UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
FACULDADE DE MEDICINA

Mariana Alvarez Arantes

Follow-up metabólico e biométrico de pacientes com hiperglicemia na gestação e seus conceptos

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

Orientadora: Prof.ª Emérita Marilza Vieira Cunha Rudge
Coorientador: Dr. Carlos Antonio Negrato
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1. Diabetes Mellitus Tipo 2. 2. Diabetes gestacional. 3. obesidade. 4. Gravidez - Complicações. 5. Hiperglicemia.

Palavras-chave: Diabetes mellitus gestacional; Diabetes mellitus tipo 2; Gravidez - complicações; obesidade.

Epígrafe

“Primeiro pense. Segundo, acredite.

Terceiro, sonhe. E por último, ouse”.

Walt Disney

Dedicatória

*A **Deus** por sempre estar ao meu lado me guiando pelo caminho certo.*

Aos meus pais, ***Lucy e Sidnei****, por amor, vocês aceitaram meus momentos de ausência quando a batalha me exigia dedicação. Por amor, vocês compartilharam das minhas preocupações e dos meus medos. Por amor, vocês mantiveram-me segura, deram-me as mãos e seguiram ao meu lado. Obrigada por me ensinarem a aproveitar todas as oportunidades que a vida oferece. Vocês me permitiram vencer!*

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E enfim, a todos aqueles não citados, mas que de alguma forma, tornaram possível a realização deste trabalho. Muito obrigada!

Sumário

Seção 1
Contextualização

Timeline do Grupo de Pesquisa

Marilza Rudge junto ao Programa de Pós-graduação em Ginecologia, obstetrícia e mastologia da Faculdade de Medicina de Botucatu/UNESP, através do Grupo de Pesquisa “Diabetes e Gravidez: Clínico e Experimental” realiza diversas investigações relacionadas à gravidez complicada pelo diabete desde 1980.

Em sua tese de livre docência em 1984, Rudge deu início a investigações relacionadas com hiperglicemia gestacional leve, direcionando o grupo a estudos com diferentes níveis glicêmicos, gestação e suas complicações.

Ao longo destes anos foram realizados estudos clínicos e experimentais (pré-clínicos), além de estudos translacionais de grande importância para maior entendimento deste “estado clínico” e suas repercussões.

Foram publicados 354 artigos, sendo 242 com repercussões maternas, 81 com repercussões maternas e seus descendentes e 31 com repercussões em descendentes; onde destes temos 136 trabalhos focados na hiperglicemia gestacional e suas repercussões. Na figura 1 apresentamos os números de artigos publicados.

