

ARTÍCULO ORIGINAL

## Serum IGF-I and IGFBP-3 levels in pregnant adolescents in an economically depressed community

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The growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis is believed to play a role in growth during postnatal and fetal life and is regulated by nutrition. However, very few studies have examined the effects of malnutrition on the regulation of the GH/IGF-I axis in human pregnancy during adolescence. In this study we compared the serum IGF-I and IGFBP-3 levels in a group (n=62) of pregnant adolescents in their second trimester of pregnancy and living in a poor area in the city of Bogotá, with those of a group (n=36) of non-pregnant adolescents from the same area. As reference, a group (n=20) of non-pregnant adolescents from a middle-class district in the same city was utilized. It was observed that the non-pregnant adolescents from the poor area were all below the 3<sup>rd</sup> percentile and showed significantly ( $p<0.05$ ) reduced height and weight in comparison with subjects from middle-class area, suggesting growth retardation in this group of subjects. Serum IGF-I and IGFBP-3 levels were significantly ( $p<0.0001$ ) reduced, in comparison with subjects from the middle-class area, although there was no evidence of delay of puberty based on Tanner stage of sexual development and only subjects at Tanner 5 were included in this study. When the serum concentrations of IGF-I and IGFB-3 in the population of pregnant adolescents were investigated, no differences were found with those observed in the non-pregnant adolescents from the poor district, which means that pregnancy was not accompanied by the elevation in IGF-I levels observed in normal pregnancies. In conclusion, the low circulating IGF-I levels observed in pregnant adolescents could mirror abnormalities on the normal physiology of the GH/IGF-I axis, whose effects on fetal growth are not completely understood.

**Key words:** IGF-I, IGFBP-3, adolescence, pregnancy, malnutrition.

### Niveles séricos de IGF-I e IGFBP-3 en adolescentes embarazadas provenientes de un sector socioeconómico de bajos ingresos

El eje de la hormona de crecimiento (GH)/factor de crecimiento similar a la insulina tipo-I (IGF-I) participa en el crecimiento durante la vida postnatal y fetal y se encuentra regulado por la nutrición. Sin embargo, muy pocos estudios se han adelantado con el fin de comprender los efectos de la mala nutrición sobre dicho eje durante el embarazo en la adolescencia. En este estudio se determinaron los niveles séricos del IGF-I y de IGFBP-3 en un grupo (n=62) de adolescentes en el segundo trimestre de embarazo y provenientes de un estrato pobre de la ciudad de Bogotá y se compararon con los de un grupo (n=36) de adolescentes del mismo estrato. Como referencia se tomaron los valores obtenidos en un grupo (n=20) de adolescentes de un estrato de clase media de la misma ciudad. Se encontró que las adolescentes del estrato pobre presentaban un crecimiento por debajo del percentil 3 con talla y peso significativamente ( $p<0,05$ ) menores en comparación con los adolescentes de clase media, lo que sugiere retardo en el crecimiento. Los niveles séricos de IGF-I/IGFBP-3 fueron significativamente ( $p<0,0001$ ) más bajos, en comparación con los de las adolescentes del estrato más alto, sin evidencia de retardo en el desarrollo pubertal, con base en la clasificación Tanner de desarrollo sexual y sólo los sujetos en Tanner 5 se incluyeron en este estudio. No se encontraron diferencias entre las concentraciones de IGF-I/IGFBP-3 en el suero de embarazadas y no embarazadas del estrato pobre, lo que muestra que no se presentó el incremento esperado de un embarazo normal. En conclusión, los bajos niveles de IGF-I

circulante que se encontraron en las adolescentes embarazadas podrían estar reflejando anomalías en la fisiología normal del eje GH/IGF-I, cuyos efectos sobre el crecimiento fetal no están completamente dilucidados.

**Palabras clave:** IGF-I, IGFBP-3, adolescencia, embarazo, mala nutrición.

The insulin-like growth factor-I (IGF-I) is believed to mediate many of the anabolic and mitogenic actions of growth hormone (GH) (1). IGF-I serum level is stable during the day due mainly to the complexing with a family of IGF-binding proteins (IGFBPs). Of the six known high affinity binding proteins, IGFBP-3 is normally the major serum carrier of IGF-I in the form of a large ternary complex (150kDa) together with an acid-labile subunit (2). Both acid-labile subunit and IGFBP-3 are GH dependent. Limited proteolysis by a variety of serine proteases now appears to be a fundamental mechanism in regulating the bioavailability of IGF-I, both in the bloodstream and at the cellular level (3).

