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Social Determinants and Cortisol Levels in Fetal growth of Adolescent Pregnant Women. Colombia (2022-2023)

Determinantes sociales y niveles de cortisol en el crecimiento fetal de gestantes adolescentes. Colombia (2022-2023)

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Abstract

Introduction: Biopsychosocial risk (BPR) is associated with preeclampsia and low birth weight. **Objective:** To evaluate the association between BPR and cortisol levels in adolescent pregnant women with intrauterine growth restriction, a case-control nested in a cohort study was performed. Eight regions of Colombia were evaluated. **Methodology**: Cases (IUGR- Intrauterine Growth Restriction) (< 10th percentile) and controls ($\geq$ 10th percentile) (1/3) were matched and nested in a cohort. PBR and salivary cortisol were evaluated with respect to preeclampsia and IUGR. A sample size was calculated (α error= 0.05 β error= 0.2) and univariate, bivariate analysis and logistic regression were performed. **Results:** 138 adolescent pregnant women (33 cases and 105 controls) with age of 17.4 ± 1.5 years and pregnancy of 30.4 ± 4.4 weeks were recruited. High PBR (Prenatal biopsychosocial risk) were observed in Afro-American or indigenous. 74.6 % in high school, 39.5 % working, 26.9 % without social support, 15.7 % malnourished (Body Mass Index < 18.5), 13.4 % with high levels of cortisol (> 21.6 nmol/L). 12 (9.0 %) developed preeclampsia. Having good nutrition (BMI 18.5-29.9) was protective to IUGR [OR= 0.27 confidence interval 95 % 0.09- 0.84, p= 0.02]. Social support, employment and education were shown to be protective factors to IUGR [OR= 0.08 (CI 95 % 0.01-0.31) p= 0.001] and was not associated with cortisol levels. East region was identified as the highest risk for IUGR [OR= 8.44 (95 % CI 2.89 - 27.22) (p= 0.001)]. **Conclusions:** Social determinants were protective, and cortisol levels were not associated with risk. Regional differences were observed.

Keywords: Biopsychosocial Risk; Intrauterine Growth Restriction; Adolescence; Education; Low Birth Weight; Preeclampsia.

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Resumen

Introducción: El riesgo biopsicosocial (RBP) se asocia con preeclampsia y bajo peso al nacer. **Objetivos:** Evaluar la asociación entre RBP, cortisol, y el crecimiento fetal en gestantes adolescentes en Colombia. **Metodología**: Un estudio de casos (pequeño para la edad gestacional (PEG) (< percentil 10) y controles (≥ percentil 10) (1/3) apareado y anidado en una cohorte fue realizado. Se evaluaron ocho regiones de Colombia. Se evaluó RBP y el cortisol con respecto a preeclampsia y BPN. Se calculó el tamaño de la muestra (α error= 0.05 β error= 0,2) y se realizó análisis univariado, bivariado y regresión logística. **Resultados:** Se estudiaron 138 embarazadas adolescentes (33 casos/105 controles) (edad de 17.4 ± 1,5 años) (30.4 ± 4,4 semanas). Se observó un RPB alto en afroamericanas o indígenas. El 74.6 % cursaba estudios secundarios, 39.5% trabajaba, 26.9 % carecía de apoyo social, 15.7 % eran desnutridas (Índice de Masa Corporal < 18.5), 13.4 % presentaba niveles elevados de cortisol (> 21.6 nmol/L). 12 (9.0%) desarrollaron preeclampsia. Una buena nutrición (IMC 18,5-29,9) se observó protector para RCIU [OR= 0.27 IC 95 % 0.09- 0.84, p= 0.02]. El apoyo social, el empleo y la educación se observaron cómo protectores para RCIU [OR= 0.08 (IC 95 %: 0.01-0.31) p= 0.001] sin relación con los niveles de cortisol. La región oriental de Colombia fue la de mayor riesgo [OR= 8.44 (IC 95 % 2.89 – 27.22) (p= 0.001)]. **Conclusiones:** Los determinantes sociales fueron protectores y el cortisol no se asociaron con el riesgo. Se observaron diferencias regionales.