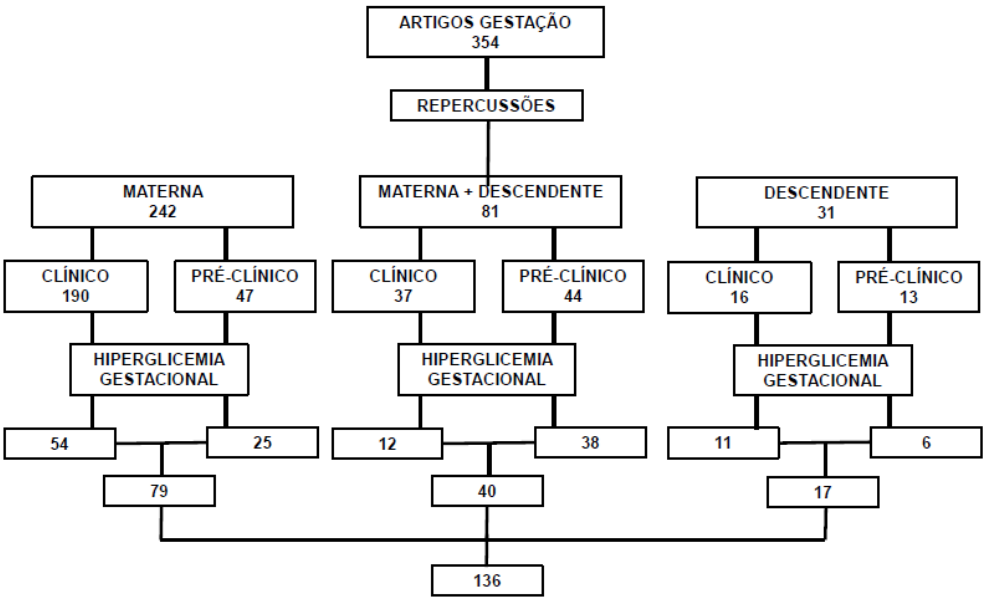

Figura 1. Apresentação do número de publicações com repercussões materna e/ou do descendente, considerando estudo clínico e pré-clínico e hiperglicemia gestacional ou na prenhez.

O Grupo de Pesquisa desenvolve estudos clínicos e pré-clínicos com o foco em repercussões maternas sobre o feto e ao longo da vida destas e de seus filhos. Projetos multicêntricos são realizados para estabelecer protocolos de diagnóstico e condutas na gestação.

Estudos translacionais são feitos para observar o comportamento fisiológico do organismo em relação ao estado hiperglicêmico materno e isto passado para a parte clínica, observando assim repercussões materno-fetais.

O Grupo de Pesquisa vem trabalhando a internacionalização de pesquisas e assim firmando parcerias com centros universitários internacionais, tendo como objetivo a troca de experiência e a elucidação destas repercussões.

A prevalência do DMG aumenta alarmante nos dias de hoje, por isso é de grande importância conhecer os mecanismos e assim melhorar os resultados perinatais e os efeitos à longo prazo para estas mães e seus filhos.

Todas as referências mencionadas no texto encontram-se no endereço eletrônico: http://buscatextual.cnpq.br/buscatextual/visualizacv.do?id=K4787962U6

Seção 2

Fundamentação teórica

Resumo

Introdução e objetivos: as mulheres com *Diabetes mellitus* gestacional (DMG) estão em maior risco de resultados adversos na gravidez, bem como, desenvolver o *Diabete mellitus* tipo 2 (DM2) e outras síndromes metabólicas no futuro, em comparação com mulheres sem DMG. A co-ocorrência de DMG com obesidade "diabesity", é provavelmente a maior epidemia da história humana. As alterações metabólicas no útero podem influenciar os padrões fisiológicos e estruturais que "programam" a saúde a longo prazo na idade adulta. A prole destas mães tem o risco aumentado ao longo da vida para doenças metabólicas e obesidade.

Métodos: Este estudo descritivo deriva de uma coorte prospectiva de mulheres grávidas que foram seguidas no Centro de Pesquisa sobre Diabetes Perinatal - FMB-UNESP. Todos os pares de mulheres e recém-nascidos que realizaram a triagem para DMG durante a gravidez foram contatados e convidados a retornar para o estudo de acompanhamento de longo prazo com seus filhos.

Resultados: Nossos resultados mostram que DMG anterior foi preditor significativo para DM2 isolado [2.56 (95% C.I. 1.73- 3.79)]. Quando avaliamos a "diabesidade" com sobrepeso pré-gestacional e DMG, houve significancia para a progressão para DM2 [6.00 (IC 95% 2.42- 14.84)], sobrepeso no futuro [2.37 (IC 95%: 1.56- 3.61)], resistência à insulina [3.14 (IC 95% 1.79- 5.49)] e dislipidemia [5.47 (IC 95% 2.17- 13.76)].

Conclusão: O DMG foi fortemente associado ao maior risco tanto materno quanto para os descendentes, esses achados sustentam a idéia da forte associação entre exposições ambientais durante o início da vida (pré e pós-natal) e o condicionamento das respostas biológicas que definem o risco de doença ao longo da vida da prole e da mãe. Além disso, os processos de adaptação fisiológica decorrentes da exposição à obesidade materna e diabetes "diabesidade" durante a gravidez afetam descendência fetal, resultando em adaptações nos níveis do sistema celular, tecido e órgão. Mudanças epigenéticas ao longo do curso de vida em conjunto com fatores como dieta e estilo de vida pós-natal levam ao desenvolvimento de distúrbios metabólicos na idade adulta jovem que continuam na idade adulta e na velhice.

