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Gestational diabetes and pregnancy-induced hypertension increase risk of metabolically unhealthy status in prepubertal children with and without obesity

La diabetes gestacional y la hipertensión durante el embarazo incrementan el riesgo de enfermedad metabólica en niños prepúberes con y sin obesidad

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Abstract

Background: Metabolic complications during pregnancy, such as gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH), are involved in the development of obesity and insulin resistance in the offspring. Moreover, children with a metabolically unhealthy (MU) status are at higher cardiovascular risk later in life. **Aims**: To examine the risk of both a worse body mass index (BMI) and a MU status in children born to mothers with GDM or PIH. **Methods**: A total of 257 Spanish prepubertal children were selected for this study out of 801 participants recruited in primary care centres and schools. Information regarding the presence or not of GDM and PIH during pregnancy was recorded. Anthropometry and blood pressure were measured, metabolic biomarkers were analysed and children were classified according to their BMI and MU status. Student's t-test and logistic regression analyses were performed to examine associations. **Results**: MU children showed higher BMI and waist circumference and a worse cardio-metabolic profile than metabolically healthy (MH) participants. There were more children born to mothers with complicated pregnancies in the MU group, this was paralleled by greater mean differences for diastolic blood pressure (DBP) in children of mothers with GDM, PIH or both than in children born to healthy pregnancies.

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Finally, children born to mothers with GDM or PIH had a higher risk of having a MU status and overweight/obesity. **Conclusions**: Children born to mothers with metabolic complications during pregnancy displayed higher DBP values and had an increased probability of having the combination of a MU status and overweight/obesity.

Key Words: gestational diabetes, pregnancy-induced hypertension, paediatric obesity, metabolically unhealthy obesity, blood pressure, insulin resistance

Resumen

Antecedentes: Las complicaciones metabólicas durante el embarazo como la diabetes mellitus gestacional (DMG) y la hipertensión durante el embarazo (HE) están relacionadas con el desarrollo de obesidad y resistencia a la insulina en los hijos. Además, los niños metabólicamente no sanos (MNS) tienen mayor riesgo cardiovascular. **Objetivos**: Examinar la probabilidad de tener mayor índice de masa corporal (IMC) junto a un estado MNS en hijos de madres con DMG o HE. **Métodos**: Se seleccionaron 257 niños españoles prepuberales de un total de 801 participantes reclutados en escuelas y centros de atención primaria. Se recogió información relativa a la presencia de DMG e HE en el embarazo de la madre. Se midió la antropometría, la tensión arterial y se analizaron marcadores cardio-metabólicos para clasificar a los niños según IMC y estado metabólico. Finalmente, se realizaron análisis t de Student y de regresión logística para examinar las asociaciones. **Resultados**: Los niños del grupo MNS mostraron mayor IMC, mayor circunferencia de cintura y peor perfil cardio-metabólico que los participantes metabólicamente sanos. Hubo un mayor número de niños de madres con DMG e HE entre los niños MNS, que además presentaron mayores valores de tensión arterial diastólica (TAD) que los hijos de madres con embarazos sanos. Los niños cuyas madres presentaron DM o HE mostraron mayor probabilidad de presentar la combinación de sobrepeso/obesidad y estado MNS. **Conclusiones**: La presencia de DMG o HE se asocia con mayor TAD en la descendencia, junto con una mayor probabilidad de tener exceso de peso y un estado MNS.

Palabras clave: *Diabetes gestacional, hipertensión inducida en el embarazo, obesidad pediátrica, obesidad metabólicamente enferma, presión sanguínea, resistencia a la insulina.*

Introduction

Childhood obesity is a world threatening pandemic with many adverse consequences. To date, the most prevalent complication associated to obesity is cardiovascular disease [1], which occurs following the appearance of cardio-metabolic derangements traditionally clustered under the metabolic syndrome, already present in childhood [2]. However, the more recent concept of metabolically unhealthy (MU) status has also proven useful for the detection of children and adults at risk of cardiovascular disease [3]. Previous studies have shown a great variability of MU obesity (MUO) prevalence, ranging from 30 to 75% of MUO children and adolescents with obesity [4].

