of the young people. For statistical analysis, adolescents were stratified according to sex. A correlation between BMI and WC was observed in adolescence with pre-gestational weight and BMI only in boys (r=0.906; p=0.001, r=0.878; p=0.002/ r=0.909; p=0.001, r=0.865; p=0.003). Moreover, in males, triglycerides correlated with pre-gestational BMI (r=0.712, p=0.048), and LDL-c with GWG (r=0.699, p=0.024). Serum leptin concentration correlated with pre-gestational weight and BMI in girls (r=0.532, p=0.006; r=0.440, p=0.028) and, in boys, with GWG (r=0.901, p=0.037).

Results: In view of the results, it is suggested that gestational anthropometric variables can influence the BMI, WC and biochemical variables of the offspring in a gender-dependent way, largely affecting boys.

Keywords: Metabolic programming; Sex dependent; Adolescence; Pregnancy

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Introduction

Adolescence plays a key role in the long-term development of diseases. Exposure to adverse conditions, such as excess weight or metabolic disorders, in such an early stage of life, potentiates health risks in adulthood, increasing the probability of developing chronic non-communicable diseases (NCDs), such as cardiovascular diseases and diabetes mellitus, substantially contributing to the morbidity and mortality rate in the population [1-3]. Just as adult life suffers from the conditions to which the individual was previously exposed, adolescence is also influenced by a previous period, extremely important for human development: intrauterine development [4,5]. According to the theory of "Metabolic Programming", during intrauterine life, conditions related to the maternal environment can program the metabolism of the developing fetus and affect its health condition throughout life, favoring or protecting from the emergence of metabolic disorders and risk of NCD, for example [6-8]. In line with this theory, it has been observed that higher values of pre-gestational BMI and gestational weight gain (GWG) are associated with damage to the cardiometabolic profile of the offspring in adolescence, conferring greater risk of

abdominal obesity, increased BMI and Waist Circumference (WC) and changes in insulinemia and glycemia. These data deserve attention, especially considering the increasing prevalence of obesity among women of fertile age [4,9]. In addition, there is increasing evidence, both in experimental studies and in humans, suggesting that the influence of the maternal environment can be potentiated or attenuated depending on the sex of offspring. Studies have indicated that males are more sensitive to adverse conditions during intrauterine life and develop long-term health damage to when exposed to them [6,7,10-14]. Thus, considering the importance of the gestational period and its impact on health -- especially in adolescence, a time that is also considered critical for human development--, and of the questioning of whether its effects would be sex dependent, this study aimed to evaluate the correlation between maternal anthropometric variables and anthropometric and biochemical alterations, indicative of cardiometabolic risk, in adolescents according to sex.

Research Methodology

This is a cross-sectional cut of a cohort conducted at the Adolescent Reference Center (Centro de Referência ao Adolescente/CRA), in Macaé, Rio de Janeiro, which evaluated the cardiometabolic profile of adolescents. This study comprised individuals from 10 to 19 years of age, volunteers, who had medical records in the CRA, information on gestational variables, variables at birth confirmed in the Maternal and Child Health Handbook (MCHH) and who had signed the consent form and informed consent, the latter being signed by parents or guardians, when under 18 years of age. Pregnant or nurturing adolescents and those who had inadequate conditions for anthropometric evaluation (use of prostheses, plaster or physical disabilities) were excluded. Adolescents whose gestational information could not be collected from their respective mothers were also excluded. Data collection was performed in previously scheduled interviews, where socio-demographic, clinical, laboratory and anthropometric variables were addressed. The entire process was performed by a trained evaluator. Birth weight and gestational age were obtained by consulting the MCHH.

At the meeting, the blood pressure was measured [15] and anthropometric evaluation was performed, where body weight, height and waist circumference were measured [16] all in duplicate. BMI was calculated according to the WHO in 2007 [17], and the cut-off points proposed by the Food and Nutritional Surveillance System/SISVAN were used, classifying the adolescents according to the BMI-for-age percentile in: underweight (BMI < 3rd percentile), normal weight (BMI >= 3rd percentile and =< 85th percentile), overweight (BMI > 85th percentile and =< 97th percentile), obesity (BMI > 97th percentile and =< 99th percentile) and severe obesity (BMI >99th percentile) [18]. For biochemical variables, blood was collected by venous puncture from the adolescent after a 12-hour fast, with about 20mL of whole blood, in 5mL tubes with ethylenediaminetetraacetic acid (EDTA). Blood glucose, total cholesterol, LDL-c, HDL-c, triglycerides, and leptin, which was dosed using the enzyme-linked immunosorbent assay (ELISA) method, were analyzed.