Palavras-chave: Obesidade, *Diabetes mellitus* tipo 2, diabesidade, *Diabetes mellitus* gestacional, obesidade infantil.

Abstract

Background and aims: Women with gestational Diabetes mellitus (GDM) are at increased risk of adverse pregnancy outcomes, as well as, developing type 2DM and other metabolic syndrom in the future compared to women non-GDM, and the co-occurrence of GDM with obesity “diabesity”, is probably the major epidemic in human history. The metabolic changes *in utero* may influence the physiological and structural patterns that “program” long-term health in adulthood, offspring of these mother have an increased lifetime risk of metabolic disease and obesity.

Methods: This descriptive study derives from a prospective cohort of pregnant women that were followed at Perinatal Diabetes Research Center- FMB-UNESP. All women-newborns pairs who performed a screening for GDM during pregnancywere contacted and invited to return for the long-term follow-up study with their children.

Results: Our findings show that previous GDM was significant predictor of type 2DM isolated [2.56 (95% C.I. 1.73-3.79)]. When we evaluated GDM plus pregestation overweight “diabesity”, were significantly for progression to type 2DM [6.00 (95% C.I. 2.42- 14.84)], overweight in the future [2.37 (95% C.I. 1.56- 3.61)], insulin-resistance [3.14 (95% C.I. 1.79- 5.49)], and dyslipidemia [5.47 (95% C.I. 2.17- 13.76)].

Conclusion: GDM was strongly associated with greater risk of both

maternal and offspring, these findings support the idea of a strong association between environmental exposures during early life (pre and postnatal) and the conditioning of biological responses that define disease risk over the life course of the offspring and mother. Besides, the physiological adaptive processes upon exposure to maternal obesity and diabetes “diabesity” during pregnancy affect fetal offspring resulting in adaptations across the cellular, tissue, and organ system levels. Epigenetic changes throughout the life course in conjunction with postnatal diet and lifestyle factors lead to the development of metabolic disorders in young adulthood which continue into adulthood and old age.

Keywords: Obesity, type 2 Diabetes mellitus, diabesity, gestational Diabetes mellitus, offspring obesity.

Fundamentação teórica

Diabetes mellitus gestacional (DMG) foi definido como qualquer grau de intolerância à glicose iniciado ou detectado pela primeira vez na gestação. A Associação Americana de Diabetes (ADA) alterou a definição do DMG para "*o diabetes diagnosticado no segundo e terceiro trimestre da gestação*" [1]. O DMG aparece em geral na segunda metade da gravidez e afeta principalmente o ritmo de crescimento fetal. Os filhos de mães com DMG têm maior risco de evoluírem com macrossomia e hipoglicemia neonatal. Como conseqüência, obesidade e desenvolvimento psicomotor mais lento são complicações que podem se desenvolver a longo prazo [2].

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 [1].

O DMG e a hiperglicemia gestacional leve (HGL) têm consequências importantes para a mãe, o feto e o recém-nascido [3-6]. As gestantes com HGL não atingem os critérios diagnósticos para DMG, porém, os recém-nascidos apresentam macrossomia mediada pela glicemia, mortalidade perinatal e resultados perinatais adversos semelhantes aos das DMG [6-10]. Esse grupo de gestantes com hiperglicemia leve caracteriza-se por apresentar o teste de tolerância à glicose normal (TTG) e perfil glicêmico (PG) alterado [8, 10-11]. A literatura recente, desde os resultados publicados no HAPO, tem

valorizado níveis menores de hiperglicemia na gestação como responsáveis por repercussões perinatais adversas [13, 14]. As gestantes portadoras de HGL têm as mesmas repercussões perinatais do diabete gestacional [7, 15] e correspondem a 13,8% da população de gestantes com rastreamento positivo para DMG que, somados aos 7,0% das gestações complicadas por diabete, aumentam a ocorrência de distúrbios hiperglicêmicos na gestação para cerca de 20% [16].