Since absolute numbers of children with overweight or obesity keep increasing worldwide [5], the contributing elements must be clearly defined in order to establish appropriate prevention strategies [6]. Indeed, obesity risk is known to be modulated by many factors, such as the health status of the mother prior to conception, the course of pregnancy, individual's genetic predisposition as well as environmental and socioeconomic circumstances. Among these, one of the most influencing agents of the child's well-being is the mother's health status, before, during and after pregnancy. Studies have shown the early developmental stages to be critical, during which the exposure to maternal health alterations may predispose to higher metabolic risk in the offspring [7, 8]. Gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (PIH), which are common complications occurring to pregnant women with excess weight, have been shown to increase the risk of obesity and insulin resistance in the offspring [9]. Since GDM and PIH complicate around 5% of pregnancies [10, 11], near a 10% of children may be at a higher risk of developing cardio-metabolic alterations.

The prepubertal stage is an ideal developmental point to study the onset of metabolic complications in childhood, since adolescence is associated with hormonal changes which can mask the appearance of other abnormalities[12]. For this reason, we conducted the present study exclusively in prepubertal children.

The aim of the present work was to examine the BMI and metabolic health status of prepubertal Spanish children born to mothers who displayed healthy or complicated pregnancies (GDM or PIH).

Methods

Study sample

801 children were recruited from primary care centres and schools in three Spanish cities: Santiago de Compostela, Zaragoza and Córdoba. Out of them, 257 prepuberal children of 5 to <11 years old were

selected. For the purpose of this study, inclusion criteria were: having data for all the metabolic parameters included in the definition of metabolic health [high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), glucose, systolic blood pressure (SBP), diastolic blood pressure (DBP) and insulin] and having information regarding the presence or not of GDM or PIH during pregnancy. In contrast, exclusion criteria were: subjects from mothers who consumed alcohol, tobacco and/or drugs during pregnancy, subjects with a birth weight lower than 2000 g and those children with a gestational age of less than 30 weeks or more than 42 weeks.

Written informed consents were obtained from the parents and caregivers and children gave their assent. The study was performed according to the ethical guidelines of the Edinburgh revision of Declaration of Helsinki (2000) and the local Ethics Committees of each study centre approved the protocol.

Anthropometric measures

Weight and height were measured according to standardized procedures. In addition, body mass index (BMI) was calculated (kg/m^2). BMI categories were created according to Cole *et al.*[13], using age- and sex- specific cut-off points linked to adult values of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity. SBP and DBP were measured twice by the same examiner following international recommendations.

Questionnaires

A questionnaire to gather information regarding energy balance related behaviours, socioeconomic status and medical history was fulfilled along with the parents or caregivers. The presence or not of GDM and PIH was self-reported by the mother and recorded in the questionnaire. Perinatal information such as birth weight, gestational age and type of birth was also self-reported and checked with the medical history. Macrosomia was considered when birth weight was higher than 4000 g.

Biomarker analysis

Blood withdrawal was performed via the antecubital vein after an overnight fast, and routine analyses were performed at each participating hospital as described previously [2]. Plasma insulin was analysed by radioimmunoassay (CV: 2.6%) using an automatic microparticle analyzer (AxSYM; Abbott Laboratories, Chicago, Ill., USA). Insulin resistance was calculated by means of the homeostasis model assessment of insulin resistance (HOMA-IR) defined by the equation HOMA-IR = fasting glucose (mmol/L)/fasting insulin (IU/L)/22.5 [14].

Metabolic health definition

Children were classified as metabolically healthy (MH) or MU according to the definition proposed by Olza *et al.*[2]. Children were considered MU when meeting one or more of the following criteria: a SBP or DBP equal or higher than the 90th percentile for age, sex and height, TG plasma concentration higher than the 90th percentile for age, sex and race, HDL-C plasma concentration lower than the 10th percentile for age, sex and race, glucose plasma concentration equal or higher than 100 mg/dL or HOMA-IR higher than 2.5. Children who did not meet any of these criteria were considered MH.

Statistical analysis

Normality of distributions was assessed with the Kolmogorov–Smirnov test. Mean differences, expressed as means ± SD, were compared between groups according to the metabolic health status. In addition, mean differences between MH and MU children were also assessed by the analysis of covariance (ANCOVA), adjusted for age and BMI.

Percentages of children born to mothers with GDM and PIH among subjects with normal-weight and overweight/obesity were calculated. For comparison of the studied parameters between offspring of healthy or complicated pregnancies, four categories were created: 1.Children born to mothers with neither GDM or PIH, 2. Children born to mothers with GDM, 3.Children born to mothers with PIH, and Children born to mothers with both GDM and PIH. Student's t test analyses were performed between group 1 and the rest of the groups of children born to mothers with complicated pregnancies.

