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Lucas Pontesde Camargo

Alterações Metabólicas 6-11 anos pós nascimento em filhos de mães com síndrome metabólica na gestação

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Ginecologia, Obstetrícia e Mastologia.

Orientadora: Prof.ª Emérita Dra. Marilza Viera Cunha Rudge
Coorientador: Dr. Carlos Antonio Negrato
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Palavras-chave:Grande para idade gestacional; síndrome metabólica; obesidade; gravidez; resultados da gravidez; macrossomia; nascimento prematuro.

Epígrafe

"Tudo é considerado impossível,
até acontecer"
Nelson Mandela

Dedicatória

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Sumário

Capítulo 1

Seção redigida como Artigo Original de acordo com as normas de publicação da Revista **The Journal of Pediatrics** para a qual será submetida. Qualis A2 para Medicina- FI: 3.66

Effects of Pre-pregnancy Metabolic Syndrome (MetS) on Short and Long-term Adverse Consequences for the Offspring: An Exploratory Secondary Data Analysis of a Cohort Study of Low Income Brazilian Mothers

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Abstract

Objective: To assess the pre-pregnancy metabolic syndrome (MetS) exposure and its effects on the perinatal outcomes (large-for-gestational age infants, macrosomic and preterm birth) and on short and long-term risk for the development of MetS and metabolic repercussions among offspring of low income population of Brazilian mother.

Study design: This unplanned, exploratory analysis includes a cohort of pairs of mother-offspring diagnosed and treated in the Perinatal Diabetes Research Center-University Hospital-UNESP, Brazil from 2004-2011. This study evaluated women with previous gestational diabetes mellitus and the risk of developing type 2 diabetes after 6-11 years after delivery and the data was collected from February 2016 to July 2018. Mothers and infants (n=152) were selected as pairs and a follow up study was conducted as secondary data analysis of the effects of pre-pregnancy MetS. Follow-up examinations, including maternal and offspring were performed at 0-2 years and from 6-11 years after delivery. All analyzes were performed using SAS for windows, v.9.4. In all tests the significance level of 5% or the corresponding *p*-value was used.

Results: The prevalence of pre-pregnancy MetS was 9.1%, a contributor for the occurrence LGA, macrosomic infants and preterm at birth. Our results confirmed that, the pre-pregnancy MetS mothers had correlation ($p<0.0001$) between the hip circumference, waist circumference and weight which were also directly leading to higher levels ($p<0.05$) of hypertension as compared to that of non-MetS mothers. Follow-up study showed that children of pre-pregnancy MetS mothers had increased abdominal obesity as per the *z* score. The children suffering from MetS between 6 to 11 years are 2.09 times more likely to have obesity as per the waist circumference (RR=2.09; 95% CI 1.32-3.31) and 51% chance of being obese.

Conclusions: Pre-pregnancy MetS has become an important contributor to the occurrence of adverse perinatal, short and long-term outcomes in low income Brazilian mother.

Keywords: metabolic syndrome, pregnancy outcomes, large for gestational age, preterm birth, macrosomia, cardiovascular, assessment, obesity

Introduction

Childhood obesity is a public health problem either in developed or underdeveloped countries.[1] Obesity has reached epidemic proportions and pregnancies have increased the risk of complications in obese mothers, including gestational diabetes, C-section, pre-term birth and hypertensive disorders. Children of these mothers are more likely to develop obesity[2,3] and metabolic disease and are liable to develop neuropsychiatric and cognitive disorders.[3] A meta-analysis reveal that pre-pregnancy obesity is an important risk factor for macrosomia (>4000 g) and childhood obesity.[4] In a systematic review and meta-analysis in a paper from 26 countries demonstrated that high birth weight is a predictor of overweight/obesity during childhood and later in life.[5]

In a mediation analysis, a recent paper demonstrated that pre-pregnancy body mass index (BMI), especially obesity have a direct effect on childhood BMI-for-age, weight-for-age and weight-for-height outcomes, not mediated by offspring's birth weight. In this paper the authors consider the potential pathways between pre-pregnancy BMI, offspring's birth weight and childhood anthropometric measures taken together the influence of gestational diabetes mellitus (GDM) and hypertension development during pregnancy in birth weight as mediator parameters.[6]

Metabolic Syndrome (MetS), is referred to as a cluster of various conditions that occurs inside the human body. These conditions include high blood pressure, increased sugar level, abnormality of cholesterol and obesity, which are the prime causes for increased risk of type 2 diabetes (T2DM) and cardiovascular disease.[7, 8]

There are a lot of papers related to maternal obesity and offspring repercussion although the intrauterine environmental in MetS could be altered as hyperglycemia and obesity are more linked to increase the fetal growth and hypertension with reduced placental vascularity, blood flow and restrict placental

nutrient delivery to the developing fetus more likely to the development of intrauterine restriction.[9] These sometimes contradictory signals that regulate placental function can contribute to the diversity of short and long-term results seen in pregnant obese women[3] and probably in MetS mothers. So, longitudinal outcome studies and further research on the progression and etiology of the metabolic syndrome are required in order to detect early and severe signals of offspring of pre-pregnancy MetS mothers not only during delivery but also in the first year of life that could be used in at-risk children as long-term markers of MetS development.

A strong results confirms that adult offspring of women who were obese during pregnancy have increased cardiometabolic risk factors and increased risk of premature death and hospitalization for cardiovascular events. These results are worrisome since offspring of overweight women also have higher risk of adverse events in later life. All cause of mortality and hospital admissions for cardiovascular events in adult offspring who were born between 1950 and 1976 were followed up till January 2012. It was detected that all cause of premature mortality was increased in offspring of obese mothers (BMI >30) compared with offspring of mothers of normal BMI after adjustment for maternal age at delivery, socioeconomic status, sex of offspring, birth weight, gestation at delivery, and length of gestation at measurement of BMI (hazard ratio 1.35, 95% confidence interval 1.17 to 1.55). In adjusted models, the offspring of obese mothers had also increased the risk of hospitalization to a cardiovascular event (1.29, 1.06 to 1.57) compared to the offspring of normal BMI mothers. The offspring of overweight mothers also had a higher risk of adverse outcomes. The authors assume that the link between maternal obesity and adverse outcome in offspring will persist as rates of maternal obesity rise.[10]

Gestational diabetes in pregnancy may increase the risk of developing T2DM, obesity and cardiovascular complications either in mother or offspring later in life.[11-15] Furthermore, a high rate of T2DM has been observed in the obese mothers

and their children recently.[16, 17] Hence, cardiovascular and renal disease are significant consequences of the GDM, which can be found during and after pregnancy. The epigenetic process affects the fetus during the pregnancy. It is identified that hyperglycemia, hyperlipidemia and altered maternal hormones are significant reasons behind the development of maternal obesity. [17, 18] As defined, besides the presence of such stated subtracts, potential diet and lifestyle factors also play an impeccable role in developing metabolic disorders in mothers and their offspring.[19] Therefore, the significance of the Developmental Origins of Health and Disease (DOHaD) concept can be explained. The notions of DOHaD reflect on the environmental factors that determine the development of diseases in later life.

It has been found that 30% of the youth in the United States are overweight and on the risk of developing atherosclerotic cardiovascular disease and T2DM.[20, 21] However, studies show that babies could be of normal weight when they born, but in later years (3 to 11), the child could become seriously overweight. At this point people realize that the child is developing health issues that can become difficult to control. [3, 22, 23] While, most studies discuss the rising issue of GDM and MetS, are more focused on the development of MetS during early pregnancy.[24-26]

With rise in the number of people suffering from MetS across the world, recent studies conducted in Brazil have revealed alarming results regarding the occurrence of MetS in the adult population of Federal District.[16, 27] Studies have found that women in Brazil are at a higher risk of MetS and it is mainly because of the inequality in the education sector. The first Brazilian nationwide study-ERICA demonstrated that the prevalence of MetS in adolescents was 2.6%. The most common combinations of components, referring to 3/4 of combinations were includes enlarged waist circumference (WC), low HDL-cholesterol (HDL-c) and high bloodpressure; followed by enlarged WC, low HDL-c and high triglycerides; and enlarged WC, low HDL-c, high triglycerides and blood pressure. Low HDL

was the second most frequent component, but the highest prevalence of metabolic syndrome (26.8%) was observed in the presence of high triglycerides.[28]

The women are unaware of this harmful condition and the adverse effect that MetS brings to their children in future. Research states that obesity and birth weight have a strong connection; women who are classified as obese II or obese III give birth to overweight infants as compared to women with normal weight. Moreover, obese women tend to develop diabetes, which lead to alterations in their placental development. This directly impacts the nutrients flowing to the growing fetus. [29, 30]

The idea for this paper was motivated as numerous research studies revealed the existence of the MetS and its growth in major parts of the world, especially in the west. [17, 21, 31] To find evidence for the impact of maternal MetS environment on their offspring, this research was initiated and it mainly focuses on the impact of pre-pregnancy MetS on children short and long-term health. The research question of this study was to find out whether pre-pregnancy MetS associated with an early and increased risk of child health weight and metabolic compromise not only at birth but also in the short and long-term outcomes? Furthermore, the aim of this research was to assess the pre-pregnancy MetS exposure and its effects on the perinatal outcomes (large-for-gestational age infants (LGA), macrosomic and preterm birth (PTB)) and on short and long-term risk for the development of MetS and metabolic repercussions among offspring of low income population of Brazilian mother.