Trabalho realizado no Brasil envolvendo duas universidades estaduais paulistas (Unesp e Unicamp) e com co-autoria da Prof. Lois Jovanovic evidenciou que essas gestantes portadoras de HGL apresentam hiperglicemia, hiperinsulinemia e resistência à insulina (HOMA-IR e HOMA-β) na gestação que persiste no pós-parto [3]. Em outras palavras, estas gestantes apresentam insulino-resistência e insulino-deficiência. A investigação realizada por esse grupo mostrou que vários componentes da síndrome metabólica estão também presentes como hipertensão, obesidade, acantose nigricans, aumento de adiposidade central e da circunferência abdominal. Foi demonstrado também, nesse trabalho, que a HGL esteve associada com resultado perinatal adverso [7,8]. É importante salientar que as placentas das gestantes com HGL mostram elevada incidência de endarterite, lesão considerada *post-mortem* com aparecimento de feto vivo, justificando talvez a mortalidade perinatal elevada [17]; aumento da apoptose e diminuição do Bcl-2 [18] e vilosidades pequenas com

aumento da vascularização [19].

Mulheres com HGL apresentam a mesma incidência de desenvolvimento de DM2 2 a 12 anos após a gravidez, indicando sua similaridade em relação às portadoras de DMG [20]. Esses resultados evidenciam que o PG na gestação identifica um grupo de alto risco materno e perinatal com alterações metabólicas independentes do TTG justificando sua inclusão nas investigações relacionadas ao DMG [2, 21]. Sendo assim essas duas entidades clínicas (DMG e hiperglicemia gestacional leve) devem ser investigadas em conjunto durante a gestação e alguns anos após o término da mesma, pois existem dúvidas se são duas entidades clínicas diferentes ou apenas níveis distintos de uma mesma doença.

Dados na literatura demonstram que crianças nascidas de mães com DMG têm risco aumentado para o desenvolvimento de obesidade na vida adulta. Estudos recentes demonstram que eventos intrauterinos podem interferir na expressão de certos genes e, assim, alterar sua atividade [22].

Essa alteração no meio intrauterino pode ser a razão do aumento alarmante da obesidade e do diabete tipo 2 na infância que o mundo hoje está observando. Segundo a Organização Mundial da Saúde (2012), o sobrepeso e a obesidade são o 5° maior fator risco para a morte no mundo além de agravar o diabete, doenças cardiovasculares e alguns tipos de câncer. Esse índice só tende a

aumentar devido à “programação fetal”, tornando então de extrema importância que essas crianças sejam acompanhadas [23].

Neste contexto esta tese se insere com a hipótese da importância do sobrepeso pré-gestacional na influência do desenvolvimento do DMG e o estado da diabesidade em um efeito a longo prazo para o desenvolvimento do DM2, além deste estado materno influenciar no futuro desenvolvimento de obesidade infantil e perfil metabólico alterado em seus filhos. O objetivo geral foi investigar a repercussão biométrica e metabólica destas entidades clínicas nas mães e nos conceptos 5 a 11 anos após o parto e avaliar se a janela de oportunidades para doenças que ocorre na gestação está relacionada com doenças metabólicas nestas crianças**.**

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Seção 3

Artigo Científico 1

Seção redigida como Artigo Original de acordo com as normas de publicação da revista **Diabetes Research and Clinical Practice** para a qual foi submetida.
Qualis A2 para Medicina 3 - FI: 3,63

Type 2 *Diabetes mellitus* development in mother-infant pairs of Brazilian GDM women: a 5-11 years follow-up descriptive study derives from a prospective cohort.

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ABSTRACT

Aims: To compare both the long-term risk to develop type 2 *Diabetes mellitus* (type 2DM) as well as metabolic abnormalities among mother-infant pairs of low income Brazilian Gestational *Diabetes mellitus* (GDM) and non-GDM mother5-11 years after delivery.

Methods:110 mother-infant pairs of GDM women in a descriptive study from a prospective cohort followed at Perinatal Diabetes Research Center-PDRC-UNESP from 2004-2011, were included. All pregnant women who performed a screening/diagnosis for GDM with tight glycemic control during pregnancy at PDRC, were contacted and invited to return for the long-term follow-up study with their children.