Palabras clave: Riesgo Biopsicosocial; Restricción del Crecimiento Intrauterino; Adolescencia; Educación; Bajo Peso al Nacer; Preeclampsia.

Introduction

Preeclampsia is a leading cause of maternal death, perinatal death, and low birth weight in middle- and low-income countries[1], disorders associated with elevated levels of stress[2], inflammation[1] affect fetal growth and facilitate low birth weight (LBW)[3]. Adolescent pregnant women have been associated with behavioral disorders elevated cortisol and elevated uterine vascular resistance[4,5,2] . Prenatal biopsychosocial risk (PBR)[6] evaluates a set of biological and psychosocial risk factors that have been associated with maternal, perinatal complications, and LBW[3]. Social support facilitates fetal growth[7]. The psychosocial risks of pregnancy together with biological factors in adolescence could affect fetal growth with negative consequences. It's known the association between IUGR and cognitive deficits in children[8], learning disorders[9], adolescent suicide[10], and fetal programming for adult cardiovascular diseases[11]. To evaluate the association between social determinants and cortisol levels in adolescent pregnant women with intrauterine growth restriction was performed this study.

Methodology

The study was a matched case-control nested in a cohort and was conducted within a prospectively assembled cohort specifically created for this research. The source cohort consisted of pregnant adolescents recruited between 2022-2023 in eight regions of Colombia [Eastern [metropolitan area of Bucaramanga (Santander)], Cali (Valle del Cauca), Montería (Córdoba), [Popayán and Santander de Quilichao (Cauca)], Sierra Nevada de Santa Marta (Magdalena), [Tuchín and Montería (Córdoba)], Uribia (Guajira)]. Eligible participants were clinically healthy pregnant adolescents under 19 years of age, with a gestational age between 28 and 33 weeks at enrollment, who agreed to participate voluntarily (with authorization from their legal guardian when applicable). Participants were followed prospectively until birth, allowing for the identification of cases and the selection of controls from the same cohort. This cohort has not been previously published, as it was established exclusively for the purposes of the present study.

Cases were characterized by having fetal growth below the 10th percentile by fetal biometry determined by obstetric ultrasound, and controls had normal fetal growth (percentile >10 and < 90)[12]. Cases were matched for ethnicity, school level, educational level, and place of residence, in a 1:3 ratios (one case: three controls). Processes were standardized in all regions before the start of the study both clinically and in the laboratory. The exclusion criteria were chronic maternal pathologies associated with pregnancy 2. Cognitive deficiency 3. Refuse participation. The sample size was estimated for a nested case-control study within a cohort. An expected prevalence of intrauterine growth restriction (IUGR) of 7.32% in pregnant adolescents was used as a reference, with a confidence level of 95% (α = 0.05) and a power of 80% (β = 0.20). A matching ratio of 1:3 (one case per three controls) and a minimum detectable odds ratio of 2.0 were assumed. Under these assumptions, the calculation yielded a total sample size of 128 participants. A loss or incomplete record rate of less than 10% was considered, so no additional adjustment was made. Matching was performed by ethnicity, educational level, and place of residence in order to control for possible confounding factors related to the risk of IUGR.

Once they voluntarily accepted their participation in the study and signed the consent form, they were scheduled in the morning at the assigned institution. Dependent variables were preeclampsia defined as the acute development of hypertension (> 140/90 mm Hg) in a woman who before the 20th week of gestation had normal blood pressure, accompanied or not by proteinuria greater than 300 mg in 24 hours or organ dysfunction[1]. The other dependent variable was Small for gestational age (newborn < percentile 10 according the gestational age at birth [3], as outcome variables, neonatal APGAR at one and five minutes of the newborns were evaluated. Independent variables were sociodemographic characteristics [ethnicity, educational level, socioeconomic level, having a job, prenatal biopsychosocial risk[3], cortisol levels]. The confounding variables were alcohol intake during pregnancy, smoking habits, and biomedical variables related to IUGR [maternal malnutrition (BMI < 18.5), chronic viral infections (TORCH, viral hepatitis), psychoactive substance use, anemia (hemoglobin < 11 g/L)]. The data collection form contained the following information: 1. Socio Demographics Characteristics (ethnicity, socioeconomic level, rural or urban residence, educational level) 2. PBR (Herrera & Hurtado Scale) [high biopsychosocial risk (≥ 3 points) or low biopsychosocial risk (< 3 points)][3] 3. Body mass index (BMI) (weight/height2). 4. Salivary cortisol. 5. Fetal biometry to establish if it was a case (< 10th percentile) or control (≥10th percentile) (Hadlock 4 Tables)[13] 6. Color Doppler ultrasound of the uterine arteries determining pulsatility indices[14] (abnormal > 95th percentile) using the respective previously validated tables. The results of fetal biometry and vascular Doppler study were transmitted in real-time to the project database. 7. Maternal-perinatal outcomes [Newborn weight, neonatal APGAR, small for gestational age (< 10th percentile), preeclampsia, and LBW].