For the evaluation of gestational variables, the following information was collected with the mothers through the application of a questionnaire by a trained interviewer: age during pregnancy, history of previous pregnancies, pre-gestational weight, height, pre-gestational BMI, GWG and type of delivery. For statistical analysis, adolescents were stratified according to sex. The Kolmogorov-Smirnov test was applied to assess normality in the distributions of continuous variables. The measures of central tendency and dispersion of numerical variables and frequency for continuous variables were calculated. The Mann-Whitney test was used to evaluate the correlation between maternal variables and the variables in adolescence. A significance value of $p<0.05$ was adopted. Statistical analysis was performed using the SPSS software, version 20. The work was approved by the Research Ethics Committee of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro (CEP/HUCFF/UFRJ).

Results

The study comprised 49 adolescents who had information on pregnancy and childbirth, with a predominance of females (71.4%). Sample characterization according to clinical, anthropometric, and biochemical variables can be observed in **Table 1**, while the information on gestational and birth variables can be seen in **Table 2**. According to the BMI, in the total sample, 36.1% of the evaluated adolescents had excess weight classified as follows: 10.6% were overweight, 8.5% obese and 17% severely obese. No significant differences were observed between sexes regarding the BMI categorization (**Table 3**).

BMI in adolescence correlated with weight and pre-gestational BMI in the total sample (r=0.339; p=0.043, r=0.341; p=0.042) and in boys (r=0.906; p=0.001, r=0.878; p=0.002), after the sex-specific analyses. There were no significant correlations between BMI and gestational variables in girls. Similar to BMI, WC correlated with the maternal variables weight and pre-gestational BMI only in the total sample (r=0.412; p=0.012, r=0.441; p=0.007) and in boys (r=0.909; p=0.001, r=0.865; p=0.003).

For the lipid profile, no significant correlation with gestational variables was observed neither in the general sample, nor in girls. However, in males, triglycerides correlated with pre-gestational BMI (r=0.712; p=0.048), and LDL-c with GWG (r=0.699; p=0.024). The concentration of serum leptin in the total sample correlated with the pre-gestational weight (r=0.445, p=0.015). In girls, this hormone also showed positive correlation with pre-gestational weight and BMI (r=0.532, p=0.006; r=0.440, p=0.028). In males, GWG was correlated with hormone levels (r=0.901, p=0.037). Regarding the other biochemical variables in adolescence, no significant correlations with gestational variables were observed.

Discussion

In view of the results presented, it is suggested that pre-gestational BMI and GWG can influence anthropometric and biochemical parameters of the offspring in adolescence. Although the mechanisms explaining the long-term impacts of pregnancy

Table 1: Characterization of the sample of adolescents participating in the study according to clinical, anthropometric, and biochemical variables (Mean ± Standard Deviation).

Variables	Total n=49	Girls n=35	Boys n=14	p* value
Age (years)	14.8 ± 2.0	14.9 ± 2.1	14.5 ± 1.7	0.513
BMI (Kg/m²)	23.0 ± 6.3	23.8 ± 6.3	21.1 ± 5.9	0.125
WC (cm)	74.5 ± 12.4	75.2 ± 12.7	72.6 ± 11.9	0.433
Total Cholesterol (mg/dL)	158.8 ± 29.1	159.6 ± 29.3	156.6 ± 29.7	0.735
LDL-c (mg/dL)	90.0 ± 24.1	90.4 ± 23.6	88.9 ± 26.3	0.725
HDL-c (mg/dL)	49.8 ± 10.6	50.2 ± 11.7	48.7 ± 7.0	0.702
TG (mg/dL)	86.5 ± 40.5	83.2 ± 38.4	95.7 ± 46.6	0.388
SBP (mmHg)	102.5 ± 12.6	101.9 ± 13.3	104.1 ± 10.9	0.827
DBP (mmHg)	63.7 ± 9.3	62.5 ± 9.8	66.6 ± 7.5	0.201
Glycemia (mg/dL)	80.4 ± 5.0	79.9 ± 5.2	82.0 ± 4.1	0.149
Leptin (ng/mL)	16.7 ± 20.7	18.3 ± 22.0	7.99 ± 8.7	0.201
CC: Waist Circumference; TG: Triglycerides; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure/*Mann Whitney Test.				