Results: The incidence rate of Type 2DM was 69.6% for women with GDM and 22% for their counterparts, without GDM at follow-up ($p < 0.0001$). Previous GDM was a significant predictor of type 2DM for mother [2.56 (95% C.I. 1.73- 3.79)]. At 5-6 years the offspring of GDM mothers exhibit high BMI, high waist and hip circumferences associated with high fasting glucose and HbA1c.

Conclusion: GDM exposure was strongly associated with high risk for adverse long-term mother-infant pairs outcome, with strong risk for type 2DM, obesity and metabolical abnormalities5-11years after delivery. These findings suggest that GDM exposure increased the

risk for obesity and Type 2DM later in life in both mother-infant pairs .

Keywords: Gestational *Diabetes mellitus*, type 2 *Diabetes mellitus*, offspring.

1. Introduction

The prenatal care is typically focused on the current pregnancy, even with the recommendations from Williams Obstetrics, a book with the thoroughness of scientific basis for practical application of obstetrical art. There is a clear advice that “prenatal care was not an end in itself but a systematic *gateway* to coordinate intrapartum and postpartum care and often even beyond into woman’s later life” that has to be followed by all the maternal health team [1].

Barker et al and several other investigators firmly established that some complications during pregnancy increase the risk for chronic disease later in life [2-5]. Complications during pregnancy are predicted by first-trimester algorithms, amplify a pre-existing maternal phenotype and accelerate risks for chronic diseases in the offspring up to adulthood (Barker hypothesis). Recent evidence suggests that *vice versa*, pregnancy diseases also indicate maternal and even grandparent’s risks for chronic diseases (reverse Barker hypothesis) [6,7].

Pregnancy itself seems to represent an underutilized opportunity for mother-infant pairs for the prevention of some relevant diseases of XXI century as Type2 DM epidemy [6].

Gestational *Diabetes mellitus* (GDM) a transitory disorder of glucose and insulin metabolism, first diagnosed during pregnancy [8] complicates between <1% and 28% of all pregnancies with short and

long-term consequences for both mother and offspring [9,10]. It is well established that GDM women are at increased risk of adverse pregnancy outcomes [11,12], as well as, several fold higher risk of type 2 *Diabetes mellitus* (type 2DM) and other metabolic syndrome developing later in life compared to non-GDM women [12-14]. The DM onset rate in women with GDM is approximately 7 times higher than in those without GDM [15].

Offspring of GDM mothers have an increased lifetime risk of metabolic disease and obesity, with a two-fold greater risk of being overweight or obese compared to unexposed counterparts [16,17]. The mechanism by which GDM exposure impacts increased risk of obesity in offspring remains unclear. Fetal programming of later adiposity amongst offspring exposed to diabetes was demonstrated in EPOCH study. GDM exposure was associated with a higher body mass index (BMI), greater waist circumference, more visceral and subcutaneous adipose tissue and centralized fat distribution pattern 6-13-year multiethnic youth [18,19].

The Developmental Origins of Health and Disease (DOHaD) concept states that environmental factors acting in early life have independent and profound effects on vulnerability to disease development later in life [20]. The DOHaD theory proposes that during specific developmental periods (e.g. conception, gestation, and the first few years of life), tissues and organs are particularly sensitive to

environmental exposures that condition or program the organism for disease susceptibility later in life [21-23]. The biological mechanisms by which fetal and early life exposures influence physiology and lifelong health are complex and remain under intense investigation.

A lack of a well-organized follow-up study of the mother-infant pairs of previous GDM in low- and middle-income countries were found [9] and need to be analyzed within the DOHaD theory. In this current study, we tested the hypothesis that previous GDM increased the risk of type 2DM and metabolical abnormalities in mother-infant pairs. The aim of this study was to compare both the long-term risk to develop type 2DM as well as the metabolic abnormalities among mother-infant pairs of low income Brazilian GDM and non-GDM mother 5-11 years after delivery.