The changes in IGF-I levels throughout life are similar to those of GH. With the onset of puberty there is a two- to three-fold rise in serum IGF-I concentrations, followed by a decline such that average adult levels are reached by the twenties (4). Similar to IGF-I but less age-dependent, serum IGFBP-3 levels rise to a peak during puberty and then slowly decline during adulthood (5). During pregnancy there is a continuous rise in maternal serum IGF-I levels resulting in a two- to three-fold elevation during the last trimester, in spite of the attenuation of pituitary GH release (6). The responsible factors for this increase are not clearly understood, but the GH family of hormones secreted by the placenta have been postulated as possible modulators of IGF-I levels during pregnancy (7).

Pregnancy during adolescence is associated with low birth weight and increasing morbidity and mortality rates. Malnutrition is also considered to be a cause of fetal growth failure. Many studies have documented the regulatory role of nutrition on the GH/IGF-I axis (8,9) and serum IGF-I levels are widely used as index of the nutritional state

(10). However, very few studies have been described to understand the effects of malnutrition on the GH/IGF-I axis in human pregnancy during adolescence. The aim of the present study was to compare the IGF-I /IGFBP-3 serum concentrations in a population of pregnant adolescents living in a poor area, with those of a group of non-pregnant subjects from the same area. As reference, a group of non-pregnant adolescents from a middle-class district were used.

## Methods

### Subjects

118 volunteer adolescents, with chronological ages between 13 and 19 years, living in Bogotá, Colombia, were studied. Subjects were distributed into three groups: pregnant adolescents (n=62) from an economically depressed district were in their second trimester of pregnancy (group 1). Non-pregnant adolescents were either from the same poor district as the pregnant (n=36) (group 2) or from a middle class area (n=20) (group 3). All subjects were examined by the same physician. Height and weight were measured with a health o meter instrument and body mass index (BMI) was calculated. Sexual development of non-pregnant adolescents was classified according to Tanner stages and only subjects at Tanner 5 were included in this study. Subjects with chronic diseases, under medication or abnormal TSH and/or free T4 levels, were excluded from this study.

### Measurements

Blood samples were obtained the day of clinical examination and serum was stored at -20 °C until assayed. Serum TSH levels were determined by IRMA (Diagnostic Products Corporation, USA, reference range: 0.3-5 µIU/ml) and free T4 levels by RIA (Diagnostic Products Corporation, USA, reference range: 0.7-2.2 ng/dl). All subjects showed serum concentrations of these hormones in the normal range.

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Serum albumin levels were measured by the bromocresolulphophthalein method (11).

Total IGF-I levels were determined in acid-ethanol extracted serum using a specific radioimmunoassay. Human IGF-I (receptor grade) and polyclonal anti-IGF-I were obtained from GroPep (Adelaide, Australia). Truncated des(1-3)IGF-I (Pharmacia, Sweden Lot No. L1B-Do1) was used as tracer to avoid interference from IGF-binding proteins residues remaining after acid-ethanol extraction (12). Intra- and inter-assay coefficients of variation were 6 and 12%, respectively.

IGFBP-3 was determined by IRMA (DSL-6600) (Diagnostic Systems Laboratories, Inc.) sensitivity 0.5 ng/ml. Intra- and inter-assay coefficients of variation were 1.8 and 1.9%, respectively.

### Statistics

Results were compared utilizing two-way ANOVA by the General Linear Models procedure of the Statistical Analysis Systems program (SAS Institute Inc., 1985). Values were considered to be significantly different if p values were less than 0.05.

### Results

Chronological age was similar for the three groups of adolescents (table 1). However, the middle class group of non-pregnant adolescents (group 3) displayed significantly higher ( $p < 0.05$ ) height in comparison with the other two groups of adolescents (pregnant and non-pregnant) living in the poor district. Accordingly, all subjects in group 3 were above or at least at the 25<sup>th</sup> percentile, whereas subjects in group 3 were all below the 3<sup>rd</sup> percentile according to NCHS tables (Maryland, USA).

When weight was compared (table 1), the lowest value was seen in the group of adolescents from the poor district (group 2), which was significantly ( $p < 0.0005$ ) lower than the value exhibited by the group of adolescents living in the middle-class (group 3).

Serum albumin was significantly ( $p < 0.0001$ ) lower in the pregnant group 1 compared with the non-pregnant groups 2 and 3. No significant differences were obtained between groups 2 and 3 (table 1).

