

Research Article

Serum Levels and Gestational Curve of Adiponectin and Leptin During Adolescent Pregnancy

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Abstract

Adiponectin and leptin have a characteristic pattern and play important roles during pregnancy in adults, although little is known about them in adolescent gestation. The objective of this study was to develop a gestational curve for the weekly serum levels of adiponectin and leptin among adolescent pregnant women. Pre-gestational BMI and weight gain were also evaluated and correlated with the serum concentration of these molecules. The study evaluated adolescents with pre-gestational BMI of eutrophy during the evolution of gestation. Peripheral blood samples were collected to evaluate serum adipokine concentrations by the ELISA method. A total of 157 pregnant women participated in the study, totaling 471 blood samples. Serum levels of adiponectin showed significant differences, showing a drop in concentration during gestation ($p = 0.0003$), we did not observe a correlation between pre-gestational BMI, weight gain and serum levels ($p = 0.36$; $p = 0.10$, respectively). With the advancement of gestation, we identified an increase in serum leptin levels ($p < 0.0001$), a positive correlation between serum levels and pre-gestational BMI and also between weight gain ($p = 0.003$; $p = 0.0007$, respectively). We conclude that adiponectin decreases with the evolution of pregnancy, however it has no correlation with BMI and weight gain and leptin increases during pregnancy presenting a direct correlation with BMI and weight gain. The pattern of adiponectin and leptin production observed in adolescent pregnant women is similar to that seen in adult pregnant women.

Keywords: Leptin; Adiponectin; Adolescent; Pregnancy; Adipokine

Introduction

Adipokines are proteins secreted by adipose tissue, described as molecules with diverse physiological structures and functions [1,2]. They act as classical cytokines, growth factors and complementary systemic proteins, are involved in the regulation of blood pressure, vascular homeostasis, angiogenesis, lipid and glycemia metabolism [3]. Adiponectin and leptin are the most abundant adipokines synthesized by adipose tissue [4].

Adiponectin exhibits antihyperglycemic, antiatherogenic and anti-inflammatory properties, promotes insulin sensitization, decreases the hepatic production of glucose and increases the action of insulin in the liver [5-7]. Serum levels may vary according to sex, being higher in women [8,9]. Research does not indicate that this difference also occurs with adolescents, but they report lower concentrations between the pubescent and obese [10]. At puberty the levels are significantly lower than those observed in the pre-pubertal period, this is presumed to be a function of the decrease in Insulin Resistance (IR) that occurs at this stage [11,12].

The serum concentration of adiponectin during pregnancy decreases with the advancement and installation of IR, returning to the pre-gravid concentration after delivery. Studies indicate that there is a negative correlation between serum levels and gestational age [5-7,13-15], it seems that during pregnancy, adiponectin acts on the energy balance, on the fatty oxidation of fatty acids, decreasing production glucose and increasing the action of insulin by the liver

[13,16,17].

Leptin is involved in inflammatory processes, immune mediated responses, appetite regulation [18], energy storage, modulation of the homeostatic system and regulation of blood pressure, aid in thermogenesis, angiogenesis, insulin secretion by the pancreas, in the production of glucose by the liver and in its uptake through the muscle [19,20-22]. Its synthesis is directly related to the amount of adipose tissue present in the individual's body, therefore, plasma levels differ in people with the same Body Mass Index (BMI) [23]. In addition to BMI, other factors such as sex, age, fasting, overeating, diet composition and hormones may influence the serum levels of this adipokine [6,7,9,10].

In adults, plasma concentration is higher in females when compared to values found in males [18,28]; in children and adolescents, leptin levels are related to changes in body composition [53-55]. In the gestational period, the major changes in plasma levels of this adipokine occur, being significantly higher [18,29,30]. During pregnancy, leptin plays a key role in regulating placental growth, nutrient transfer, angiogenesis, pulmonary maturation, and trophoblast invasion [31].

Research has shown that blood levels of adiponectin and leptin are related to physiological changes during pregnancy in adult women, but information on the behavior of these molecules in adolescent gestation so far remains unknown.

Thus, the objective of this study was to evaluate the serum levels

Table 1: Adiponectin serum concentrations (ng/mL) during the gestational weeks of adolescents attended in the prenatal sector of adolescents of Escola Paulista de Medicina - UNIFESP.