Methods

Participants

This study was a secondary analysis of a cohort that consisted of women recruited from the Perinatal Diabetes Research Center -University Hospital of Botucatu Medical School-UNESP, Brazil. This analysis was approved by the Institutional Review Board (IRB) of Botucatu Medical School- UNESP/ Brazil

(CAAE:67543417.3.0000.5411) and conducted in accordance with the Declaration of Helsinki.

Study design

The data for this unplanned, exploratory secondary analysis were derived from a prospective cohort of pairs of mother- offspring that were diagnosed, treated and followed at Perinatal Diabetes Research Center- FMB-UNESP; Brazil from 2004-2011 as a part of Project (Proc. 563808/2010-1). Pregnancy complicated by mild gestational hyperglycemia and GDM as a window of susceptibility, identified by maternal, placental and cord blood biomarkers for the prevention of T2DM) with financial support from CNPq/Brazil Health Ministry (MCT/CNPq/CT-Saúde/MS/Decit nº 42/2010).

The original study allocated women with GDM during pregnancy and compare the long-term risk to develop T2DM after 6-11 of years pregnancy and was collected in 2016 (Figure 1). The Perinatal Diabetes Research Centre (PDRC) is located at Botucatu University Hospital- UNESP, a public, tertiary referral health unit with financial support from the Brazilian Public Health System (SUS). The study population was obtained from an existing clinical pregnancy registry at the PDRC, between January, 2004 and December, 2011. The newborn birth weight and gestation age at birth were abstracted from the original obstetric records. All women and newborn who completed the baseline survey were eligible for this study. Further, as inclusion criteria, these women needed to have had singleton pregnancy, underwent screening, GDM diagnosis between 24-28 weeks ofgestation, prenatal care assistance and long-term follow-up at PDRC (n=534).

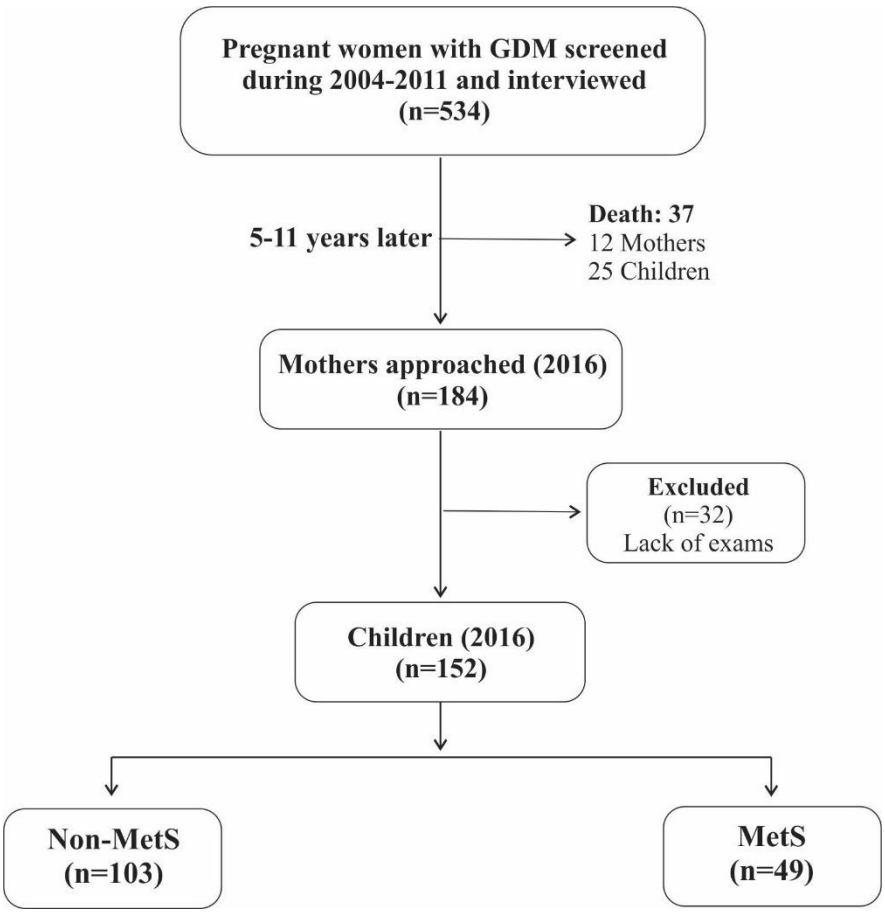

Figure 1. Flowchart of study participants.

Data source

All women who performed a screening and treatment for GDM during pregnancy at PDRC between 2004 and 2011were followed during two years after delivery and were invited for long-term follow-up study in 2016. A total of 534 women and their offsprings wer econtacted by our research team and invited to participate the study. Of these, 37 were not eligible (death) and 43 refused to participate in study. One hundred and eighty four mother-infant returned for the follow-up visit and 32 were excluded for missing values. A total of 152 childrens were included in this secondary analysis according to the estabilished groups at pre-pregnancy: non-MetS and MetS (Figure 1). Follow-up examinations were performed during the first two years, at every 3 months and after 6 years until 11 years thereafter

(Figure 2). The data was collected over the two years span from February 2016 to July 2018.

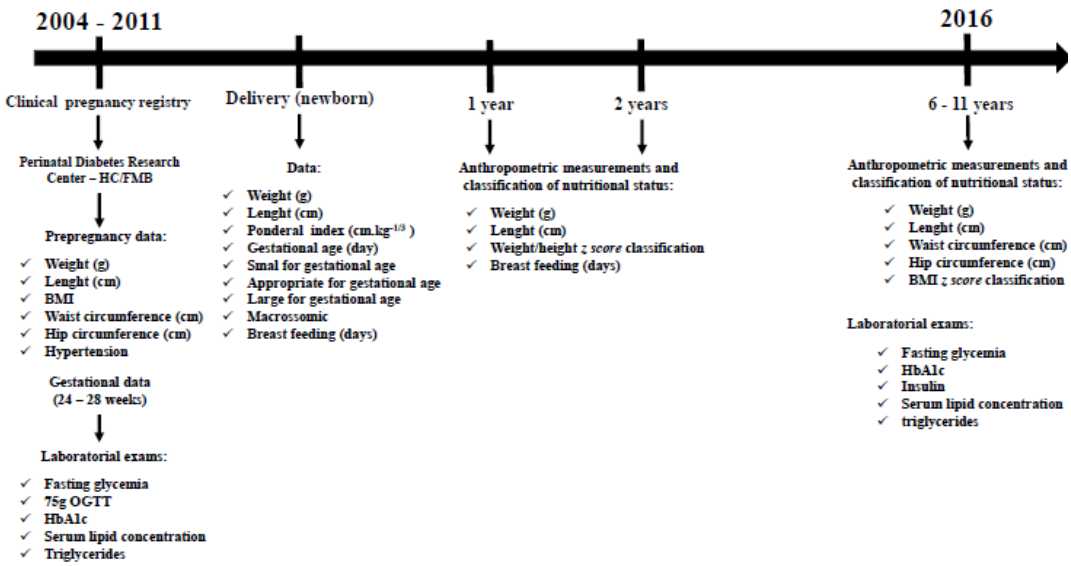

Figure 2. Research design and material and methods.