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2. Subjects, materials and methods

This descriptive study derives from a prospective cohort of pregnant women that were followed at Perinatal Diabetes Research Center (PDRC)- FMB-UNESP; Brazil (mothers-infant pairs) as 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 Type 2DM)* with financial support from CNPq/Brazil Healt*h* Ministery (MCT/CNPq/CT-Saúde/MS/Decit nº 42/2010). 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 (mothers- newborn pairs). 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 their GDM diagnosis between 24-28 weeks of gestation and treated during pregnancy at PDRC (n=534)

The protocol has been approved by the Institutional Review Board (IRB) of Botucatu Medical School- UNESP. Informed consent was obtained from all selected participants for their participation, and in case of children both parents gave signed consent. This study has

adhered to the STROBE guidelines for observational studies.

2.1 Ascertainment and treatment of GDM

The maternal diagnostic protocol for GDM included the 100g oral glucose tolerance test (100g-OGTT) and glycemic profile (GP) [24,25]. All mothers who performed a 100g-OGTT and GP at 24 and 28 gestation weeks, to confirm or not the diagnosis GDM between 2004 and 2011 were used as long-term follow-up group. A total of 322 women previously non-diabetic women were diagnosed in GDM group if two plasma glucose values exceed the following limits >95 mg/dl (fasting) before an oral glucose tolerance test, >180 mg/dl after 60 min, >155 mg/dl after 120 min, and >140 mg/dl after 3h and 212 pregnant women with normal glucose tolerance (normal 100g-OGTT and GP) served as non-GDM group. Women with mild gestational hyperglycemia (MGH), normal OGTT and abnormal GP, were placed in GDM group.

Pregnant women diagnosed with GDM received glucose-lowering treatment consisting firstly of diet and exercise, and antepartum insulin therapy if necessary. Glycemic control and management of diabetes were evaluated by 24h GP (fasting, pre and post-prandial glycemic levels) at 2-week intervals until week 32, and weekly until delivery. The glycemic means obtained in the GP during pregnancy, was used to classify the quality of maternal glycemic control in adequate (GM <120 mg/dL) or inadequate (GM ≥120 mg/dL).

Data at delivery were obtained from labor and delivery database at our center and included total lenght of gestation, infant birth weight, macrosomia, 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 were calculated [26]. The placentas were weighed immediately after childbirth.

These mother-infant pairs followed at PDRC at 6 weeks after delivery were contacted and invited to participate on this long-term follow-up study (2016). Only mother-infant pairs were included in this study. For different reasons, a substantial number of mother-infant pairs did not accept the invitation to return for follow-up 5-11 years postpartum. Records were not kept for pairs who refused participation on follow-up.

