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Serum levels and gestational curve of adiponectin and leptin during adolescent pregnancy

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SUMMARY

OBJECTIVE: This study aimed to develop a curve of weekly serum levels of adiponectin and leptin among pregnant adolescents. In addition, pre-gestational body mass index and weight gain were assessed and correlated with the serum concentration of these molecules.

METHODS: This was a prospective cohort study, including only pregnant adolescents with eutrophic pre-gestational body mass index who were weekly followed during the evolution of gestation. The serum concentrations of adipokines were determined using commercial ELISA kits and were correlated to pre-gestational body mass index and pregnancy weight gain. A total of 157 pregnant women participated in this study.

RESULTS: Adiponectin levels showed a significant decrease among the trimesters (p=0.0004). However, we did not observe significant differences among its levels when compared weekly, neither of which was between adiponectin concentration and pre-gestational body mass index or weight gain (p=0.36 and p=0.10, respectively). In contrast, we detected a significant increase in weekly serum leptin levels (p<0.0001), positively correlated to both pre-gestational body mass index and weight gain (p=0.003 and p=0.0007, respectively).

CONCLUSION: These adipokines present a different profile throughout adolescent pregnancy.

KEYWORDS: Adiponectin. Adipokines. Adolescent. Leptin. Pregnancy. Body mass index.

INTRODUCTION

Adipokines are involved in diverse processes. Serum adiponectin levels may vary according to sex, and it is higher in women[1]. This difference is not observed between adolescents.

In adult pregnancy, it is established that the serum adiponectin concentration decreases with the advancement and installation of insulin resistance (IR), returning to the pregravid concentration after delivery. Studies indicate that there is a negative correlation between serum levels and gestational age[2-4]. Contrarily, there is a significant increase in plasma leptin levels with pregnancy progress[4,5] which seems to play a crucial role in regulating placental growth, nutrient transfer, angiogenesis, pulmonary maturation, and trophoblast invasion[5,6]. Impaired levels of adipokines have been associated with obstetric pathologies such as preeclampsia, intrauterine growth retardation (IUGR), gestational diabetes, and preterm birth[7-10]. Few studies have evaluated adipokines in adolescent pregnancy[11-13]. Noreña et al.[14] reported that, in teenagers' pregnancy, increased serum leptin levels are positively associated with IUGR.

It is now recognized that leptin, in addition to being an important mediator of energy balance, acts in the control of fertility and growth[4,5]. Leptin serum concentrations are greater in pregnant women than in non-pregnant women. Substantial increases in leptin levels occur early in pregnancy, before any significant increase in body weight, suggesting that factors other than adiposity are involved in the control of serum leptin levels[10-13]. Leptin concentrations peak in the second trimester of pregnancy and remain high until delivery[6-8]. The proposed physiological role of leptin during pregnancy is not yet known.

Adolescents appear to be at increased risk for adverse pregnancy outcomes, such as premature birth, low birth weight, preeclampsia, maternal death, and perinatal death[15,16]. In addition, it is known that pregnancy and childbirth complications are the main causes of mortality among adolescents in developing countries[17]. Despite the investigations carried out, it remains unclear whether these changes are associated with biological or sociodemographic factors. Therefore, this study aimed to evaluate weekly serum levels of adiponectin and leptin and investigate whether these adipokines' levels are related to pre-gestational body mass index (BMI) and total weight gain throughout adolescent pregnancy.

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METHODS

This prospective cohort study was approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP) under the consubstantiated opinion nº 1514/1. All adolescents attended in the Adolescent Prenatal Sector of the UNIFESP from February 2013 to March 2018 were included in the research after reading, understanding, and signing the informed consent form. As well as the respective guardians signed confirming their consent to participate in the study. The patients were followed during gestational evolution; every 15 days, their nutrition status was evaluated through weight, height, and BMI. Blood samples were collected throughout pregnancy (from 9 to 39th gestational weeks), once in every trimester. In this study, pregnant women were between 12 and 20 years of age and presented eutrophic pre-gestational BMI (18.5-24.9 kg/m²). Exclusion criteria were multiple gestations, use of corticosteroids, antibiotics, immunosuppressants, and anti-inflammatories, and adolescents with systemic disorders such as hypertension, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, rheumatic fever, and asthma. In addition, patients who developed obstetric intercurrence with pregnancy progress were excluded. On the first prenatal visit, BMI was calculated based on the pre-gestational weight and height reported by the pregnant girl; after all, the weight gain of pregnant women usually changes in a short period of time. The nutritional diagnosis was established according to the Institute of Medicine (2009)[18]. Gestational weight gain was determined by the difference between the pre-gestational weight and the patient's weight on her last pre-delivery visit.