Exposure

For the present analysis, the primary exposure were pre-pregnancy MetS. All women were classified either as having MetS, if before pregnancy they had central obesity (pre-pregnancy body mass index -BMI ≥30kg/m^2 or waist circumference (WC) ≥80cm), plus any two of the following four factors criteria according to the International Diabetes Federation- The consensus worldwide definition of the MetS:[32] (i) systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg; triglycerides (TG) level ≥150 mg/dL; (iii) hight density lipoprotein (HDL) level ≤50 mg/dL; fasting plasma glucose (FPG) ≥100 mg/dL.[32, 33]

Measurements

Demographic and Family health hystory

The questionnaire collected information on maternal hystory of MetS, obstetric hystory including prepregnancy weight, height and pregnancy gain weight; perinatal and postnatal complications; sex, birth weight, infant feeding and gestational ageat delivery. Based of these informations the ponderal index [PI=(weight/lenght^3)*100], and classification according to weight/gestational age were calculated.[34] These children followed at PDRCfor 1-2 years and returned for the 6-11 years follow-up visit, and 32 were excluded for missingvalues. The pre-pregnancy weight was obtained by self-reports at the time of the first prenatal visit, or during the informed consent application process.

Children's Anthropometric measures

Newborn

Data at delivery were obtained from delivery database at our center and included gestation age (in days), infant birth weight and height, gender, mode of delivery and apgar scores. Based on these informations the ponderal index [(weight/lenght^3)*100], and classification according to weight/gestational age (SGA, AGA, LGA)[34] and macrossomia (>4000g)[35] were calculated. [34]

1-2 years

Anthropometric measurements were taken for infants. The weight (in kilograms) and length (in centimeters) were measured using a length board. Based on these information, the weight-for-length z score (WFL-z) was calculated,[36] WFL-z is the anthropometric standard recommended by the American Academy of Pediatrics for assessment of weight status in children aged <2 years.[37, 38]

6-11 years

Trained researchers measured child weight, and standing height was measured without cloths and shoes and waist circumference was measured at the end of normal expiration with a non-elastic tape held midway between the lower rib margin and the iliac crest. American Academy of Pediatrics recomended body mass index (BMI) for the assessment of weight status in children >2 years. We

calculated BMI, derived age- and sex specific height and BMI z score using WHO[36] reference data, and defined as obesity, if BMI value shows ≥ +2 z score.

Definitions of MetS for children and adolescents have been even more varied than the definitions used for adults.[39] The new IDF definition is derived according to age-groups because of developmental challenges presented by age-related differences in children and adolescents.[40] IDF suggest that the MetS should not be diagnosed in children younger than 10 years, but that a strong message for weight reduction should be delivered for those with abdominal obesity. MetS cannot be diagnosed, but further measurements should be made if there is a family history of MetS, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.For children age 10 or older, MetS can be diagnosed with abdominal obesity (WC ≥90^{th}) and the presence of two or more other clinical features: (i) elevated tryglycerides (TG) ≥150 mg/dL; (ii) low HDL ≤40 mg/dL; (iii) high blood pressure ≥130/85 mmHG; (iv) increased plasma glucose ≥100 mg/dL.

Metabolic measurements

Blood samples were collected according to the study protocol. Blood samples were collected for fasting glycemia, glycosylated hemoglobina (HbA1c), insulin, total cholesterol, hight density lipoprotein (HDL) and TG estimation. The insulin resistance (HOMA-IR) was calculated to determine the degree of insulin resistance, according to the following equation, proposed by Mattews et al[41]. The calculation is as follows, HOMA-IR = ((glycaemia (mMol) X insulin (U/mL)) /22.5L).

Outcomes

The primary outcomes for the present analysis were fetal and offspring growth and metabolic parameters of MetS as measured by using the following: (1) at birth-weight-for-gestational (2) ponderal index, (3) Infant growth percentiles using large-for-gestational-age plus macrossomia measures and (4) MetS for children and adolescents. All neonatal outcome data were extracted from medical records.

For children under 2 years the WHO curve with weight/lenght z scores and for children ≥5 years the BMI z scores was used.

Statistical Analysis

Descriptive statistics were used to characterize and compare sociodemographic variables according to BMI category. Initially descriptive analysis were obtained for the quantitative variables with the calculation of mean and standard deviation and for categorized variables, obtaining frequencies and percentages stratifying by groups with and without metabolic syndrome for mothers and children.The comparisons between averages of the quantitative variables were made using Student's t-test for mothers and children with and without metabolic syndrome. The association between categorized variables and the presence or absence of metabolic syndrome was performed through chi-square test, obtaining the relative risk considering the follow-up of mothers and children. In all tests the significance level of 5% or the corresponding p-value was used. All analyzes were performed using SAS for windows, v.9.4.

Results

The anthropometric, clinical and biochemical parameters of the mothers and newborn are presented in Table I, according to pre-pregnancy MetS status. In pre-pregnancy, the MetS group had higher BMI at pre-gestational period (p<0.0001), as well as weight (p<0.0001), waist circumference (p<0.0001), hip circumference (p=0.0003), higher relation in between the index waist/hip (p<0.0001) and hypertension (p=0.0071) compared to the non-MetS.

The biochemical analyzes of pre-pregnancy MetS mothers at 24-28 weeks showed significantly higher fasting plasma glucose (p=0.0141), HbA1c (p<0.0238), fasting glucose at OGTT (p=0.0001), 2 hours post load at OGTT (p<0.0001) and red blood cells (p=0.0025) and low for total cholesterol (p=0.0088) and LDL

(p=0.0041) compared with of pre-pregnancy non-MetS mothers. At birth, children of pre-pregnancy MetS mothers had significantly higher mean birth weight (p=0.0342), higher mean of the ponderal index (p=0.0005), higher percentage of LGA (p=0.0013), macrosomic (p=0.0008) and premature. (p=0.0322). There were no significant interactions between maternal pre-pregnancy MetS and non-MetS pre-pregnancy group, HDL-c, TG, hemoglobin, hematocrit, white blood cells, postpartum age gestation (in days), length, male sex, breast milk (in days) and breast milk + formulas at 24-28 weeks of gestation (Table I).

Table I. Characteristics of study participants by pre-pregnancy maternal MetS status (2004-2011).

	non-MetS (*n*= 103)	MetS (*n*= 49)	*p-value*
Maternal characteristcs prepregnancy (2004-2011)			
Maternal prepregnancy BMI (kg/m²)	25.53 ± 6.24	33.31 ±7.57	**<0.0001**
Weight (kg)	66,98 ± 13,81	86,42 ± 20,75	**<0.0001**
Waist circumference (cm)	77.61 ± 10.41	97.40 ± 15.88	**<0.0001**
Hip circumference (cm)	100.14 ± 7.4	111.75 ± 13.95	**0.0003**
Waist/hip index (cm)	0.77 ± 0.07	0.87 ± 0.09	**<0.0001**
Maternal prepregnancy hypertension (%)	16.5% (17)	34.6% (17)	**0.0071**
Biochemical Parameters (24 - 28 Weeks)			
Fasting glucose (mg/dL)	85.73 ± 25.26	102.09 ± 30.95	**0.0141**
HbA1c (%)	5.39 ± 1.13	5.99 ± 1.07	**0.0238**
Fasting glucose at OGTT (mg/dL)	82.66 ± 17.58	107.01 ± 33.37	**0.0001**
2 hours postload at OGTT (mg/dL)	129.17 ± 31.82	191.51 ± 79.10	**<0.0001**
Total cholesterol (mg/dL)	238.49 ± 49.03	207.86 ± 45.59	**0.0088**
LDL cholesterol (mg/dL)	131.82 ± 34.82	105.03 ± 43.12	**0.0041**
HDL cholesterol (mg/dL)	64.68 ± 14.77	57.92 ± 15.45	0.0621
Triglyceride (mg/dL)	192.07 ± 89.79	207.13 ± 66.32	0.4458
Red blood cells (million/mm³)	3,94 ± 3,61	4,19 ± 3.02	**0.0025**
Hemoglobin (g/dL)	11.70 ± 1,16	11.96 ±1 .08	0.3323
Hematocrit (%)	35.05 ± 3.26	36.06 ± 2.81	0.1790
White blood cells (/mm³)	9684 ± 2256	10144 ± 2109	0.3840
Offspring	**non-MetS (*n*= 103)**	**MetS (*n*= 49)**	***p-value***
Newborn			
Ethnicity			
white	81.55% (84)	59.18% (29)	**0.0083**
Gestation (days)	267.98 ± 10.95	264.7 ± 10.10	0.0889
Weight (g)	3199.1 ± 473.4	3383.0 ± 523.9	**0.0342**
Length (cm)	48.27 ± 2.32	48.22 ± 2.21	0.9080
Ponderal index (cm.kg-1/3)	2.83 ± 0.26	3.01 ± 0.32	**0.0005**
Male sex (%)	48.5% (50)	46.9% (23)	0.8531
LGA (%)	10.7% (11)	26.5% (13)	**0.0013**
Macrosomic (%)	2.91% (3)	14.29% (7)	**0.0008**
Premature (%)	13.59% (14)	20.4% (10)	**0.0322**
Breast milk (days)	180.82 ± 281.18	208.00 ± 307.87	0.6247
Breast milk + Formulas (days)	147.88 ± 120.68	157.73 ± 109.58	0.8174