Table 2: Characterization of the sample of adolescents participating in the study according to gestational and at birth variables (Mean ± Standard Deviation).

Variables	Total n=49	Girls n=35	Boys n=14	*p* value*
Age of mother (Years)	25.8 ± 6.9	24.3 ± 3.6	26.0 ± 6.3	0.835
Pre-gestational BMI (Kg/m²)	21.7 ± 3.8	20.8 ± 3.6	21.9 ± 5.3	0.516
Pre-gestational Weight (Kg/m²)	55.9 ± 10.4	54.5 ± 12.4	55.6 ± 13.5	0.493
Gestational Weight Gain (Kg)	15.4 ± 10.4	10.0 ± 6.5	19.6 ± 11.5	0.163
Interbirth intervals (Months)	53.11 ± 54.8	57.5 ± 54.4	24.1 ± 13.9	0.023
Gestational age (Weeks)	37.8 ± 0.91	38.1 ± 0.53	37.6 ± 1.1	0.130
Birth weight (Kg)	3,246.9 ± 772.2	3,374.3 ± 607.3	3,229.2 ± 981.1	0.905
SD: Standard Deviation/**Mann Whitney test.				

Table 3: Percentage distribution of BMI classes according to the sex of the evaluated adolescents.

Sex	Classification according to BMI (%)					p* value
	Underweight	Normal Weight	Overweight	Obesity	Severe Obesity	
Female	0	58.8	14.7	11.8	14.7	0.059
Male	15.4	61.5	0	0	23.1	
*Chi-square Test						

have not yet been fully elucidated, some hypotheses have been raised.

The unfavorable intrauterine environment seems to be able to promote epigenetic alterations in the genome of the offspring, influencing gene expression, and interfering with their lifelong health condition. Experimental studies have shown that inadequate diet and nutritional status of the mother can cause innumerable alterations during critical periods of fetal development, such as in the levels of DNA methylation, including sites related to adiposity. As a result, for example, changes occur in the signaling of neurotransmitters and hormones related to the accumulation and distribution of body fat, along with an increase in the pre-disposition to metabolic disorders [7,13,19,20].

In addition to the maternal nutritional status, evidence increasingly points to the importance of gestational weight gain for child health. In a meta-analysis with 12 studies, which assessed the influence of GWG on the nutritional status in childhood/adolescence, it was observed that such gain, when excessive, was associated with increased risk of obesity/overweight in this period of life [21]. It is important to stress that this variable negatively influences the nutritional status of the offspring, even in normal weight pregnant women [22]. In this study, GWG was correlated with variables in adolescence, even if the mean BMI of mothers was normal weight, which corroborates what is suggested in the literature.

Some mechanisms have already been proposed by experimental and human studies to explain the relationship between GWG and the nutritional status in childhood/adolescence. Children of mothers who have GWG above adequate can share the maternal genetic and environmental factors, such as calorie-rich food and sedentary lifestyle, which would provide lifelong weight gain. In addition, excessive GWG, as well as high pre-gestational BMI, is associated with higher birth weight, which in turn is associated with childhood/adolescence obesity. Another point raised is that excessive weight gain during pregnancy would cause alterations

both in the expression of adipogenic, lipogenic, and adipokine genes in the adipose tissue, as well as neurological alterations, related to weight regulation and gut-brain communication, interfering in the network of appetite regulation [23-26].

In the present study, gestational variables (BMI and pre-gestational weight and GWG) were correlated with anthropometric (BMI and WC) and biochemical (triglycerides, LDL-c and leptin) parameters in male adolescents, and such correlations ranged from moderate to even very strong. On the other hand, in females, the observed correlations only occurred with leptin during adolescence and they were of a weak order. These findings suggest the existence of a sex-dependent maternal influence on the health of the offspring in adolescence, largely affecting boys.