According to the Ministry of Health, it is considered the first trimester of pregnancy from 0 to 14 weeks, the second trimester from 14 to 26 weeks, and the third and last trimester and pregnancy from 27 to 40 weeks (2016)[19].

A volume of 8 mL peripheral blood was collected (after 12 h fasting) in tubes with spray-coated silica and polymer gel for serum separation (BD Diagnostics, Franklin Lakes, NJ, USA). After clot retraction, the sample was centrifuged, and the resultant serum was aliquoted and stored at -80°C until its assessment. We used commercial kits for all tests, and they were performed at the same time.

For serum adipokine levels, ELISA commercial kits were used – Human Adiponectin, Human Leptin Duoset (R&D Systems®, USA). Adiponectin and leptin sensitivity were 0.06 ng/mL and 32.25 pg/mL, respectively. Intraassay and interassay coefficients of variation (%) for adiponectin and leptin were 3.5 and 6.5 and 3.2 and 4.4%, respectively.

The normality tests such as skewness and kurtosis, Kolmogorov-Smirnov, and Shapiro-Wilk were applied to evaluate the quantitative variables. For the analysis of variance (ANOVA) between the groups, the repeated-measures ANOVA test was applied to measure parametric distributions, and the Friedman test was used to analyze the non-parametric ones, followed by Durbin-Watson post-tests or Dunn-Bonferroni post-test, respectively. For the analysis of categorical variables, the chi-square test was adopted. The Pearson test was applied to calculate the correlation coefficients. The level of significance was set at $p<0.05$. Statistical analyses were performed using the standard software GraphPad Prism, v6.0 for Windows (SPSS Inc., Chicago, IL, USA). No studies have been found allowing the calculation of sample size; therefore, we proposed to carry out a study that serves as the basis for future research. Thus, the totality of patients who suited the established parameters was included in the study period.

RESULTS

The study included 157 healthy pregnant adolescents, comprising 471 blood samples collected between the 9 and 39th gestational weeks. Table 1 shows the main characteristics of the participants. Pregnant women were between 12 and 20 years of age, with a mean age of 16.51 years (standard deviation 1.76).

Serum adiponectin levels exhibited significant differences with the evolution of pregnancy, characterized by a drop in concentration ($p=0.0004$; Friedman test). The data are presented in Table 2 and Figure 1A.

We did not observe a correlation between pre-gestational BMI, pregnancy weight gain, and serum adiponectin levels ($p=0.36$ and $p=0.10$, respectively). In addition, there were no statistical differences in serum adiponectin levels between the adolescents' gestational weeks (Dunn-Bonferroni post-test). Conversely, we detected an increase in serum leptin levels with pregnancy progress ($p<0.0001$; repeated-measures ANOVA). The results are described in Figure 1B. We also observed significant differences regarding serum leptin levels between gestational weeks (Durbin-Watson post-test), particularly after the second trimester.

Finally, we identified a positive correlation between pre-gestational BMI and pregnancy weight gain with serum leptin levels ($p=0.003$ and $p=0.0007$, respectively).

DISCUSSION

This research demonstrated the weekly changes in serum adiponectin and leptin levels throughout gestation (from the 9 to 39th gestational weeks). Similar to previous studies, we observed significant differences in adipokines concentrations between

pregnancy trimesters[7,20,21]. These adipokines present different profiles comparing weekly levels. Adiponectin concentration did not show relevant variations between weeks; neither was related to pre-pregnancy BMI and weight gain; contrarily, leptin exhibits significant changes considering week values; moreover, it is positively correlated with the evaluated variables.

Different studies have shown that these two adipokines exert different effects and present an opposite pattern during healthy pregnancy progress. Adiponectin seems to exhibit anti-inflammatory properties, whereas leptin plays an inflammatory role[2-4,20].

Evidence supports that, in adult pregnancies, adiponectin is negatively correlated with gestational age[20]. Similar results were observed in this study with adolescents.

Some authors have reported that plasma adiponectin concentrations decrease gradually with the advancement of pregnancy due to fat tissue increase[3]. However, these values return to normal soon after delivery[3]. Studies have revealed that, in

Table 1. Adiponectin serum concentrations (ng/mL) during the gestational weeks of adolescents.