Finally, a logistic regression analysis adjusted by age was performed to assess the odds ratio (OR) of having a worse status of BMI and metabolic health for children born to mothers who displayed GDM or PIH. For this analysis, the following groups were included: MH normal-weight, MU normal-weight, MH overweight/obesity and MU overweight/obesity.

Results

Descriptive characteristics of the children participating in the present study are presented in Table 1. Children allocated in the MU group had higher BMI and WC than those in the MH group. Also, there were significant differences for the number of chil-

Table 1. Descriptive characteristics of children included in the study grouped by their metabolic health status.

	MH (N=114)	MU (N=143)	P
Age (years)	8.57±1.38	8.43±1.38	0.417
BMI (kg/m²)	19.68±4.59	23.87±4.67	<0.001
WC (cm)	67.29±11.97	77.44±12.52	<0.001
Birth weight (g)	3362±505	3350±497	0.848
Body mass index categories			
Normal weight	54 (47%)	20 (14%)	<0.001
Overweight/Obesity	60 (53%)	123 (86%)	
Gestational Diabetes Mellitus			
No	109 (95.6%)	125 (87.4%)	0.017
Yes	5 (4.4%)	18 (12.6%)	
Pregnancy Induced Hypertension			
No	107 (93.9%)	122 (85.3%)	0.022
Yes	7 (6.1%)	21 (14.7%)	
Macrosomia			
No	100 (87.7%)	128 (89.5%)	0.398
Yes	14 (12.3%)	15 (10.5%)	
Type of birth			
Natural	73 (64.0%)	91 (63.6%)	0.492
C-section	25 (22.0%)	38 (26.6%)	
Others	16 (14.0%)	14 (9.8%)	

Results are mean±SD or count (percentage). P: significance of Student's t test or chi-square test conducted to examine differences between groups. BMI: Body mass index; MH: Metabolically healthy; MU: Metabolically unhealthy; SD: standard deviation; WC: waist circumference.

dren of different BMI categories, normal weight and overweight/obesity, between the two metabolic health status groups. There were significant differences in the number of children born to mothers with GDM or PIH between the two metabolic health status groups, with more children born to mothers with complicated pregnancies in the MU group. In contrast, no mean differences were found for birth weight between MH and MU groups nor in the number of children displaying macrosomia or born by different types of birth.

Regarding differences for the cardio-metabolic parameters by group of metabolic health status, we found significant differences for the components that are included in the definition of the metabolic health while adjusting the analysis by BMI and age. MU children had lower HDL-C (p=0.012) and higher TG (p<0.001) and glucose (p=0.001) concentrations, and higher HOMA-IR (p<0.001), SBP (p<0.001) and DBP (p<0.001) values than MH children (Table 2). No mean differences were found for WC, birth weight and uric acid concentrations between groups.

As for prevalence of complicated pregnancies, children born to mothers who had GDM or PIH were 4.1% and 5.4% in the normal-weight group, and 10.9% and 13.1% in the overweight/obesity group. The comparison between the mean values of cardio-metabolic parameters of children born to mothers who had healthy and complicated pregnancies is shown in Table 3. For this analysis, the group of children born to mothers with neither GDM or PIH was individually compared with the other groups: 2. children born to mothers with GDM, 3. children born to mothers with PIH, and 4. children born to mothers with both GDM and PIH. Significant differences were found for DBP, which showed higher values in all complicated pregnancies groups than the healthy pregnancy group. In addition, WC and SBP were also increased in children born to mothers with

Table 2. Cardio-metabolic parameters of metabolically healthy (MH) versus metabolically unhealthy (MU) children.

	MH	MU	P
	Mean (95% CI)	Mean (95% CI)	
WC (cm)	72.54 (71.49-73.59)	73.29 (72.36-74.21)	0.315
Birth weight (g)	3401.18(3304.30-3498.05)	3318.47 (3232.93-3404.02)	0.203
HDL-C (mg/dL)	58.11 (55.52-60.70)	53.44 (51.14-55.75)	0.012
TG (mg/dL)	51.14 (45.28-56.99)	74.30 (69.09-79.51)	<0.001
Glucose (mg/dL)	81.58 (80.16-83.01)	84.92 (83.66-86.19)	0.001
HOMA-IR	1.32 (1.06-1.58)	2.36 (2.13-2.60)	<0.001
SBP (mmHg)	100.70 (98.63-102.77)	109.13 (107.29-110.98)	<0.001
DBP (mmHg)	60.66 (58.96-62.36)	67.22 (65.71-68.73)	<0.001
Uric acid (mg/dL)	4.03 (3.87-4.20)	4.22 (4.07-4.36)	0.121

P: Significance of the analysis of covariance using body mass index and age as covariates. CI: confidence interval; DBP: Diastolic blood pressure; HDL-C: High density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance; SBP: Systolic blood pressure; TG: Triglycerides; WC: Waist circumference.