For the collection of biological samples (saliva and blood), protocols of good clinical practices were followed. All blood and saliva samples were obtained at 8 am to avoid differences in cortisol levels according with circadian cycle. Instructions were given to collect saliva samples: after chewing a sterile absorbent flexible swab for one minute, the pregnant woman would place it in a special device (salivette), then it was sealed and centrifuged at 4,000 RPM for ten minutes to separate the supernatant. The same device was labeled with the assigned code by site and consecutive number and kept in custody in a cold chain at 20°C (School of Basic Sciences) (Faculty of Health - University of Valle). The saliva samples, once collected, were processed by the hormonal research laboratory independently and blindly (Santa Fe de Bogotá, Colombia). The method used was chemiluminescence reported in nmol/L. Some saliva samples were randomly selected for counter-sample analysis at the Virgen de la Arrixaca Hospital laboratory (Department of Obstetrics and Gynecology) (University of Murcia) (Spain). Blood samples were collected by drawing 5 ml of venous blood through phlebotomy, centrifuging the sample according to the standardized protocol, labeling each sample in a coded and sequential manner, and storing them in a cold chain at -20°C until their final reading with all the study samples.

The information was managed online as it was obtained, feeding into a central database managed exclusively and independently by the project's statisticians and epidemiologists. The statistical analysis began with a descriptive analysis of sociodemographic variables, social determinants, clinical characteristics, and classification of biopsychosocial risk, analyzing the data distribution and calculating the measures of central tendency according to their normality or abnormality in distribution. The variables identified with statistically significant differences were included in the multivariate analysis. A multivariate analysis was performed, including the variables of matching [ethnic self-identification (indigenous and non-indigenous), level of education (secondary or non-secondary), and place of residence (urban or rural)]. Non conditioned logistic regression was performed. Differences were considered statistically significant when the p-value was < 0.05**.**

Results

191 pregnant adolescents agreed to participate; six were excluded for being multiparous, sixteen because the Doppler of the uterine arteries could not be performed and reported, eleven pregnant adolescents were excluded because they were lost. The median to follow-up, and data on delivery or the newborn could not be

obtained for twenty pregnant women due to lack of institutional delivery care, especially in rural indigenous areas where the project was conducted. In the end, 138 pregnant adolescents with complete information on all protocol parameters were included.

The average age of the patients included in the study was 17.4 ± 1.5 years, 50 (36.23%) belonging to ethnic minority populations (Afro-American or Indigenous), 50 (36.23%) resided in rural areas, and 100 (72.46%) were in secondary education. 53 (38.40%) worked outside the home, 36 (26.08%) did not have a stable partner, and 5 (3.62%) were internally displaced due to armed conflict in rural areas. 82 (59.42%) resided in the Caribbean region [Monteria, Tuchín (Córdoba), Sierra Nevada de Santa Marta (Magdalena), Uribia (Guajira)], 30 (21.73%) resided in the eastern region (metropolitan area of Bucaramanga), and 22 (15.94%) in the southwestern region [Cali (Valle del Cauca), Santander de Quilichao, Popayán (Cauca)]. 126 (91.30%) were affiliated with the government-subsidized health regime, 6 (4.34%) with the contributory regime as health contributors (making contributions to the system), and 6 (4.34%) were not affiliated with any health social security regime due to being foreign migrants without temporary residence permits. 72 (52.17%) had a monthly family income below the legal minimum wage, and 62 (44.92%) had between 1 and 2 legal minimum wages as family income.