Gestational Week	N	Minimum	25% Interquartile Interval	Medium	75% Interquartile Interval	Maximum
9 ^a	16	1726	2047	3473	4331	6282
10 ^a	16	1141	2507	3733	5267	7295
11 ^a	15	1350	2596	3786	6389	7575
12 ^a	15	1058	2891	3677	5263	6924
13 ^a	18	2392	2958	3578	4442	8879
14 ^a	16	1507	1570	3149	3823	5690
15 ^a	15	1258	1913	2635	6579	14284
16 ^a	15	1001	1514	2569	6250	10943
17 ^a	15	1205	2447	3735	5690	8377
18 ^a	15	1205	2476	3781	4483	6579
19 ^a	15	1575	2964	3835	7362	9697
20 ^a	15	1322	1599	2998	3459	5960
21 ^a	15	1526	2224	3520	5784	10943
22 ^a	15	1579	2152	3369	4954	9697
23 ^a	15	1569	1632	2363	5236	5471
24 ^a	15	1233	3349	4183	6940	8520
25 ^a	15	1511	2569	3120	4250	6199
26 ^a	15	1540	1789	2286	4445	5391
27 ^a	15	1278	2157	3292	3697	5541
28 ^a	15	1353	2458	3520	4723	8588
29 ^a	15	1036	1599	2362	3261	5367
30 ^a	15	1169	1838	2372	3336	4445
31 ^a	15	1247	1831	2534	3687	7287
32 ^a	15	1007	1951	2326	3372	6352
33 ^a	15	1252	1568	2160	2470	5037
34 ^a	15	1158	1336	2564	3569	5348
35 ^a	15	1506	1800	2963	3185	22103
36 ^a	15	1621	1883	2610	4789	9056
37 ^a	15	1036	1659	1931	3466	9754
38 ^a	15	1509	1943	2964	3233	5031
39 ^a	15	1504	1863	2275	3103	3589

Kruskal-Wallis test, $p=0,0003$.

of these molecules during the evolution of gestation in adolescents and to develop a gestational curve for weekly serum levels, and to correlate pre-gestational BMI and total weight gain of adolescents with concentrations of these adipokines.

Materials and Methods

This was a prospective cohort study performed with adolescent pregnant women attended in the Adolescent Prenatal Sector of the Paulista School of Medicine from February 2013 to March 2018. The study was submitted to the Research Ethics Committee of the Federal University of São Paulo / Hospital São Paulo, being approved under the consubstantiated opinion nº 1514/11. Included in this study were adolescent eutrophic pregnant women who were being followed in the prenatal sector of adolescents of Escola Paulista de Medicina

(EPM) - UNIFESP.

All patients who accepted to participate in the study spontaneously were included in the sample after reading, understanding and signing the informed consent form.

The patients were followed during gestational development, and blood samples were collected during pregnancy (3 samples, one in each trimester). Pregnant women, older than 10 years and younger than 20 years [32], who presented with pre-gestational BMI of eutrophy (18.5-24.9 kg/m²) were included in this study [33]. Those with multiple gestation, or on the use of corticosteroids, antibiotics, immunosuppressant's and / or anti-inflammatories, and those that evolved with some clinical intercurrent during pregnancy progression, such as gestational diabetes, preeclampsia, intrauterine

Table 2: Serum leptin concentrations (ng/mL) during the gestational weeks of adolescents attended in the prenatal sector of adolescents of the Escola Paulista de Medicina - UNIFESP.

Gestational Week	N	Minimum	Maximum	Average	Standard Deviation
9 ^a	16	9,6	59,75	24,29	14,83
10 ^a	16	9,57	45,9	22,11	10,09
11 ^a	15	11,29	98,01	38,46	30,29
12 ^a	15	5,83	95,65	40,10	32,56
13 ^a	18	11,48	103,3	29,91	22,45
14 ^a	16	5,59	54,48	26,12	15,27
15 ^a	15	2,15	65,16	24,51	16,51
16 ^a	15	5,29	82,23	32,91	22,24
17 ^a	15	7,74	43,74	18,47	10,69
18 ^a	15	7,73	38,06	19,54	8,867
19 ^a	15	8,84	55,34	28,1	11,16
20 ^a	15	11,56	96,91	38,42	23,87
21 ^a	15	12,85	54,45	28,34	11,01
22 ^a	15	12,15	54,46	24,37	11,97
23 ^a	15	7,18	55,45	33,53	15,64
24 ^a	15	3,42	46,22	20,01	13,26
25 ^a	15	4,76	61,51	21,84	17,05
26 ^a	15	11,7	48,05	31,00	12,96
27 ^a	15	4,47	51,06	26,15	13,98
28 ^a	15	1,31	40,67	24,89	11,11
29 ^a	15	11,05	69,42	31,59	16,25
30 ^a	15	4,67	87,76	39,67	23,52
31 ^a	15	11,88	83,12	40,42	23,78
32 ^a	15	4,49	77,36	39,57	22,15
33 ^a	15	11,04	160,2	39,30	39,22
34 ^a	15	7,56	68,42	30,62	17,49
35 ^a	15	12,38	85,75	45,52	21,32
36 ^a	15	2,87	77,51	42,39	22,37
37 ^a	15	14,17	79,61	40,15	16,93
38 ^a	15	19,63	85,75	49,93	22,51
39 ^a	15	11,07	85,5	34,75	20,57