Table 3. Cardio-metabolic parameters of the offspring of mothers with healthy or complicated pregnancies.

	Healthy pregnancies (213)	GDM (16)	PIH (21)	GDM+PIH (7)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
WC (cm)	71.63 (12.75)	77.97 (13.47)	77.44 (14.12)	89.21 (11.60)*
Birth weight (g)	3345.43 (493.86)	3455.94 (434.74)	3386.43 (537.90)	3327.14 (740.37)
HDL-C (mg/dL)	56.38 (15.90)	51.50 (12.87)	51.24 (16.96)	52.86 (17.84)
TG (mg/dL)	62.38 (30.71)	67.13 (31.67)	66.57 (31.95)	96 (84.54)
Glucose (mg/dL)	83.49 (7.58)	84.13 (5.81)	83.71 (6.84)	79.29 (8.73)
HOMA-IR	1.86 (1.52)	2.14 (1.67)	1.83 (1.24)	2.19 (1.34)
SBP (mmHg)	104.33 (11.58)	111.66 (10.49)	107.43 (18.34)	116.00 (7.93)*
DBP (mmHg)	63.02 (8.753)	69.19 (9.48)*	68.02 (9.50)*	80.14 (13.44)*
Uric acid (mg/dL)	4.07 (0.94)	4.72 (1.17)*	4.15 (0.85)	4.74 (0.82)

*P<0.05 in the student's t test comparing mean differences of group and the other three groups GDM, PIH and GDM+PIH. DBP: Diastolic blood pressure; GDM: gestational diabetes mellitus; HDL-C: High density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance; PIH: pregnancy induced hypertension; SBP: Systolic blood pressure; SD: standard deviation; TG: Triglycerides; WC: waist circumference.

both GDM and PIH when compared with those born to mothers with healthy gestations.

Finally, Table 4 shows the OR for having a worse BMI status (overweight or obesity) and a worse metabolic health status (MU) of children born to mothers with complicated pregnancies. Analyses sho-wed that the probability of being in a worse BMIcategory combined with a MU status significantly increased in a 298% for offspring of mothers with GDM and in a 271% for those of mothers with PIH.

Discussion

The presence of metabolic complications during pregnancy has been extensively studied given the importance of this period for the future health of

Table 4. Association between the presence of GDM or PIH during pregnancy and risk of obesity and metabolic status the child.

		BMI/metabolic Status	
		OR (95% CI)	**P**
GDM	No (Ref)	-	-
	Yes	2.981 (1.203-7.387)	0.018
PIH	No (Ref)	-	-
	Yes	2.713 (1.199-6.138)	0.017

P: Significance of the logistic regression analysis between GDM or PIH (independent variables) and BMI/metabolic status (dependent variable). The four groups of BMI/metabolic status are: normal weight-healthy, normal weight-unhealthy, overweight/obesity-healthy and overweight/obesity-unhealthy. BMI: body mass index; CI: confidence interval; GDM: gestational diabetes mellitus; OR: odds ratio; PIH: pregnancy-induced hypertension; Ref: reference.

both mother and child. In light of our findings, this is further confirmed in the present study, since the offspring of mothers with complicated gestations show a triple risk of developing overweight, obesity and metabolic abnormalities.

Our results regarding the observed differences in cardio-metabolic parameters between MH and MU groups are in line with what has been previously observed in the literature [4, 15]. However, although these variables are included in the definition of MU status, it must be taken into account that the analyses were adjusted by age and BMI, further confirming the metabolic derangement. Moreover, in the present study we also show that children born to mothers with GDM or PIH display a higher probability of having a combination of obesity and MU status. An early relationship between GDM, PIH and childhood obesity has been recently reported, with children born to women with GDM or PIH having a higher risk of excess weight at 1-5 years[16]. Moreover, studies in young adults [17] have observed the same relationship with PIH, although another study in school-aged children did not show firm associations between GDM and obesity risk[18]. Thus, the present study validates previous data and goes a step further, as a novel relationship is shown between metabolic abnormalities during pregnancy and the future metabolic health status of the child.