The gestational age at study entry was 30.4 ± 4.41 weeks, with an average of six prenatal check-ups (range 2-16). 9 (6.5%) were diagnosed with periodontal disease by the dentist. The approximate fetal weight calculated by ultrasound at entry showed a median of 2090 grams [range 1110 – 3550 grams], and the average pulsatility index of median of the pulsality index (PI) of the uterine arteries (Doppler) was 0.75 (range 0.38 - 2.30), considered abnormal (> 95th percentile) in 8 (5.79%) pregnant women [6/75.0% cases and 2/25.0% controls]. IUGR (percentile < 10 in fetal biometry) was observed in 33 (23.91%) pregnant women (cases).

Regarding nutritional status [body mass index evaluated in the first trimester (weight/height [2])], 21 (15.21%) had maternal malnutrition (body mass index < 18.5). Prenatal biopsychosocial risk (HH Scale) was observed to be high ($\geq$ 3 points) (8,9) in 50 (36.23%) pregnant women, 27 (19.56%) had emotional tension, 19 (13.76%) neurovegetative symptoms of distress, 26 (18.84%) depressive symptoms, and 14 (10.14%) pregnant adolescents reported some type of violence (physical, psychological, or sexual). High PBR was associated with general obstetric complications (p= 0.03).

Cortisol levels had a mean of 12.9 [3.77-26.6] nmol/L, and immunoglobulin A of 162 [38.9, 357] [normal (40-350 mg/dl)]. 8 (5.8%) pregnant women had high cortisol levels (> 21.6 nmol/L). In these eight pregnant adolescents with high cortisol levels, the median was 25.0 (range 22.0-59.3 nmol/L), 5 (62.50%) were from the metropolitan area of Bucaramanga, 2 (25.0%) from the indigenous community of Guajira, and 1 (12.50%) from the indigenous community of Córdoba. Pregnant adolescents who developed preeclampsia had a mean cortisol level of 12.3 [range 2.91 - 19.8] nmol/L, those who had preterm delivery of 13.1 [range 7.94 - 26.6 nmol/L], those with IUGR of 12.1 [5.14- 26.6] nmol/L, and those without obstetric complications of 12.1 [3.77- 59.6] nmol/L) (p > 0.05). Although high cortisol levels were more frequent in cases than in controls (p= 0.01) however there was not associated with IUGR in adolescent pregnant women.

It is important to highlight that social determinants, sociodemographic and clinical characteristics at the time of inclusion did not show statistically significant differences between cases and controls (**Table 1**). The bivariate analysis between cases and controls observed that the only statistically significant relative inequalities were: 1. Having insurance (paid by the state) [OR= 0.17 (95% CI 0.03-0.96, p= 0.03] (protective) 2. The eastern region observed 12 (57.1%) cases and 18 (15.4%) controls [OR= 8.44 confidence interval 2.89 - 27.22 (p= 0.001)] (Risk). 3. Having good nutrition (BMI 18.5-29.9) was protective [OR= 0.27 confidence interval 95% 0.09- 0.84, p= 0.02]. 4. LBW was observed in 5 (19.0%) cases and in 4 (3.4%) controls [OR= 7.5 confidence interval 95% 1.62 - 35.15, p= 0.01] (Risk). 5. Social determinants (having a partner, having a job, secondary or higher education level) [OR= 0.08 (95% confidence interval) (0.01-0.31) p= 0.001] (Protective) (**Table 2**).

Table 1. Sociodemographic and clinical characteristics of adolescent pregnant women according to fetal growth. Colombia (2022-2023)