Gestational week	n	Minimum	25% Interquartile range	Medium	75% Interquartile range	Maximum
9th	16	1,726	2,047	3,473	4,331	6,282
10th	16	1,141	2,507	3,733	5,267	7,295
11th	15	1,350	2,596	3,786	6,389	7,575
12th	15	1,058	2,891	3,677	5,263	6,924
13th	18	2,392	2,958	3,578	4,442	8,879
14th	16	1,507	1,570	3,149	3,823	5,690
15th	15	1,258	1,913	2,635	6,579	14,284
16th	15	1,001	1,514	2,569	6,250	10,943
17th	15	1,205	2,447	3,735	5,690	8,377
18th	15	1,205	2,476	3,781	4,483	6,579
19th	15	1,575	2,964	3,835	7,362	9,697
20th	15	1,322	1,599	2,998	3,459	5,960
21th	15	1,526	2,224	3,520	5,784	10,943
22th	15	1,579	2,152	3,369	4,954	9,697
23th	15	1,569	1,632	2,363	5,236	5,471
24th	15	1,233	3,349	4,183	6,940	8,520
25th	15	1,511	2,569	3,120	4,250	6,199
26th	15	1,540	1,789	2,286	4,445	5,391
27th	15	1,278	2,157	3,292	3,697	5,541
28th	15	1,353	2,458	3,520	4,723	8,588
29th	15	1,036	1,599	2,362	3,261	5,367
30th	15	1,169	1,838	2,372	3,336	4,445
31th	15	1,247	1,831	2,534	3,687	7,287
32th	15	1,007	1,951	2,326	3,372	6,352
33th	15	1,252	1,568	2,160	2,470	5,037
34th	15	1,158	1,336	2,564	3,569	5,348
35th	15	1,506	1,800	2,963	3,185	22,103
36th	15	1,621	1,883	2,610	4,789	9,056
37th	15	1,036	1,659	1,931	3,466	9,754
38th	15	1,509	1,943	2,964	3,233	5,031
39th	15	1,504	1,863	2,275	3,103	3,589

Friedman test, p=0.0004.

Table 2. Serum leptin concentrations (ng/mL) during the gestational weeks of adolescents.

Gestational Week	n	Minimum	Maximum	Mean	Standard deviation
9th	16	9.6	59.75	24.29	14.83
10th	16	9.57	45.9	22.11	10.09
11th	15	11.29	98.01	38.46	30.29
12th	15	5.83	95.65	40.10	32.56
13th	18	11.48	103.3	29.91	22.45
14th	16	5.59	54.48	26.12	15.27
15th	15	2.15	65.16	24.51	16.51
16th	15	5.29	82.23	32.91	22.24
17th	15	7.74	43.74	18.47	10.69
18th	15	7.73	38.06	19.54	8.86
19th	15	8.84	55.34	28.1	11.16
20th	15	11.56	96.91	38.42	23,87
21th	15	12.85	54.45	28.34	11.01
22th	15	12.15	54.46	24.37	11.97
23th	15	7.18	55.45	33.53	15.64
24th	15	3.42	46.22	20.01	13.26
25th	15	4.76	61.51	21.84	17,05
26th	15	11.7	48.05	31.00	12.96
27th	15	4.47	51.06	26.15	13.98
28th	15	1.31	40.67	24.89	11.11
29th	15	11.05	69.42	31.59	16.25
30th	15	4.67	87.76	39.67	23.52
31th	15	11.88	83.12	40.42	23.78
32th	15	4.49	77.36	39.57	22.15
33th	15	11.04	160.2	39.30	39.22
34th	15	7.56	68.42	30.62	17.49
35th	15	12.38	85.75	45.52	21.32
36th	15	2.87	77.51	42.39	22.37
37th	15	14.17	79.61	40.15	16.93
38th	15	19.63	85.75	49.93	22.51
39th	15	11.07	85.5	34.75	20.57

Repeated-measures ANOVA, p<0.0001.

healthy women, serum adiponectin concentration may be altered since the first trimester[21].

The literature suggests that, unlike other hormones secreted by adipose tissue, serum adiponectin levels decrease as adiposity increases, correlating inversely with obesity, IR, and metabolic syndrome[21].

Regarding leptin, our study showed the opposite result. We detected a significant increase as pregnancy trimesters advanced, which was also observed comparing values of gestational weeks. The literature indicates that plasma leptin concentrations increase during pregnancy in adults, especially when comparing the three trimesters of gestation with the postpartum decline[21,22].