Concerning the prevalence of GDM and PIH, our results are similar to those previously reported in the literature for general population, which are around 5% [10, 11]. Indeed, in our study, the percentage of normal-weight children born to mothers with GDM and PIH was 4.1% and 5.4%.

Interestingly, our findings indicate that different cardio-metabolic alterations also appear at early developmental stages in children born to mothers with either GDM or PIH. Similar findings have been observed in the study by Boney *et al.* (2005) [18], where large-for-gestational age (LGA) children of mothers with GDM had a higher risk of metabolic syndrome. Moreover, previous studies have also shown that PIH increases the offspring risk of cardiovascular disease in childhood, adolescence and adulthood [17, 19]. However, in this study we observe for the first time that children born to mothers with GDM or PIH also display a higher risk of MU status, despite the fact that their birth weight was not different from those of healthy pregnancies. Indeed, we did not observe differences in the distribution of children with macrosomia among MH and MU children. These results disagree with previous findings, which have observed how offspring of women with GDM or PIH had increased weight for gestational age and birth weight for length, as well as higher odds of macrosomia [16]. However, a low birth weight has also been associated with a higher type 2 diabetes and metabolic syndrome risk under the "thrifty phenotype hypothesis" [20]. In this aspect, higher SBP in pregnant mothers is associated with lower birth weight [21]. However, in the present study it is shown that birth weight is not increased in MU individuals, and we also do not observe differences in birth weight between children of mothers with healthy pregnancies and those of mothers with GDM, PIH or both. Given this result, the association between birth weight and pregnancy complications, when present, is most probably mediated by the increase in obesity risk.

The fact that we observe higher values of DBP in children born to mothers with complicated pregnancies is of great importance. Although it is not surprising that hypertension is observed as an individual risk factor in MUO children and adolescents, given the inclusion of this trait in the definition of metabolic health [22], hypertensive disorders have been previously observed in children born to mothers who had complicated pregnancies such as GDM, PIH or pre-pregnancy obesity [23]. A potential explanatory hypothesis has been raised by relating the hypertension and vascular dysfunction of the pregnant mother with a higher glucocorticoid (GC) expression that could derive in a lower nephron number in the foetus, which would affect the renal excretory function contributing to the child's future hypertension [24].

It has also been shown how the risk of future type 2 diabetes in the offspring is also increased in mothers who had pregnancy hypertensive disorders [19, 25] or GDM [26]. However, we do not observe statistically significant differences in parameters related with glucose metabolism, glucose or HOMA-IR between children born to healthy mothers and those born to mothers with PIH. In contrast, children born to mothers with GDM or both GDM and PIH display

higher values of HOMA-IR than those born to healthy mothers, although differences were not significant, most probably due to the low number of children in the groups of complicated pregnancies.

A number of limitations shall be stated for the present study. First, we used self-reported information regarding presence of GDM and PIH. Second, information on prenatal maternal body weight is lacking, which could have allowed us to stratify results by obesity status of the mother. And third, the relatively low number of children born to mothers with complicated pregnancies in comparison with children born to healthy mothers made it difficult to conduct thorough statistical analyses. On the opposite, the high number of variables included in the analysis is a strength of this study which shall also be considered, together with the use of a rigorous definition of metabolic health status that accounts for sex, age and insulin resistance.

Altogether, our findings confirm previous individual studies in a broader dimension where the two main pregnancy complications, GDM and PIH, as well as obesity and metabolic health status in children, were considered and investigated in terms of their relationship with key cardio-metabolic factors. In addition, results regarding DBP show its potential interest for the follow-up of children with cardio-metabolic risk and overweight. The main conclusion derived from our study is that children born to mothers who displayed GDM or PIH have a significantly increased risk of cardio-metabolic complications, and thus, shall be closely followed in order to maximize prevention strategies during the sensitive periods of childhood and adolescence.

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Author contributions: RV, MGC, RL and GB recruited the children. JOM, CAG and AG contributed to biomarker analysis. AIR conceived the study and planned the literature search. AIR, EGG, LM and GB designed the analysis. EGG performed the statistical analysis and created the figures and tables. AIR, EGG and GB were involved in the interpretation of the results. AIR and EGG wrote the manuscript. All authors discussed drafts and approved the final manuscript.

Conflicts of interest

Authors declare no potential Conflicts of Interest

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