Data are presented as mean ± (SD) or % (number)

Chi-square or ANOVA. Statistically significant *p* value < 0.05

Larger for gestational age (LGA), Macrosomic (>4kg), Premature (<37 weeks).

Metabolic Syndrome (Mets), Body mass index (BMI), Glycosylated hemoglobin (HbA1c), Oral glucose tolerance test (OGTT), Low density lipoprotein cholesterol (LDL), High density lipoprotein cholesterol (HDL).

Table II describes the children´s follow-up 6-11 years according to pre-pregnancy MetS status. At 2 years, the risk of overweight + overweight by weight/height z score classification were higher (p=0.0002) for offspring of mothers with pre-pregnancy MetS. Follow-up 6-11 years postpartum, 51% offspring of mother with pre-pregnancy MetS and 29.1% of offspring of mothers non-MetS were with obesity (p=0.0145) by of BMI z score classification, presenting the same for offspring's waist circumference (p=0.0034) classification with MetS (48.9%) and with non-MetS (25.2%) mothers according to IDF, in children and adolescents group >6 years and <10 years presented abdominal obesity plus family.

There were no significant interactions between MetS and non-MetS groups, weight/height zscore classification to 1 year, 6–11 years, physical activity, puberty, insulin resistance, dyslipidemia, fasting glucose, HbA1C, Total Cholesterol, LDL, TG, hemoglobin, hematocrit and white cells. The MetS classification according to IDF in children and adolescents, is high in the pre-pregnancy MetS group at age 6-9 (Table II).

IDF classification for MetS in the age-group 6-9 years was abdominal obesity plus family factor. However, IDF suggest that MetS should not be diagnosed in children younger than 10 years, but need message for weight reduction of these children. In our study, we observed higher prevalence of suggested MetS in the pre-pregnancy MetS group at age 6-9 years.

Table II. Characteristics of the children of mothers by the maternal MetS status, follow-up 6-11 years postpartum.

	non-MetS (*n*=103)	**MetS (*n*=49)**	***p-value***
Offspring characteristics 1-2 years postpartum			
1 year			
Weight/height *z score* classification			
Risk overweight + overweight	8.7% (09)	14.2% (07)	0.4479
Obesity	0% (00)	0% (00)	-
2 years			
Weight/height *z score* classification			
Risk overweight + overweight	9.7% (10)	30.6% (15)	**0.0002**
Obesity	1.0% (01)	2% (01)	1
Offspring characteristics 6-11 years postpartum			
BMI z score classification			
Eutrophic	49.5% (51)	34.6% (17)	0.1228
Overweight	18.4% (19)	12.2% (06)	0.4650
Obesity	29.1% (30)	51% (25)	**0.0145**
Waist circumference classification (cm)			
Obesity	25.2% (26)	48.9% (24)	**0.0034**
Physical Active (%)	61.17% (63)	67.3% (33)	0.5764
Puberty (%)	27.1% (28)	14.2% (7)	0.1189
Insulin resistance (%)	6.7% (06)	12.2% (06)	0.2937
Dyslipidemia (%)	31% (32)	38.7% (19)	0.4491
Fasting glucose (mg/dL)	87.26 ± 7.93	86.96 ± 9.92	0.8437
HbA1c (%)	5.20 ± 0.30	5.18 ± 0.30	0.8205
Insulin (μUI/mL)	6.45 ± 5.02	7.61 ± 7.07	0.2572
Total cholesterol (mg/dL)	171.00 ± 28.86	163.60 ±35.19	0.1813
LDL cholesterol (mg/dL)	102.04 ± 24.94	97.59 ±26.51	0.3296
HDL cholesterol (mg/dL)	51.25 ± 10.84	48.41 ±12.72	0.1615
Triglyceride (mg/dL)	83.17 ± 40.51	94.72 ±63.32	0.1827
Red blood cells (million/mm³)	4.87 ± 0.35	4.80 ±0.34	0.2532
Hemoglobin (g/dL)	13.21 ±0.77	12.96 ±0.81	0.0778
Hematocrit (%)	39.13 ± 3.36	38.95 ±1.80	0.7307
White blood cells (/mm³)	7471 ± 2445	6918 ± 1483	0.1630
Metabolic Syndrome			
6 - 9 years (%) (MetS)	18.9% (14)	51.2% (22)	**0.0031**
10 - 11 years (%) (MetS)	3.4% (1)	33.3% (02)	0.1143

Data are presented as mean ± (SD) or % (number);
Chi-square or ANOVA. Statistically significant $p < 0.05$.

Suggestive of MetS for> 6 years and <10 years was, with a percentile ≥90ofwaist circumference + family factors, according to International Diabetes Federation (IDF).
The definition MetS for> 10 years was, with a percentile ≥90 or cut factors for the adult, associated with two other factors among four, as reference IDF.
Body mass index (BMI), Glycosylated hemoglobin (HbA1c), Low density lipoprotein cholesterol (LDL), High density lipoprotein cholesterol (HDL).

Relative risk (RR) of the characteristics of children of mothers by maternal MetS status, follow-up 1-2 years and 6-11 years postpartum, are presented in Table III, showing as postpartum predictor for: LGA [2.71 (95% CI 1.61-4.55)], macrosomic [3.74 (95% CI 2.16-6.48)] and premature [2.25 (95% CI 1.23-4.13)]. There were no significant differences (p>0.05) and RR between pre-pregnancy MetS and non-MetS groups for: weight/height z score classification for age 1 year.

At 2 years, RR of overweight + overweight by weight / height *z* score classification [1.69 (95% CI 1.04 - 2.77)]; the follow-up 6 - 11 years presented RR predictor for obesity by BMI *z* score classification [1.84 (95% CI 1.71-2.89)]; obesity by waist circumference classification [2.09 (95% CI 1.32-3.31)]; MetS according to IDF in children and adolescents, group > 6 years and < 10 years presented abdominal obesity plus family factors [2.12 (95% CI 1.36-3.32)] and MetS classification according to IDF, group > 10 years and < 16 years [5.33 (95% CI 1.58-18.01)].