Characteristics	Cases (IUGR) (33)	Controls (105)	P value
Age (years old) (mean/SD)	17.6 ± 1.53	17.4 ± 1.57	0.47
Have Job (%/n)	27.27 (9)	44.76 (47)	0.15
Without Social support (%/n)	30.30 (10)	24.76 (26)	0.28
Indigenous pregnant women (%/n)	36.36 (12)	36.19 (38)	0.73
Living in Rural area (%/n)	42.42 (14)	34.28 (36)	0.18
Familiar income (< 1 SMV) (%/n)	36.36 (12)	57.14 (60)	0.73
High School (%/n)	75.75 (25)	71.42 (75)	0.73
Gestational age (weeks) (mean/SD)	31.7 ± 3.2	30.2 ± 4.5	0.16
Periodontal disease (%/n)	9.09 (3)	5.71 (6)	0.21
Biopsychosocial Risk (≥ 3 points) (%/n)	36.36 (12)	36.19 (38)	0.99
Fetal weight (ultrasound) (g) (mean/SD)	1950 ± 334	2100 ± 454	0.17
Uterine resistance artery Index (mean/SD)	0.70 ± 0.2	0.79 + 0.2	0.12
Abnormal resistance Index (%/n)	9.09 (3)	4.76 (5)	0.74

IUGR= Intrauterine Growth Restriction (< percentile 10) SMV= actual minimum legal salary. Chi square test was used to compare proportions of categorical variables.

Table 2. Bivariate analysis. intrauterine growth restriction versus sociodemographic and clinical characteristics in adolescent pregnant women in Colombia (2022-2023)

Variable	OR (CI 95%)	p-value
Age (Years old)	1.12 (0.83-1.58)	0.47
Have Job (Yes/No)	0.49 (0.18-1.27)	0.15
Without social support	1.75 (0.61-4.68)	0.28
Afro Descendant or indigenous	1.87(0.7-5.54)	0.23
Rural residence (Yes/No)	1.39 (0.54-3.9)	0.51
East region (Yes/No)	8.44 (2.8-27.2)	<0.01
Family income (< 1 LMS)	1.18 (0.46-3.09)	0.73
High School (Yes/No)	1.77 (0.45-11.8)	0.47
Gestational age (weeks)	1.10 (0.97-1.28)	0.16
Subsidized Health Insurance (Yes/No)	0.17 (0.03-0.96)	0.03
Normal Nutrition (BMI 19-29.9)	0.27 (0.09-0.84)	0.02
Periodontal disease (Yes/No)	2.58 (0.50-11.17)	0.21
Biopsychosocial Risk (≥ 3 Points)(Yes/No)	2.07 (0.75-6.69)	0.18
Uterine resistance artery Index (mean)	0.13 (0.01-1.4)	0.12
Abnormal Uterine resistance artery Index (Yes/No)	1.31 (0.33-8.75)	0.74
Appointments of antenatal care (>or = 3) (Yes/No)	1.24 (0.99-1.58)	0.06
High cortisol levels ((> 21.6 nmol/L)	0.97 (0.88-10.7)	0.55
Low Birth Weight (< 2.500 g) (Yes/No)	7.5 (1.62-35.15)	0.01
Cesarean section (Yes/No)	0.5 (0.16-1.55)	0.23

LMS= Legal minimum salary BMI= Body Mass Index (weight/height^2) (first trimester).

Preeclampsia was observed in 12 (8.69%) pregnant adolescents and LBW in 12 (8.69%) pregnant adolescents. The gestational age at delivery was 38.6 ± 1.32 weeks. The average weight of the neonate was 3090 ± 449 grams (Table 3). Small-for-gestational-age newborns (< 10th percentile) were 22 (66.66%) cases and 15 (14.28%) controls (p=0.01). The regions where small-for-gestational-age newborns were most observed were the indigenous area of Guajira (7/31.81%), Bucaramanga (5/22.72%), Popayan (5/22.72%), Monteria 4/18.18%). 15 (68.18%) pregnant women with small-for-gestational-age newborns came from rural areas. The majority (55.79%) had a neonatal APGAR score between 8-9 at one minute of birth and 64.49% between 9-10 points at five minutes. 4 (2.1%) newborns were in the intensive care unit (ICU), 4 (2.89%) had hospitalization without intensive care. A perinatal mortality rate of 10.5 per 1.000 live births was observed (**Table 3**).