Serum IGF-I concentrations were significantly ( $p < 0.0001$ ) higher in the middle-class adolescents (group 3) ( $464.3 \pm 108.0$  ng/ml) compared with the subjects in the other two groups (figure 1A). No significant difference in serum IGF-I was observed between the group of pregnant adolescents ( $262.9 \pm 78.8$  ng/ml) and the group of non-pregnant adolescents from the same poor district (group 2) ( $205.4 \pm 64.8$  ng/ml).

Similarly, serum IGFBP-3 levels were significantly ( $p < 0.05$ ) higher in group 3 ( $5,002.8 \pm 769.8$  ng/ml) in comparison with other groups 1 and 2 ( $3,657.8 \pm 433.2$  ng/ml;  $3,606.1 \pm 423.4$  ng/ml, respectively) (figure 1B). The following correlations were found between IGF-I levels and weight ( $r = 0.46$ ,  $p < 0.01$ ), height ( $r = 0.53$ ,  $p < 0.01$ ) and IGFBP-3 ( $r = 0.36$ ,  $p < 0.01$ ) for the adolescents from groups 1 and 2 together.

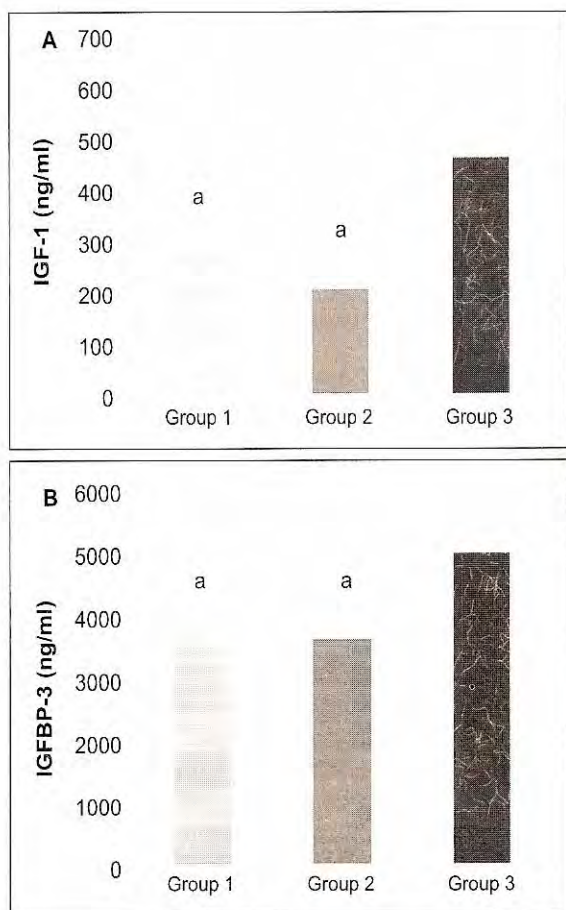
### Discussion

Pregnancy during adolescence is associated with low birth weight and increasing morbidity and mortality rates (13). The responsible factors for fetal growth and development are not as yet completely understood, although maternal nutrition appears to display an important role. The relationship between nutrition and the GH/IGF-I axis is well established, but in pregnancy it is

**Table 1.** Comparison of some variables in the three groups of adolescents; results are expressed as mean values  $\pm$  SD.

Variable	Group 1 (n= 62)	Group 2 (n=36)	Group 3 (n=20)
Chronological age (years)	16.9 $\pm$ 1.1 <sup>a</sup>	15.7 $\pm$ 1.3 <sup>a</sup>	15.9 $\pm$ 1.6 <sup>a</sup>
Height (m)	1.53 $\pm$ 0.06 <sup>a</sup>	1.48 $\pm$ 0.04 <sup>a</sup>	1.61 $\pm$ 0.07 <sup>a</sup>
Weight (kg)	56.7 $\pm$ 7.1	49.2 $\pm$ 5.7 <sup>a</sup>	57.8 $\pm$ 9.9 <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	24.1 $\pm$ 2.6	22.5 $\pm$ 2.3	22.3 $\pm$ 3.0
Albumin (g/dl)	3.98 $\pm$ 0.49 <sup>a</sup>	4.68 $\pm$ 0.34 <sup>b</sup>	4.73 $\pm$ 0.36 <sup>b</sup>

Mean values not sharing a common letter were significantly different,  $p < 0.05$ .