Table III. Relative risk of the characteristics of children by pre-pregnancy MetS status, follow-up 1-2 years and 6-11 years postpartum.

	non-MetS (*n*= 103)	**MetS (*n*= 49)**	***p-value***	**RR (95% C.I.)**
Newborn				
LGA (%)	10.7% (11)	26.5% (13)	**0.0013**	**2.71 (1.61 - 4.55)**
Macrosomic (%)	2.91% (3)	14.29% (7)	**0.0008**	**3.74 (2.16 - 6.48)**
Premature (%)	13.59% (14)	20.4% (10)	**0.0322**	**2.25 (1.23 - 4.13**
Offspring characteristics 1-2 years postpartum				
1 year Weight/height *z score* classification				
Risk overweight + overweight	8.7% (09)	14.2% (07)	0.4479	1.20 (0.77 – 1.88)
Obesity	0% (00)	0% (00)	-	-
2 years Weight/height *z score*classification				
Risk overweight + overweight	9.7% (10)	30.6% (15)	**0.0002**	**1.69 (1.04 – 2.77)**
Obesity	1.0% (01)	2% (01)	1	1.36 (0.34 – 5.44)
Offspring characteristics 6-11 years postpartum				
BMI *z score* classification				
Eutrophic	49.5% (51)	34.6% (17)	0.1228	1.52 (0.93 - 2.50)
Overweight	18.4% (19)	12.2% (06)	0.4650	1.41 (0.67 - 2.95)
Obesity	29.1% (30)	51% (25)	**0.0145**	**1.84 - (1.71 - 2.89)**
Waist circumference classification (cm)				
Obesity	25.2% (26)	48.9% (24)	**0.0034**	**2.09 (1.32 – 3.31)**
Metabolic Syndrome				
6 - 9 years (%) (MetS)	18.9% (14)	51.2% (22)	**0.0031**	**2.12 (1.36 - 3.32)**
10 - 11 years (%) (MetS)	3.4% (1)	33.3% (02)	0.1143	**5.33 (1.58 - 18.01)**

Data are presented as mean ± (SD), % (number) and RR (95% C.I.)
Chi-square or ANOVA. Statistically significant *p* value < 0.05
Suggestive of MetS for> 6 years and <10 years was, with percentile ≥90 of waist circumference + family factors, according to International Diabetes Federation (IDF).
The definition MetS for> 10 years was, with a percentile ≥90 or cut factors for the adult, associated with two other factors among four, as reference IDF.
Body mass index (BMI), Glycosylated hemoglobin (HbA1c), Low density lipoprotein cholesterol (LDL), High density lipoprotein cholesterol (HDL).

Discussion

The present study shows 9.1% of pre-pregnancy MetS prevalence according to the IDF consensus with important repercussions on the occurrence of LGA, macrosomic infants and PTB at birth. In previous papers we met that the pregnancy MetS prevalence varies according to the analyzed population and to the lifetime considered as pre-pregnancy or during pregnancy.[42,43] The pregnancy MetS prevalence varies according to the analyzed population, the criteria used to define MetS and with the life time considered. In previous papers, we met the prevalence of MetS increases with the worsening of glucose tolerance; 0%, 20.0%, 23.5% and 36.4% in normoglycemic, mild hyperglycemic, GDM, and overt GDM groups, respectively.[43] At delivery, in Angolan[42] pregnant women the crude prevalence of MetS was 36.6 % based on the JIS definition, 29.2 % based on NCEP ATPIII, 12.6 % based on Chatzi et al.[44] and 1.8 % based on Bartha et al.[45] Although the most important is that the maternal characteristics of the pre-pregnancy MetS allow us to describe the maternal environmental where the fetus will be developed. The intrauterine MetS environmental is characterized by maternal obesity, chronic hypertension, hyperglycemia and low total cholesterol and LDL compared with of non-MetS mothers. These results describe two opposite maternal environmental: one that could be altered as hyperglycemia and obesity that are more linked to increase the fetal growth and the other is hypertension with reduced placental vascularity, blood flow and restrict placental nutrient delivery to the growing fetus more likely to the development of intrauterine restriction.[9]These sometimes conflicting signals for placental function can contribute to the diversity of short and long-term results observed in pregnant obese women.[3]and probably in MetS mothers. In our results the hyperglycemia and obesity were the most usual maternal environmental and, therefore, high prevalence of LGA and macrosomic fetus in the pre-pregnancy MetS group were found endorse our previous results.[43] These results confirm the "fuel-mediated teratogenesis," of Norbert Freinkel[46] reflecting the effects of fetal hypernutrition

and setting the stage for further amplification of the pathophysiological effects of encountering an obesogenic environment postnatally. [47]

Moreover, it is further proved from this experiment that physical activity played a minor role in determining the impact of MetS.[48] While both non-MetS and MetS participants had almost the same level of physical activity, obesity was again differentiating factor between the two categories of participants. Despite relatively same level of physical activity, obesity percentage was higher for MetS participants. This reflects that the MetS could be a cause of high-calorie and low fiber diet.[48] This could mean that women taking a diet low in fresh fruits and vegetables, and high in junk food and sugary items were more prone to suffer from metabolic syndrome.[16] The high calorie and unhealthy diet could also be a cause of insulin resistance.[29] The offspring of pre-pregnancy MetS mothers that was developed in intrauterine over nutrition environment and shared the same familial and postnatal factors confirm the development over nutrition hypothesis that is responsible for the process of maintaining of a non-virtuous cycle of obesity.[49]

It is interesting to analyze the evolution of LGA and macrossomic newborn in mothers of both groups during the first 2 years of life. These children show similar growth pattern from 0-2 years mean while there is an increased risk of overweight + overweight using z score weight/height classification in offspring of pre-pregnancy MetS mothers. Considering the high prevalence of LGA and macrossomic newborn in pre-pregnancy MetS mother and the impact of these characteristics at 2 years after birth, an effective intervention to reduce the prevalence of MetS in pre-pregnant women could have significant beneficial effects on 2 years off spring outcomes. It is the familial effect.

Another interesting finding from this secondary analysis of a cohort is that the children of pre-pregnancy MetS women had higher risk of obesity from the age of 6 to 11 years. The initial results showed obesity as an alarming health condition in children in the first two years. Later from the follow-up study it was found that

children of MetS women had increased abdominal obesity as per the zscore. This was further proved by the CI indicating obesity by classification of waist circumference to be 2.09 (95% CI 1.32-3.31) for children between 6 to 11 years. This act as supporting evidence to most literature which states a positive correlation between women with MetS and short term impact on their children's weight to be higher as compared to children of non-MetS women.[3]

It seems that relative risk factors for children of mothers suffering from MetS tend to increase over the years.[50] The research study has significantly proved that children are at high risk of MetS as the relative risk index indicates higher risk (RR=1.69) of being overweight in children along with the z score classification for weight and height (p=0.0002). The postpartum and the follow-up study results depict that obesity percentage tends to increase for children of mothers suffering from MetS.[7] These children also tend to have a higher BMI and their bodies start to adapt to an unhealthy and sedentary lifestyle.[51] This can be said based on the IDF in children it appears that abdominal obesity plus family factors are higher for children between 6 to 10 years at p-value 0.0031. The Development Origins of Health and Disease (DOHaD) theory states that this develops at an early life stage but the risks of cardiovascular health issues tend to increase as the child grows.[48] The IDF level also indicates that for children of women with pre-pregnancy MetS, the tissues and organs become particularly sensitive to environment changes and exposure therefore becoming more disease susceptible in later years of life.[29]

Some studies stated that infants of mothers who suffered from MetS were more likely to be at a higher risk of developing diabetes mellitus.[52] However, from the research experiment conducted between mothers suffering from MetS, little evidence is found based on the z-score on their infants having risk of diabetes based on the fasting glucose levels between MetS and non-MetS. The glucose levels are relatively similar hence it was difficult to evaluate the risk of diabetes mellitus in children. Although, important evidence found from the results of this research experiment is that obesity and BMI classification changed for children

from the time they were infants to the follow-up study that was for 6 to 11 years. This implies that risk of diabetes as an outcome of increased obesity[53] is definitely evident for the children of mothers suffering from pre-pregnancy MetS.