Different investigators have reported that, throughout gestation, median adipokine levels differed significantly according to pre-gestational BMI. Changes in serum adipokines concentrations in overweight/obese seem to be different from those in lean and eutrophic groups[23,24]. Therefore, we selected only eutrophic adolescents. However, it is important to note that the accuracy of BMI to diagnose obesity is limited[25].

Our results are consistent with data obtained in adult pregnancy studies, where a positive correlation was observed between maternal plasma leptin concentration and anthropometric data at the beginning and the end of gestation. This association suggests that body weight and, probably, adiposity gain are critical factors for the increase in circulating leptin levels[7,21].

Serum adipokines levels have been extensively investigated during pregnancy with the primary purpose of elucidating a possible relationship to obstetric and perinatal intercurrences such as preeclampsia, gestational diabetes, IUGR, and low birth weight[21,22].

The opposite effects of adiponectin and leptin are well-known. Several studies focused on evaluating these serum adipokines levels, in both adult and adolescent pregnancies, showing significant differences between the gestational trimesters[7,21,22]. However, this is the first study addressing serum adiponectin and leptin

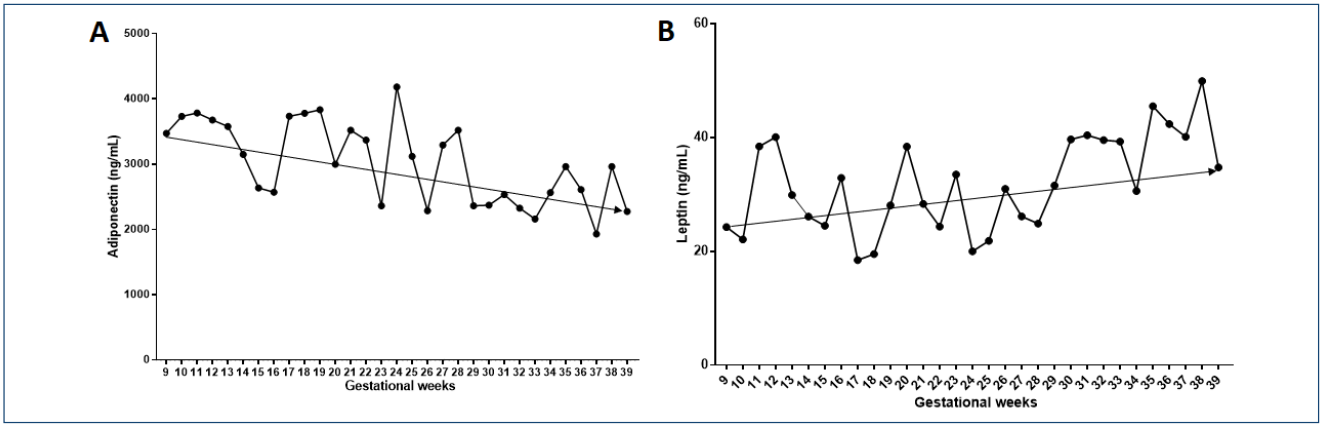

Figure 1. Serum adiponectin (A) and leptin (B) levels (ng/mL) during gestational weeks of adolescents.

levels weekly, from the 9 to 39th gestational weeks. The observed weekly differences in serum leptin levels seem to be associated with the development of considerable maternal-fetal interface changes. Thus, samples collected at the same trimester of pregnancy, although in different weeks, may explain at least part of the existing contradictions between the studies. Furthermore, in the early third trimester, leptin concentration may be correlated with weight gain. However, this difference may not be detected later.

This study limitation is that we analyzed only peripheral blood samples. In addition, we only assessed the complete form of the adiponectin molecule. Specific forms (high or low molecular weight form) evaluation could lead to different results (i.e., significant differences between weeks or association with pre-pregnancy BMI or weight gain). Further research is required to confirm these findings, and it is crucial checking whether similar gestational curves of adipokines are observed in adult pregnant women.

CONCLUSION

Adiponectin levels showed a significant decrease when comparing the three trimesters, whereas there were no significant level changes when compared weekly, and there was no correlation between adiponectin concentration and pre-gestational BMI or weight gain. In contrast, we detected a significant increase in weekly serum leptin levels, positively correlated to both pre-gestational BMI and weight gain.

AUTHOR'S CONTRIBUTIONS

CAFG: Conceptualization, Project administration, Validation, Visualization. **IB**: Data curation, Visualization, Writing – original draft. **MDF**: Data curation, Visualization. **KPTP:** Formal Analysis, Visualization. **EAJ**: Visualization, Writing – review & editing. **TFL**: Investigation. **SD:** Methodology, Supervision, Validation, Visualization.

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