Table 3. Perinatal and maternal outcome of adolescent pregnant women of eight regions of Colombia (2022-2023)

Variable	Cases (RCIU) (n=33)	Controls (n=105)	p-value
Gestational age at birth (mean/SD)	38.2 ± 1.31	38.7 ± 1.35	0.23
Small for gestational age (<p10) (%/n)	66.66 (22)	14.28 (15)	0.01
Hypertensive disorders of pregnancy (%/n)	12.12 (4)	7.61 (8)	0.04
Cesarean section (%/n)	24.24 (8)	39.04 (41)	0.23
Birth Weight (g) (mean/SD)	2790 ± 535	3180 ± 419	<0.01
Low Birth Weight (< 2.500 g) (%/n)	12.12 (4)	3.80 (4)	0.01
Neonatal APGAR > 5 at 1 minute (%/n)	69.69 (23)	99.04 (104)	0.99
Neonatal APGAR > 5 at 5 minutes (%/n)	72.72 (24)	99.04 (104)	0.99

Chi square test was used to compare proportions of categorical variables.

Discussion

The pregnant adolescents included in the study were mostly of low socioeconomic status (51.3%); almost half were from ethnic minority populations, mainly Indigenous, with high proportion of small-for-gestational-age children; almost half resided in rural areas with difficult access to health services; seven percent were in irregular migration or forced displacement situations, having to work in informal jobs; 15.2% had high degree of malnutrition; there was a high proportion of pregnant women working (47.8%)¸ mostly outside the home; and 37.0% had high prenatal biopsychosocial risk. (**Table 1**) So, the pregnant adolescents studied were at high risk for developing complications.

Despite the above, more than ninety percent were enrolled in the subsidized regime of the public health system and received timely medical care, reducing barriers between poverty and access to healthcare, and additionally, most had a stable partner, which is recognized as a protective factor for IUGR[10].

The association of high PBR and obstetric complications in the pregnant adolescents in this study was comparable with previous studies (p= 0.03)[3,6]. Proportions of perinatal mortality, LBW, and HDP in pregnant adolescents in this study were forty percent lower than national averages (10.47 versus 15.0 per thousand live births) (5.8% versus 9.3%) (8.7% versus 14.2%) (respectively). We believe this result is largely due to the high degree of insurance coverage; the high quality and average number of prenatal check-ups (adherence); and the high proportion of pregnant women with adequate social support. Also, it is possible that the educational level has helped to adherence and the quality of prenatal care[1] despite most being of low socioeconomic status.

The increase in vascular resistance in the uterine arteries (5%) was not associated with preeclampsia, IUGR, or LBW. Cortisol levels were increased in the case group without association with preeclampsia, IUGR, or LBW, comparable with previous studies [2,4,15].

The highest prevalence of IUGR was observed in pregnant women from the eastern region of Colombia, eight times more compared to the other seven regions, requiring studies to understand the causes.

As was expected, the presence of IUGR was a risk factor for LBW (**Table 2**). An adequate nutritional status was protective for IUGR (Table 2) as well as social determinants such as having social support with a stable partner, having secondary or university education, and having a job. Previous studies observed that the individual effect of the absence of social support during pregnancy[3,16,17], low education[18], and work-related psychosocial stress[7] have been associated with IUGR in adult pregnant women. In this research, through logistic regression analysis, it was observed that the risk reduction was enhanced by more than 90 percent by the combined effect of having social support, work, and education. To our knowledge, this is an original result with important implications for pregnant adolescents of low socioeconomic status in middle- or low-income countries.

According to the results of this study, no greater risk for IUGR was observed in rural areas (**Table 2**) nor a higher number of cases (IUGR) in rural communities. We believe that access to health services was very important for these results[19], similar results were observed in Africa[20]. Governments should be encouraged to continue efforts in youth education, promote campaigns to prevent adolescent pregnancy, and guarantee health insurance, especially for vulnerable populations such as migrant or forcibly displaced populations, who received support in their prenatal care and institutional delivery, costs assumed by the system.