An interesting finding from research and data has been that the signs of obesity and MetS risks are less likely to be visible for children between the ages of 1 to 2 years. The relative risks for the characteristics measured showed that LGA for women at 95% confidence interval was between 1.61 to 4.55, averaging to 2.71. This lead to the relative risk of being overweight and obese by waist circumference for children between 6 to 11 years to be highly probable based on 95% confidence level (2.09). The symptoms become more evident as a child grows and enters the age range from 6 years to 10 years. This is a major reason due to which it is almost impossible to classify children suffering from MetS in the early years.[54] Some literature states that the only visible factor to depict risks of MetS in children's early years is their weight. As their weight increases and their BMI moves towards a higher index of 30 or above.[55] In the long term however, increased health issues lead to the diagnosis of MetS for the children whose mothers had also suffered from it. The gestational exposures in the modern environment can be specifically targeted to reduce childhood obesity risk. Primary intervention in utero and in early life that attenuates obesity potential may be one of the most important public health efforts to enhance population health worldwide, particularly in low income population.[47]

Our results demonstrate that long-term clinical and simple lab evaluations are important options to be followed in low-income countries. However, the literature has been looking for lab markers to identify the child of risk to develop MetS and or some of its components in order to stop the world obesity epidemic. In previous paper it was found that the GDM hyperglycemic intrauterine environment promote transcriptional alterations in BCL2 and miR-181a in umbilical-cord blood cells of neonates, and both GDM neonates and obese adult subjects share the same transcriptional alteration in BCL2. The relationship between obesity and the

functions regulated by these two genes, BCL2 and miR-181a could be adopted as potential biomarkers for childhood obesity. However, further studies are recommended to confirm this hypothesis.[56]

Our findings enable us to confirm that the adverse maternal pre-pregnancy MetS environment influences the intrauterine milieu leading to increased risk for LGA and macrosomia and preterm at birth,with risk (1.69) for overweight plus overweight offspring at 2 years by weight/height z score classification. MetS risks less likely to be visible for children between the age of 1 year, the appearance of signs of obesity risks at 2 years, the risk (2.09) of being overweight and obese by waist circumference between 6 to 10 years and the development of obesity after 10 years.[57] Each anthropometric index BMI-for-age, height-for-age and weight-for-height may reflect a unique child nutrition status at specific ages.[58]

An editorial of The Journal of Pediatrics[59] provides evidence to advise pediatricians that it is time to revise the guidelines to assess the body mass index in infancy. The WHO BMI-for age percentiles curves is the suggestion to monitor weight gain in infant and toddlers. The literature has demonstrated that primary intervention in utero and in early life that attenuates obesity potentialmay be one of the most important public health efforts to enhance population.

Conclusions

The overall outcomes of this study depict that clinical and lab follow-up study showed increased risks on the health of children of pre-pregnancy mothers with MetS in alow-income population of Brazilian mother. The adverse pregnancy outcomes in pre-pregnancy MetS mother were characterized by increased risk for the LGA, macrosomia and preterm birth. There is significant statistical evidence that children of women with pre-pregnancy MetS presents risk of overweight + overweight (by z-score weight/height classification) at the second year after birth;

from 6 to 11 years there was an increase in overweight and after 10 to 11 years it was possible to characterize the increased MetS (IDF).

Our results demonstrate the consequences of pre-pregnancy MetS milieu in a low-income offspring population using clinical and lab markers. It was possible to define the tide of the physiological route of MetS development in offspring population from pre-pregnancy MetS women without nutritional guidance, acknowledged by intrauterine obesity environment, with progression to overweight during childhood and finally by MetS detection at 10-11 years creating a vicious cycle, particularly in female offspring.

These short and long-term adverse offspring consequences confirm the concept of fetal programming or developmental origins of health and disease-DOHaD.[60-65] In our view, these results suggest that strategies to prevent adult metabolic disease relies on interventions starting before pregnancy for a healthier next generation. To further evaluate other impacts of MetS in children, based on this study it is recommended that follow-up studies for children of MetS women should be conducted every 5 to 6 years to detect and control the issues that develop overtime.

References

[1]. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2014; 384:766-81. doi:10.1016/s0140-6736(14)60460-8

[2]. Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1,000 days. Am J Prev Med 2016;50:761-79.doi:10.1016/j.amepre.2015.11.012

[3]. Howell KR, Powell TL. Effects of maternal obesity on placental function and fetal development. Reproduction 2017;153:R97–R108. doi:10.1530/rep-16-0495

[4]. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-Pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: A systematic review and meta-analysis. PLoS ONE 2013;8:e61627.doi:10.1371/journal.pone.0061627

[5]. Schellong K, Schulz S, Harder T, Plagemann A. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. PLoS ONE 2012;7: e47776.doi:10.1371/journal.pone.0047776

[6]. Adane AA, Tooth LR, Mishra GD. (2019). The role of offspring's birth weight on the association between pre-pregnancy obesity and offspring's childhood anthropometrics: a mediation analysis. J Dev Orig Health Dis 2019;1-8. doi:10.1017/s2040174418001137

[7]. Phelan S. Pregnancy: a "teachable moment" for weight control and obesity prevention. Am J Obstet Gynecol 2010;202:135.e1-135.e8. doi:10.1016/j.ajog.2009.06.008

[8]. Catharina AS, Modolo R, Ritter AMV, Sabbatini AR, Lopes HF, Moreno Junior H, Faria AP de. Metabolic syndrome-related features in controlled

and resistant hypertensive subjects. Arq Bras Cardiol 2018;110:514–521. doi:10.5935/abc.20180076

[9]. Stang J, Huffman LG. Position of the academy of nutrition and dietetics: Obesity, reproduction, and pregnancy outcomes. J Acad Nutr Diet 2016;116: 677-91.doi:10.1016/j.jand.2016.01.008

[10]. Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1323275 person years. BMJ 2013;347:f4539–f4539. doi:10.1136/bmj.f4539

[11]. Rudge MVC, Calderon I de MP, Ramos MD, Abbade JF, Rugolo LMSS. Perinatal outcome of pregnancies complicated by diabetes and by maternal daily hyperglycemia not related to diabetes. Gynecol Obstet Invest 2000;50;108-12. doi:10.1159/000010293

[12]. American Diabetes Association. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019; 42(Suppl. 1):S165-S172.

[13]. Bevier W, Fischer R, Jovanovic L. Treatment of women with an abnormal glucose challenge test (but a normal oral glucose tolerance test) decreases the prevalence of macrosomia. Am J Perinatol 1999;16;269-75. doi:10.1055/s-2007-993871

[14]. Vambergue A, Nuttens MC, Verier-Mine O, Dognin C, Cappoen JP, Fontaine P. Is mild gestational hyperglycaemia associated with maternal and neonatal complications? The Diagest Study. Diabet Med 2000;17;203-8.

[15]. Åberg A, Rydhstroem H, Frid A. Impaired glucose tolerance associated with adverse pregnancy outcome: A population-based study in southern Sweden. Am J Obstet Gynecol 2001;184:77–83. doi:10.1067/mob.2001.108085

[16]. Dutra E, de Carvalho K, Miyazaki É, Hamann E, Ito M. Metabolic syndrome in central Brazil: prevalence and correlates in the adult population. Diabetol Metab Syndr 2012;4: 20. doi:10.1186/1758-5996-4-20

[17]. Yang Z, Phung H, Freebairn L, Sexton R, Raulli A, Kelly P. Contribution of maternal overweight and obesity to the occurrence of adverse pregnancy outcomes. Aust N Z J Obstet Gynaecol 2018;1-8. doi:10.1111/ajo.12866

[18]. The American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 548: weight gain during pregnancy. Obstet Gynecol 2013;121:210-2. doi: http://10.1097/01.AOG.0000425668.87506.4c.

[19]. Acosta O, Ramirez VI, Lager S, Gaccioli F, Dudley DJ, Powell TL, Jansson T. Increased glucose and placental GLUT-1 in large infants of obese nondiabetic mothers. Am J Obstet Gynecol 2015;212:227.e1–227.e7. doi:10.1016/j.ajog.2014.08.009

[20]. Agarwal P, Morriseau TS, Kereliuk SM, Doucette CA, Wicklow BA, Dolinsky VW. Maternal obesity, diabetes during pregnancy and epigenetic mechanisms that influence the developmental origins of cardiometabolic disease in the offspring. Crit Rev Clin Lab Sci 2018;55:71–101. doi:10.1080/10408363.2017.1422109

[21]. De Zegher, F., Pérez-Cruz, M., Sebastiani, G., Díaz, M., López-Bermejo, A., & Ibáñez, L. (2016). Large for Gestational Age Newborns from Mothers Without Diabetes Mellitus Tend to Become Tall and Lean Toddlers. The Journal of Pediatrics, 178, 278–280. doi:10.1016/j.jpeds.2016.08.042

[22]. Barker DJ, Eriksson JG, Forsén T, Osmond C. Fetal Origins of Adult disease: Strength of effects and Biological Basis. Int J Epidemiol 2002;31:1235-9.