ANOVA One-Way Test, $p < 0,0001$.

growth restriction, or (hypertension, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, rheumatic fever and asthma). BMI was calculated based on the pre-gestational weight and height, being mentioned by the pregnant woman at the first prenatal visit, the nutritional diagnosis was determined according to the Institute of Medicine (IOM) (2009) [33]. Gestational weight gain was determined by the difference between the weight of the patient at the last pre-delivery visit and the pre-gestational weight.

We collected and stored in dry tube, 8 mL of blood by venipuncture, and serum levels of adiponectin and leptin were evaluated by the ELISA method, and the plasma values of the molecules expressed in ng/mL (nanograms / milliliters) were determined.

The normality tests Skewness and Kurtosis, Kolmogorov-Smirnov

and Shapiro-Wilk were applied to evaluate the distribution of the quantitative variables. For analysis of variance between the groups the One-Way ANOVA test was applied to measure those of parametric distributions and the Kruskal-Wallis test was used to analyze the non-parametric ones, followed by Tukey post-tests or Dunn 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 analyzes were performed using standard software (GraphPad Prism, v6.0 for Windows). As we did not find previous studies that allowed to calculate the sample size recommended for this investigation, the proposal was to carry out a study that serves as the basis for future research. Thus, the sample was of convenience, including all the patients attended in the study period who were in

agreement with the established parameters.

Results

The study included 157 healthy adolescent pregnant women, totaling 471 blood samples collected between the 9th and 39th gestational week.

The age of the pregnant women included in this study ranged from 12 to less than 20 years, with an average of 16.51 years (standard deviation 1.76), and there was no significant difference between patients grouped by gestational age ($p = 0.06$; ANOVA One-Way Test). Regarding the race / color of the patients included, there was a statistical difference between those grouped by gestational age ($p < 0.0001$; Chi-Square test). The sample included 81 collections of blood from brown adolescents and 76 collections of blood in white adolescents.

The pre-gestational BMI was 22 kg/m² (Interquartile Interval 21,40 - 22,50), presenting a significant difference between the patients included in the study grouped by gestational age ($p = 0.004$; Kruskal-Wallis test).

We also identified statistical difference regarding smoking and alcohol variables ($p < 0.0001$, Chi-square test, both). Our results showed that 4.9% ($n = 23$) of the sample studied had smoking during gestation and 2.3% ($n = 11$) of ingesting alcohol.

With the evolution of pregnancy, serum levels of adiponectin presented significant differences, characterized by a drop in concentration ($p = 0.0003$; Kruskal-Wallis test). The data are presented in (Table 1 and Figure 1).

We did not observe a correlation between the pre-gestational BMI, the weight gain of the pregnant women and the serum levels of adiponectin ($p = 0.36$, $p = 0.10$, respectively).

After the Kruskal-Wallis test, we observed that there were no statistical differences in serum adiponectin levels between the gestational weeks of the adolescents included in the study (Dunn's post-test).

With the advancement of gestational weeks, we identified an increase in serum leptin levels ($p < 0.0001$; One Way Test-ANOVA). The results are described in (Table 2 and Figure 2).

After the One-Way ANOVA test, we observed statistical differences regarding serum leptin levels between some gestational weeks (compared to two, Tukey's post-test). We identified differences in the comparisons between the 17th to the 38th, the 18th to the 38th, the 24th to the 38th and the 25th to the 38th.

We identified a positive correlation between pre-gestational BMI and the weight gain of pregnant women with serum leptin levels ($p = 0.003$, $p = 0.0007$, respectively).