Genetic epigenesis or epigenetics refers to a genetic process by which the adult organism is realized via mechanisms that lead to the restriction in the possible fates of cells. Mechanisms involved cause heritable changes to cells without changes to DNA sequence such as DNA methylation; Histone modification; DNA replication timing; nucleosome positioning; and heterochromatization which result in selective gene expression or repression. It is known that epigenetics is how the environment influences an individual's genetic makeup. (https://www.ncbi.nlm.nih.gov/mesh/68044127) Recent evidence highlights the role of epigenetic dysregulation in intrauterine growth restriction (IUGR)[21,22]. Methylation changes in imprinted genes such as IGF2 and H19 have been associated with impaired fetal growth, particularly in contexts of maternal stress and malnutrition[23]. By the other hand, genetic susceptibility loci identified through genome-wide association studies (GWAS) have begun to reveal fetal genetic variants that may modulate the risk for IUGR independently of maternal risk factors, and those variants are located near to genes involved in placental angiogenesis and nutrient transport, such as FLT1 and VEGFA[22].

All these findings support a gene-environment interactions model for fetal growth, mediated by both genetic and epigenetic features, in which the modifiable character of the latter has implications for preventive strategies, especially under conditions of psychosocial adversity, where interventions targeting modifiable maternal exposures have potential benefits, with the potential to measure patient risk and intervention effects by genetic and epigenetic markers.

Future studies should integrate multi-omics approaches, including methylome profiling, transcriptomics, and placental microbiome characterization, oriented to better understand the pathways linking biopsychosocial stress to fetal development. These approaches could identify those genetic and epigenetic biomarkers and refine risk stratification tools beyond clinical and biochemical markers.

One strength of the study was that the sample size was adequate, thereby achieving the expected statistical power, including estimated losses, without affecting the effective power of the study. For the collection of biological samples (saliva and blood), good clinical practice protocols were followed, thereby limiting possible daily variations in cortisol in the patients included. Limitations: In matched studies, the presence of incomplete or discordant pairs may reduce the amount of useful information for analysis. Likewise, a lower frequency of exposure among controls or a real effect lower than that assumed in the sample calculation could have limited the ability to detect significant associations. Another aspect to consider is the variability in measurements and possible classification biases, which can attenuate estimates and decrease the statistical power achieved in this type of design.

Other limitation of this study were the difficulties in follow-up since almost half resided in rural areas, in geographically inaccessible and very dispersed areas. However, the analyzed sample exceeded the calculated sample size by ten patients (138 versus 128). However, the results highlight the need to encourage social support for pregnant adolescents, promote education, and facilitate job opportunities for those of legal age with low economic income. The high biopsychosocial risk is a common condition in adolescent pregnant women who increases the risk of low birth weight[3] and needs special attention.

Conclusions

Despite their high social vulnerability and high maternal-perinatal risk, insurance coverage, adherence, and quality prenatal care allow for better maternal-perinatal outcomes for pregnant adolescents. Ethnic, socioeconomic, and nutritional factors were not statistically associated with fetal growth restriction. A region with a higher risk of IUGR was observed, identifying protective social determinants for IUGR.

Authors' contributions

JAHM designed the study, supervised the fieldwork, interpreted the study results, and wrote the article. HSS conducted the fieldwork in his region, contributed to the discussion of results, and approved the manuscript. MATB supervised the fieldwork in the region, interpreted the study results, and approved the manuscript. MMAS conducted fieldwork in his region, contributed to the discussion of results, and approved the manuscript. JLI was the research epidemiologist, interpreted results, contributed to the manuscript, and approved the manuscript. AND contributed to the study design, collaborated in laboratory fieldwork, interpreted results, and approved the manuscript. LDOL conducted fieldwork in his region, interpreted results, contributed to the writing, and approved the manuscript. JTM was the epidemiologist for the neonatal section, interpreted results, contributed to the writing, and approved the manuscript. JRC contributed to the interpretation of data, contributed to the preparation of the manuscript, and approved the final version.

Ethical considerations

An informed consent form was signed by the patients and their legal guardians, where applicable. According to current regulations, this was a high-risk project because the participants were pregnant minors, but the interventions consisted solely of evaluating sociodemographic and clinical variables, taking blood and saliva samples for laboratory testing, and conducting follow-up. The project was approved by the Ethics Committee for Human Studies [Faculty of Health of the University of Valle (Number 026-021), San José University Hospital in Popayan (Number OF-RH-01), Social Enterprise of the State (ESE Ladera) in the city of Cali (15-CEH-112022)] and by the different participating institutions.

Competing interests

The authors declare that they have no conflict of interest in the research and in the publication of its results. We are researchers for academic purposes only

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