**Figure 1.** Serum IGF-I and IGFBP-3 levels in pregnant adolescents (group 1, n=62) and non-pregnant adolescents (group 2, n=36) from a low socioeconomic community, compared to a group of non-pregnant adolescents (group 3, n=20) from a middle-class community. Values are means for each group with standard deviations represented by vertical bars. Bars not sharing a common letter are significantly different,  $p < 0.05$ .

poorly documented. Some studies have shown a positive correlation between the birth weight and maternal serum IGF-I concentrations (14), although other reports do not support this correlation (15).

In this study we found significantly reduced height and weight in the group of adolescents from marginal areas in comparison with those from the middle class area, suggesting growth retardation in these subjects although no clinical evidence for delay of puberty was observed. Results showed however, an harmonic or adequate relationship

between weight and height, that can be attributed to a chronic but moderate malnutrition, which is characteristic of a deprived socioeconomic environment. These results are in agreement with previous anthropometric studies in Colombian children (16) and developing countries (17). In this study a lack of correlation was observed between serum IGF-I and BMI in the two groups of non-pregnant adolescents. Similar results were observed in a previously described study comprising 243 peripuberal girls, who failed to show a correlation between IGF-I and BMI (18).

Albumin concentration, which has been widely utilized as a nutritional marker (19), was not significantly different between the two non-pregnant groups. This finding is in agreement with the current notion that serum albumin is not a sensitive biochemical marker of the nutritional state (20,21). On the other hand, we found lower albumin concentrations in the poor pregnant group, in comparison with the other two groups. In order to distinguish the effect of malnutrition from the condition of pregnancy during adolescence, we considered important to include a reference group comprising middle class pregnant adolescents. However, information was available only from four pregnant volunteers which is not enough for the purpose of comparison. Regardless of the small size of the group, we found a similar reduction in serum albumin (results not shown), thus reflecting the albuminuria normally present during pregnancy and not the result of nutritional deficiencies.

Serum IGF-I levels in poor adolescents were significantly reduced in comparison with the group of middle-class adolescents, in agreement with a possible growth retardation, as suggested by the anthropometric study. On the other hand, pregnancy constitutes an additional factor that could worsen the condition. Adolescents were in their second trimester of pregnancy, but their circulating IGF-I was not different from the one observed in non-pregnant subjects belonging to the same area. This finding does not agree with the moderate increase that has been reported previously during pregnancy (6,22). It must be emphasized that the reported studies were performed in developed countries and in adult pregnancies, and to our knowledge a similar study

has not been performed on teenage pregnancies under poor living conditions and these are the first results reported on a population of pregnant adolescents in Colombia.

Similarly, highest IGFBP-3 levels were found in the middle class non-pregnant adolescents, but the values obtained in this study were lower than those reported by Juul (5). No differences were observed in serum IGFBP-3 levels between the two groups of adolescents (pregnant and non-pregnant) from marginal areas. It has been reported that immunoreactive IGFBP-3 is elevated in the plasma of pregnant women (23) and that proteolysis is known to be maximal during gestation giving fragments with reduced affinity for IGFs, particularly for IGF-I (24). Any small rise in IGFBP-3 in pregnant subjects, if present, was not detected by the assay method employed in this study. Alternative assay methods, like Western Ligand or Immuno Blot, which are based on electrophoretic separation of the different proteins, could discriminate between the intact IGFBP-3 and fragments, but sensitivity is lower than immunoradiometric assays.

Fetal growth is determined by multiple factors, many of which are still not understood. Substrate supply, endocrine status and placental function play important roles in fetal development (25). It has been postulated that somatomammotropin and the placental growth hormone variant are responsible for the IGF-I rise during pregnancy (26). Although IGF-I does not cross the placental membranes (27), it may be important in maternal metabolism and placental growth. The absence of such rise in the pregnant population of this study, introduces an interesting question, namely the association between reduced IGF-I/IGFBP-3 maternal levels and the high incidence of low birth weight observed in pregnancy during adolescence. It is well established that nutrition is a regulator of circulating IGF-I/IGFBP-3, therefore, the reduced levels obtained in the group of poor adolescents in comparison with the middle-class group, could reflect the depressed environment. The differences between the two groups from the poor economic area and the non-pregnant middle class group suggest a possible relationship between social class (chronic malnutrition and other stressors)

and IGF-I/IGFBP-3 levels which could be examined including a larger group of middle class pregnant adolescents, to confirm the preliminary results observed in this study. In conclusion, the present study gives evidence of growth retardation in the marginal group of adolescents, most likely due to a nutritional stress, a condition that could be more severe after pregnancy and whose consequences on fetal growth are still not completely clear.

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