[23]. Hay WW Jr. Strategies for feeding the preterm infant. Neonatology 2008;94:245-54. doi:10.1159/000151643

[24]. Boudet Berquier J, Salanave B, Desenclos JC, Castetbon K. (2017). Sociodemographic factors and pregnancy outcomes associated with prepregnancy obesity: effect modification of parity in the nationwide Epifane birth-cohort. BMC Pregnancy Childbirth 2017;17:273. doi:10.1186/s12884-017-1456-8

[25]. Liu H, Zhang C, Zhang S, Wang L, Leng J, Liu D, et al Prepregnancy body mass index and weight change on postpartum diabetes risk among

gestational diabetes women. Obesity 2014;22:1560-7. doi:10.1002/oby.20722

[26]. Young TK, Woodmansee B. Factors that are associated with cesarean delivery in a large private practice: The importance of prepregnancy body mass index and weight gain. Am J Obstet Gynecol 2002;187:312-8. doi:10.1067/mob.2002.126200

[27]. De Carvalho Vidigal F, Bressan J, Babio N, Salas-Salvadó J. Prevalence of metabolic syndrome in Brazilian adults: a systematic review. BMC Public Health 2013;13:1198. doi:10.1186/1471-2458-13-1198

[28]. Kuschnir MCC, Bloch KV, Szklo M, Klein CH, Barufaldi LA, Abreu G de A, et al. ERICA: prevalence of metabolic syndrome in Brazilian adolescents. Revista de Saúde Pública 2016;50(suppl 1):11s. doi:10.1590/s01518-8787.20160500067

[29]. Goldstein JA, Norris SA, Aronoff DM. DOHaD at the intersection of maternal immune activation and maternal metabolic stress: a scoping review. J Dev Orig Health Dis 2017;8:273-83. doi:10.1017/s2040174417000010

[30]. Reynolds RM, Osmond C, Phillips DIW, Godfrey KM. Maternal BMI, parity, and pregnancy weight gain: Influences on offspring adiposity in young adulthood. J Clin Endocrinol Metab 2010;95(12), 5365-9. doi:10.1210/jc.2010-0697

[31]. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen, TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. Diabetologia 2016;59:1396-9. doi:10.1007/s00125-016-3985-5

[32]. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Brussels: IDF, 2005. Available at: http://www.idf.org/webdata/docs/IDF_Metasyndromedefinition.pdf (accessed December 2018).

[33]. Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu H M. Association of maternal body mass index, excessive weight gain, and gestational diabetes

mellitus with large-for-gestational-age births. Obstet Gynecol 2014;123:737-44. doi:10.1097/aog.0000000000000177

[34]. Fenton TR, Nasser R, Eliasziw M, Kim JH, Bilan D, Sauve R. Validating the weight gain of preterm infants between the reference growth curve of the fetus and the term infant. BMC Pediatr 2013;13:92. doi:10.1186/1471-2431-13-92

[35]. Visser GHA, Evers IM, Giorgio Mello G. Management of the macrosomic fetus. In: Hod M, Jovanovic L, Di Renzo GC, De Leiva A, Langer O, editors. Textbook of Diabetes & Pregnancy. 2nd ed. London: Informa; 2008.

[36]. World Health Organization Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006 (312 pages).

[37]. HamillPV, DrizdTA, JohnsonCL, ReedRB, RocheAF.NCHS growth curves for children birth18 years. United States. Vital and Health Statistics Series 11 1977;165:i-iv, 1-74.

[38]. Roy SM, Fields DA, Mitchell JA, Hawkes CP, Kelly A, Wu GD. Body mass index is a better indicator of body composition than weight-for-length at age 1 month. J Pediatr 2019;204:77-83.e1. doi:10.1016/j.jpeds.2018.08.007

[39]. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S. The metabolic syndrome in children and adolescents ? an IDF consensus report. Pediatr Diabetes 2007;8:299-306. doi:10.1111/j.1399-5448.2007.00271.x

[40]. International Diabetes Federation. Metabolic syndrome in children and adolescents. Brussels: IDF, 2007. Available at: https://www.idf.org (accessed December 2018).

[41]. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

[42]. Dos Prazeres Tavares H, dos Santos DCDM, Abbade JF, Negrato CA, de Campos PA, Calderon IMP, Rudge MVC. Prevalence of metabolic

syndrome in non-diabetic, pregnant Angolan women according to four diagnostic criteria and its effects on adverse perinatal outcomes. Diabetol Metab Syndr 2016;8:27. doi:10.1186/s13098-016-0139-3

[43]. Negrato CA, Jovanovic L, Rafacho A, Tambascia MA, Geloneze B, Dias A, Rudge MV. Association between different levels of dysglycemia and metabolic syndrome in pregnancy. Diabetol Metab Syndr 2009;1:3. doi:10.1186/1758-5996-1-3

[44]. Chatzi L, Plana E, Pappas A, Alegkakis D, Karakosta P, Daraki V, et al. The metabolic syndrome in early pregnancy and risk of gestational diabetes mellitus. Diabetes Metab J 2009;35:490-4. doi: 10.1016/j.diabet.2009.07.003.

[45]. Bartha JL, Bugatto FG, Macías RF, González LN, Delgado RC, Vivancos BH. Metabolic Syndrome in normal and complicated pregnancies. Eur J Obstet Gynecol Reprod Biol 2008;137:178-84. doi: 10.1016/j.ejogrb.2007.06.011.

[46]. Freinkel N. Banting lecture 1980: of pregnancy and progeny. Diabetes, 1980:29;1023-35. doi:10.2337/diab.29.12.1023.

[47]. Friedman JE. (2015). Obesity and gestational diabetes mellitus pathways for programming in mouse, monkey, and man—Where do we go next? The 2014 Norbert Freinkel award lecture. Diabetes Care, 2015;38:1402-11. doi:10.2337/dc15-0628

[48]. Hermann GM, Dallas LM, Haskell SE, Roghair RD. Neonatal macrosomia is an independent risk factor for adult metabolic syndrome. Neonatology, 2010;98;238-44. doi:10.1159/000285629

[49]. Lawlor DA, Smith GD, O'Callaghan M, Alati R, Mamun AA, Williams GM, et al. Epidemiologic evidence for the fetal over nutrition hypothesis: Findings from the mater-university study of pregnancy and its outcomes. Am J Epidemiol 2006;165:418-24. doi:10.1093/aje/kwk030

[50]. Binder NK, Hannan NJ, Gardner DK. Paternal diet-induced obesity retards early mouse embryo development, mitochondrial activity and pregnancy health. PLoS ONE, 2012;7: e52304. doi:10.1371/journal.pone.0052304

[51]. Rooney BL, Mathiason MA, Schauberger CW. Predictors of obesity in childhood, adolescence, and adulthood in a birth cohort. Matern Child Health J 2010;15:1166-75. doi:10.1007/s10995-010-0689-1

[52]. Silveira PP, Portella AK, Goldani MZ, Barbieri MA. Developmental origins of health and disease (DOHaD). J Pediatr (Rio J). 2007;83:494-504.

[53]. Avcı ME, Şanlıkan F, Çelik M, Avcı A, Kocaer M, Göçmen A. Effects of maternal obesity on antenatal, perinatal and neonatal outcomes. J Matern Fetal Neonatal Med 2014;28: 2080-3. doi:10.3109/14767058.2014.978279

[54]. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. J Pediatr 2008;152: 201-6. doi:10.1016/j.jpeds.2007.09.010

[55]. Leng J, Li W, Zhang S, Liu H, Wang L, Liu G, et al. GDM women's pre-pregnancy overweight/obesity and gestational weight gain on offspring overweight status. PLOS ONE 2015;10: e0129536. doi:10.1371/journal.pone.0129536

[56]. Marcondes JPC, Andrade PFB, Sávio ALV, Silveira MAD, Rudge MVC, Salvadori DMF. BCL2 and miR-181a transcriptional alterations in umbilical-cord blood cells can be putative biomarkers for obesity. Mutat Res. 2018;836(Part B):90-6. doi:10.1016/j.mrgentox.2018.06.009

[57]. Dimasuay KG, Boeuf P, Powell TL, Jansson T. Placental responses to changes in the maternal environment determine fetal growth. Front Physiol 2016;7:12. doi:10.3389/fphys.2016.00012

[58]. Corsi DJ, Subramanyam MA, Subramanian SV. Commentary: Measuring nutritional status of children. Int J Epidemiol 2011;40(4):1030-6. doi:10.1093/ije/dyr108

[59]. Woo JG, Daniels SR. Assessment of body mass index in infancy: It is time to revise our guidelines. J Pediatr 2018;204:10-11. doi:10.1016/j.jpeds.2018.09.025

[60]. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989;298:564-7.