Evidence in humans also points to this greater vulnerability of males to maternal variables, especially diet and nutritional status. When comparing male and female adolescents exposed to inadequate maternal nutrition, pre-gestational excess weight and inadequate weight gain during pregnancy, studies have observed that the consequences of such exposures were more severe in boys, favoring greater BMI, body fat deposition, predisposition to metabolic alterations and, consequently, risk of chronic non transmissible diseases in these individuals. Studies addressed to some of these effects in girls have reported that they occurred with significant less intensity [7,9,27].

Such consequences can have an impact on the life of the offspring in the long term, reaching even adulthood [7,8,11-14]. In childhood, pre-gestational excess weight has already been identified as capable of influencing the nutritional status of boys more than girls, with greater risk of overweight in the first year of life [12]. In adolescence, exposure to gestational diabetes mellitus, during fetal development, increased the risk of obesity in boys, but not in girls [5].

A possible explanation for this difference is based on intrauterine growth rate. Male fetuses grow more rapidly compared to females from the earliest stages of pregnancy [10,28]. This phenomenon reflects in a lower placental growth and, consequently, a greater sensitivity to variations in the maternal nutritional status and/or the adoption of a diet poor in nutrients [5,10]. For example, maternal anthropometry (height, pre-gestational BMI and GWG) has already been identified as a predictor of the content of lean and fat masses in male but not in female newborns [29].

Gaillard et al. [4], when evaluating 1392 mothers and their adolescent children, observed that GWG and pre-gestational BMI were significantly associated with higher BMI and WC in adolescence; however, separate analyses according to sex were not performed. In our sex-dependent analysis, similar and significant results were observed in the total sample and in boys, but not in girls.

Thus, our analysis suggests the occurrence of a possible effect of pregnancy on the accumulation of body fat in adolescence, mainly abdominal. In experimental studies, it has already been observed that maternal obesity has propitiated hypertrophy and hyperplasia of adipocytes, favoring visceral, but not subcutaneous, fat deposits in the male progeny over the long term, although this result has not been observed in females [7,20].

One of the possible routes that influence the greater accumulation of fat in response to gestational variables is through the stimulus exercised by leptin. LeCoutre et al. [30] have observed, in male rodents, higher plasma concentrations of the hormone in the offspring of obese mothers and attributed this finding to epigenetic alterations in genes controlling its expression, which occurred due to obesity in pregnancy. Thus, stimulus to the expansion of fat tissue (resistant hypertrophy and hyperplasia) by leptin was observed, but only at the visceral level [7,30].

In our findings, the gestational variables influenced the concentration of serum leptin in the total sample, in boys and girls, but the correlation was weak in girls. Given the mechanisms explained above, it can be assumed that the greater impact of pregnancy on serum leptin in adolescence, in boys, potentiates the effect of gestational variables on adiposity in adolescence, especially abdominal, evaluated through WC.

In the current study, it was also possible to observe the influence of pre-gestational BMI and GWG on triglycerides and LDL-c in adolescence. In studies with animals, females fed with a high-fat diet produced offspring with an unfavorable lipid profile and hepatic steatosis, even in adolescence, and such results were associated with increased expression of genes related to lipogenesis and lipid metabolism, as well as hepatic lipogenic markers [31,32]. Alfaradhi et al. [33] have observed higher liver lipid content associated with higher levels of peroxisome proliferator-activated receptor gamma (PPAR-γ) and reduced triglyceride lipase in rats born from mothers with obesity and suggested these individuals have losses in liver lipid metabolism. Even omega-3 supplementation reduced triglycerides and cholesterol only in the offspring of females fed a standard diet, while in animals born from females fed a high-fat diet, this nutrient had no hypolipemic effect.

Conclusion and Limitations

Our study has some limitations, such as the reduced sample size, the retrospective nature of the interview with mothers and the non-evaluation of the trimester weight gain. However, given the increase in overweight/obesity in women of fertile age, our findings may contribute to public health by illustrating the possible influences of this condition on adolescent health, as it predisposes to excess weight, abdominal obesity, leptin increase and changes in lipid profile, especially in boys. The knowledge about the impacts of maternal variables on the health of the offspring allows the elaboration of strategies that shall reduce the risks for the occurrence of chronic non-communicable diseases still in youth or adult life.

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Conflict of Interest

The authors have nothing to disclose.

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