Discussion

This study performed with adolescent pregnant women evaluated the serum profile of adiponectin (ng/mL) and leptin (ng/mL) during the course of pregnancy (9th to 39th gestational weeks). Through the values found, a gestational curve was developed with the serum concentrations for these molecules.

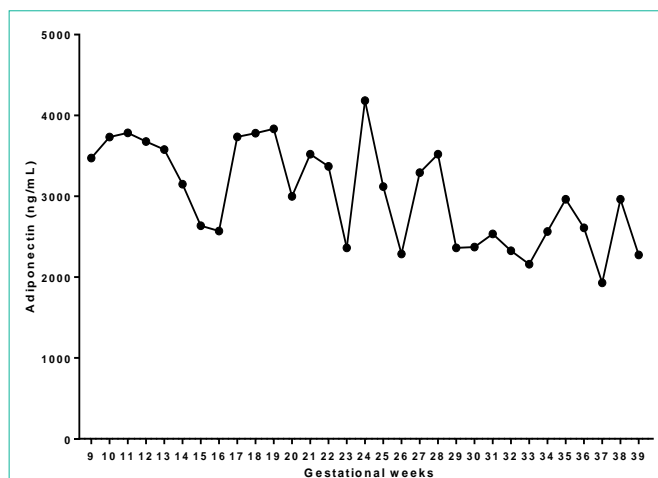


Figure 1: Adiponectin serum levels (ng/mL) during the gestational weeks of adolescents attended in the prenatal sector of adolescents of Escola Paulista de Medicina - UNIFESP.

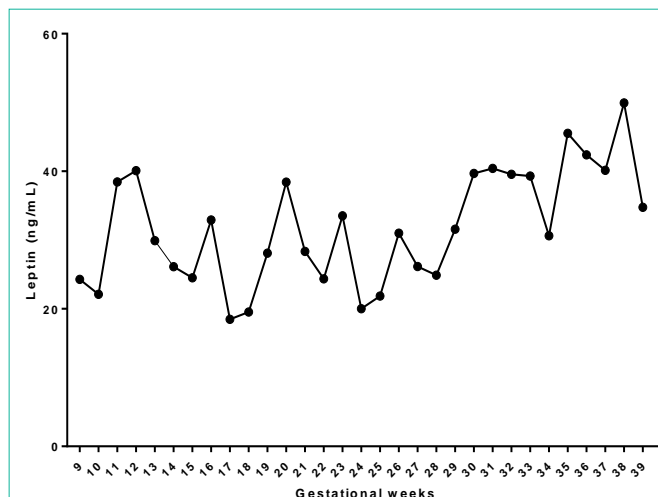


Figure 2: Serum levels of Leptin (ng/mL) during the gestational weeks of adolescents attended in the prenatal sector of adolescents of Escola Paulista de Medicina - UNIFESP.

In pregnancy, adiponectin acts on the development of the inflammatory response in the maternal-fetal unit. This reaction is physiological and needs to be modulated so that an adequate evolution of the pregnancy occurs. The involvement of this protein in local and systemic inflammatory reactions is already well known [34].

The literature indicates that this molecule presents specific behavior in pregnant women, but, unlike other adipokines, its serum concentration tends to reduce with the progression of gestation [13,17,35,36]. There appears to be a negative correlation between adiponectin and gestational age [14,15]. Similar results were observed in our study with adolescents.

Some authors have reported that plasma levels of adiponectin decrease gradually with the advancement of pregnancy because its concentration reduces as the fat tissue increases [13-15,37], but these values return to normal soon after delivery [13]. Studies have reported that the serum concentration of adiponectin at certain

periods of gestation in healthy women may be altered from the first trimester [36-38]. Some studies indicate a correlation between IR and adiponectin concentration in adult pregnant women [39-42].

In similar studies, researchers demonstrated significant differences during pregnancy progression in adults, where they observed a reduction in the serum concentration of adiponectin when they compared the first to the third trimester [6,37,39,43].

Our results show that the behavior of adiponectin in the evolution of gestation in adolescents is similar to what the literature indicates in pregnancy for adults.

When we observed the serum levels of adiponectin (ng/mL) during gestational weeks we found that the concentration of this molecule tends to be higher at the beginning of gestation (median 3473 ng/mL) than at the end of pregnancy (median 2275 ng/mL).