[61]. Barker DJ, Osmond C. Infant-mortality, childhood nutrition, and ischemic-heart-disease in England and Wales. Lancet 1986;1:1077-81.

[62]. Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals? J Physiol 2004;561:355-77. doi:10.1113/jphysiol.2004.072009

[63]. Gluckman PD. Living with the Past: Evolution, Development, and Patterns of Disease. Science 2004;305:1733-6. doi:10.1126/science.1095292

[64]. Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN. Glucose tolerance in adults after prenatal exposure to famine. Lancet 1998;351:173-7.

[65]. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med 1977;31:91-5.

Anexos

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Alterações Metabólicas 5-11 anos pós nascimento em filhos de mães com síndrome metabólica na gestação

Pesquisador: LUCAS PONTES DE CAMARGO

Área Temática:

Versão: 2

CAAE: 67543417.3.0000.5411

Instituição Proponente: Departamento de Ginecologia e Obstetrícia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.014.937

Apresentação do Projeto:

Trata-se de emenda solicitando alteração de título. O projeto de pesquisa onde o pesquisador discorre sobre o diabetes mellitus gestacional (DMG) que é definido como qualquer grau de intolerância à glicose iniciado ou detectado pela primeira vez na gestação. O DMG aparece em geral na segunda metade da gravidez e afeta principalmente o ritmo de crescimento fetal. A importância do diagnóstico do diabetes durante a gravidez foi sugerida por relatos de maior frequência de abortamentos, macrossomia e mortalidade perinatal em filhos de mulheres que desenvolveram DMG, em comparação às do grupo-controle. Essa alteração no meio intra-uterino pode ser a razão do aumento alarmante da obesidade e do diabete tipo 2 na infância e na adolescência que o mundo hoje está observando. Este projeto está sendo proposto considerando: 1) Os conhecimentos já adquiridos pelo Grupo Acadêmico: Diabete e Gravidez: Clínico e Experimental da Faculdade de Medicina de Botucatu_UNESP; 2) As dúvidas existentes com relação à presença ou não de duas entidades clínicas diferentes (DMG e hiperglicemia gestacional leve) ou de uma mesma doença em estágios distintos; 3) A repercussão biométrica e metabólica destas entidades clínicas nas mães e seus conceptos depois de 2 a 10 anos após o parto. O objetivo da pesquisa é investigar as concentrações sanguíneas de glicose e perfil lipídico, que foram diagnosticadas durante a gestação com HGL, DMG e avaliar a incidência do desenvolvimento de Síndrome Metabólica (SM) 2 a 10 após a gestação. Determinar a associação entre as concentrações glicêmicas na gestação de mulheres com DMG ou HGL, o desenvolvimento de SM.

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Continuação do Parecer: 3.014.937

Trata-se de um estudo de coorte histórica de mães diabéticas, a partir do banco de dados (Projeto: "FOLLOW-UP METABÓLICO E BIOMÉTRICO DE PACIENTES COM HIPERGLICEMIA NA GESTAÇÃO E SEUS CONCEPTOS"; CAAE: 56912316.1.000.5411; Número do parecer: 1.641.871), que contém informações sobre a evolução da gestação, classificação do diabete materno, condições de nascimento e evolução neonatal e dados clínicos do seguimento ambulatorial. Para o preenchimento do banco de dados do projeto principal, as mães e crianças incluídas foram submetidas aos seguintes procedimentos: 1. Aplicação de questionário de dados epidemiológicos e clínicos; 2. avaliações antropométricas e dos níveis pressóricos; 3. coleta de sangue (15 ml) para: glicemia de jejum, colesterol total e frações, triglicérides. Os exames bioquímicos e hormonais, o TTG75g (somente nas mães) foi realizado no Laboratório Clínico Central e no Centro de Avaliação do Bem-Estar Fetal, nas dependências do Hospital de Clínicas da FMB/UNESP, que foi devidamente ressarcido por estes procedimentos.

Será realizado levantamento do prontuário médico para coletar informações referentes à evolução da gestação, dados do parto e de nascimento e exames do recém-nascido referentes a consultas feitas anteriormente. O tamanho amostral mínimo será de 96 pacientes e seus respectivos filhos. Os critérios de inclusão e de exclusão, bem como as variáveis de controle, dependentes e independentes estão bem definidas e claras.

Objetivo da Pesquisa:

: Investigar as concentrações sanguíneas de glicose e perfil lipídico, que foram diagnosticadas durante a gestação com HGL, DMG e avaliar a incidência do desenvolvimento de SM 2 a 10 após a gestação. Determinar a associação entre as concentrações glicêmicas na gestação de mulheres com DMG ou HGL, o desenvolvimento de SM.

Objetivos específicos:

- Analisar a evolução da insulino-resistência e síndrome metabólica em mulheres que foram diagnosticadas durante a gestação com hiperglicemia gestacional leve e diabéticas: DMG e clínico, através das características do perfil glicêmico e lipídico.
- Avaliar os exames laboratoriais: perfil lipídico (triglicérides, colesterol total, HDL, LDL, VLDL) e glicemia de jejum destas pacientes e seus filhos.
- Avaliar medidas antropométricas (peso, estatura e IMC) destas pacientes e seus filhos.
- Correlacionar medidas antropométricas maternas (peso, altura, e IMC antes da gestação e ganho de peso durante a gestação), com medidas maternas atuais e o desenvolvimento de seus filhos.

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Avaliação dos Riscos e Benefícios:

Riscos: Não há riscos para os pacientes.

Benefícios: Elucidação da programação fetal na hiperglicemia e seus resultados.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante, elaborada adequadamente, contém todas as definições necessárias para seu entendimento. De acordo com o pesquisador, serão estudados apenas as informações de banco de dados e de prontuário médico, com garantia de sigilo. O pesquisador informa que não haverá gastos. Projeto já foi aprovado pelo CEP em 06/06/2017. Pesquisador solicita alteração no título do projeto, que é pertinente ao objetivo da pesquisa.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados os seguintes documentos:

- folha de rosto da FMB: adequado;
- Anuência da instituição: EAP
- Ofício para alteração do título do projeto;
- Projeto de pesquisa: adequado;
- Solicita dispensa do TCLE. Justificativa: "o banco de dados inicial foi montado em cima de um projeto de segmento e houve muita dificuldade no acolhimento destes pacientes, por isso não é viável reconvocá-los e é pedido a dispensa do uso do Termo de Consentimento Livre e Esclarecido (TCLE)". Os pesquisadores garantem o sigilo dos participantes.

Recomendações:

-

Conclusões ou Pendências e Lista de Inadequações:

Após análise, o Colegiado deliberou APROVAÇÃO da emenda apresentada.

Considerações Finais a critério do CEP:

Conforme deliberação do Colegiado em reunião ordinária do Comitê de Ética em Pesquisa da FMB/UNESP, realizada em 05 de novembro de 2018, a solicitação enviada na forma de "Emenda", se encontra APROVADA, sem necessidade de envio à CONEP.

Atenciosamente,

Comitê de Ética em Pesquisa da Faculdade de Medicina de Botucatu – UNESP

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Continuação do Parecer: 3.014.937

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1216343_E1.pdf	23/10/2018 14:41:18		Aceito
Folha de Rosto	folha_de_rosto.pdf	23/10/2018 14:39:43	LUCAS PONTES DE CAMARGO	Aceito
Outros	oficio_cep.pdf	23/10/2018 12:52:09	SARA ROSA STANLEY SAMPAIO	Aceito
Outros	oficio.pdf	06/09/2018 17:57:21	LUCAS PONTES DE CAMARGO	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	JustificativaAusencia.pdf	19/04/2017 16:25:13	LUCAS PONTES DE CAMARGO	Aceito
Outros	Anuencia.pdf	19/04/2017 16:15:37	LUCAS PONTES DE CAMARGO	Aceito
Cronograma	LucasCronograma.pdf	19/04/2017 16:13:07	LUCAS PONTES DE CAMARGO	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoLucas.pdf	19/04/2017 16:12:53	LUCAS PONTES DE CAMARGO	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BOTUCATU, 12 de Novembro de 2018

Assinado por:
SILVANA ANDREA MOLINA LIMA
(Coordenador(a))

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