In this study, we observed a peak serum adiponectin concentration at the 24th gestational week. Our hypothesis is that this alteration is related to the installation of IR, however we do not find other studies that support this hypothesis in the literature.

The literature shows that, unlike other hormones secreted by adipose tissue, serum adiponectin levels decrease as adiposity increases, being inversely correlated with obesity, IR and metabolic syndrome [2,44].

In relation to leptin, our study showed a significant increase ($p = 0.0001$) with the evolution of pregnancy, suggesting that this change can be gradually observed. The literature shows that plasma concentrations of leptin increase during pregnancy in adults, concluding that this is a condition in which hyperleptinemia is observed [18,45-47].

Researchers studying serum levels of leptin in adult pregnant women found that the plasma concentration had a significant increase between the first and third trimester of gestation with postpartum decline [46]. During pregnancy, the concentration of leptin in maternal serum is higher than that observed in non-pregnant women [29].

Our results were similar to those presented in recent studies with adult pregnant women [45,49,50]. Serum levels of leptin present changes during pregnancy, this increase occurs in pregnant women with and without obstetric complications. Elevation in serum concentration during the course of pregnancy has been extensively investigated with the main purpose of elucidating a possible relationship to clinical interurrences such as preeclampsia, gestational diabetes, intrauterine growth restriction and low birth weight [19,28,45,46,51-55].

Studies have shown that serum leptin concentration during pregnancy with clinical complications appears to be related to hyperleptinemia [28,45,46,51-55], and that women who experience spontaneous or recurrent miscarriage appear to have lower plasma levels such a molecule [56,57].

Our results are similar to those observed in gestation of adult women [45,52]. Serum leptin concentrations begin to rise from the onset of pregnancy and are higher than that of non-pregnant women throughout pregnancy [23].

The literature indicates that leptin values are directly related to the amount of adipose tissue present in the body, since the plasma concentration differs in people with the same BMI [23].

It is known that gestation is characterized by metabolic and endocrine adaptations of the maternal organism, including increased body weight and adipose tissue. Thus elevated serum leptin levels during pregnancy are related to weight gain and BMI, as well as changes in hormone levels that may stimulate the secretion of this molecule (eg, insulin) [59]. Our results are similar to those performed with adult pregnant women, where a positive correlation was observed between maternal plasma leptin concentration and anthropometric data at both the beginning and the end of gestation. This association suggests that body weight and, probably, adiposity gain are important factors for the increase in circulating leptin levels [58,60]. Thus, based on our study we can affirm that in adolescent pregnant there is an increase in the plasma concentration of leptin and reduction in adiponectin during the course of gestation. In adolescents we observed similar results to those observed for the adult pregnant woman, thus showing that these molecules have the same behavior independent of the age group. The continuity of this research may contribute to elucidate the doubts about the behavior of adipokines in the progression of gestation, but it is worth noting that until now the literature does not present a gestational curve with the values determined for adults and/or adolescents.

Conclusion

With the evolution of pregnancy, serum levels of adiponectin (ng / mL) presented a reduction in blood concentration, with significant differences ($p = 0.0003$). When we compared the serum values of adiponectin from two to two gestational weeks, we did not observe a statistically significant alteration, evidencing a progressive decrease. No correlation was observed between the pre-gestational BMI and the weight gain of the pregnant women and the plasma levels of adiponectin (ng/mL) ($p = 0.36$, $p = 0.10$, respectively).

With the evolution of pregnancy, serum levels of leptin (ng/ mL) showed an increase in blood concentration, with significant differences ($p < 0.0001$). The serum concentration of leptin (ng/mL) presented statistically significant differences when we compared the 17th, 38th, 18th, 38th, 24th, 38th and 25th, 38th. We observed a positive correlation between the pre-gestational BMI and the weight gain of the pregnant women and the serum concentration of leptin (ng/mL) ($p = 0.003$; $p = 0.0007$, respectively).

The pattern of adiponectin and leptin production observed in adolescent pregnant women is similar to that seen in adult pregnant women.

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Author contributions

Indiomara Baratto – Performed the laboratories tests, collected the data, collaborated in patient recruitment, made clinical contributions, wrote the manuscript.

Silvia Daher – designed the study analyzed the data and performance the statistical analysis

Thalita Frutuoso Lobo – performed the laboratories tests and the

statistical analysis

Cristina Aparecida Falbo Guazzelli – designed the study, collected the data, collaborated in patient recruitment, wrote and corrected the manuscript.

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