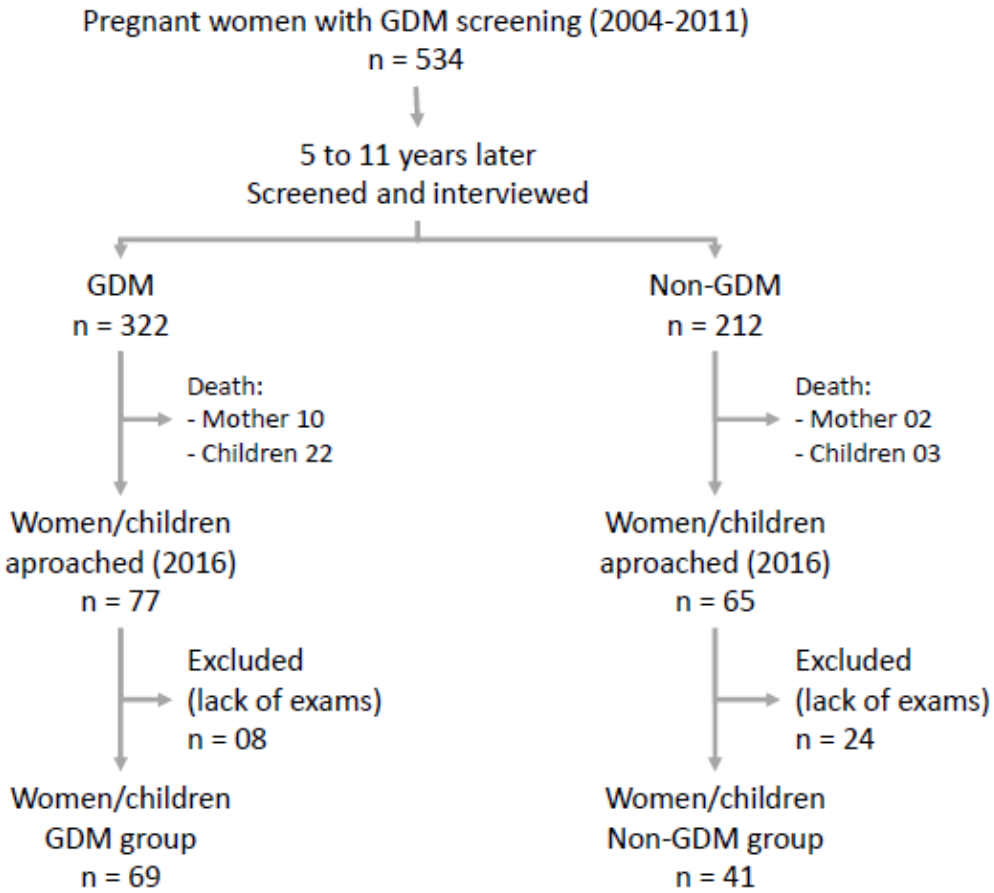

Figure. 1 Flow chart of participants and follow-up.

Exclusion criteria for pregnant women were known pre-gestational type 1 or type 2DM, or uncomplete GDM diagnosis during the index pregnancy.

2.2 Data source and participants follow-up

All women who performed a screening, diagnosis and treatment for GDM during pregnancy at PDRC were invited for this follow-up study 5-11 years after delivery with their offspring. One hundred and

forty two mother-infant pairs initially eligible returned for the 5-11 years follow-up visit and 32 were excluded because of missing values (fasting glycemia, glycosylated hemoglobin (HbA1c), insulin, total cholesterol, hight density lipoprotein cholesterol (HDL), triglycerides and 2h OGTT (75g of glucose). A descriptive study with 110 mothers-infant pairs were conducted according to the established groups at pregnancy: GDM and non-GDM (FIGURE 1).

A specific proforma for data collection, including patients' identification details, socio-economic status, demographic characteristics, obstetric history, delivery and birth outcomes, perinatal and postnatal complications, neonatal morbidity, maternal postpartum follow-up and the follow-up data of offspring, has been developed .Obstetric history including pre-pregnancy weight, height, weight at the GDM diagnosis (24-28 weeks), pregnancy weight gain, maternal and perinatal outcomes and 6 weeks postpartum data were retrieved from medical records.

2.3 Clinical and metabolic measurements

At 5-11years the mother-infant anthropometric measurements and sampling of blood specimen were collected according to the study protocol.

Anthropometric measurements were taken for mothers-infant pairs. Height was measured without shoes. 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. The participant´s weight were measured, and all outer clothing and shoes were removed. Maternal pre-pregnancy BMI were calculated dividing weight in kilograms by the square of height in metres. Overweight was defined as a pre-pregnancy BMI ≥25 kg/m². Offspring BMI were standardized for age and gender by conversion to a *z score*. This standardization was required because children were measured at different ages and BMI varies with age. To standardize BMI, *z score* was used, caused either by the normally distribution or the clearly convey magnitude of BMI difference between any two measurements at the extremes of the BMI distribution [27].

Blood fasting samples were collected to evaluate the metabolic abnormalities including fasting glycemia, HbA1c, serum lipid concentration (total cholesterol, HDL, triglycerides, and insulin. HDL and triglycerides were measured by enzymatic colorimetric assay. HbA1c was determined by high performance liquid chromatography (HPLC) and insulin using a especific radioimmunoassay kit. For glucose tolerance 5-11 years after pregnancy, a 2h OGTT (75g of glucose) was performed with sample collection at 0 and 120 minutes for plasma glucose determination.

The insulin resistance (HOMA-IR)was calculated to determine the degree of insulin resistance, according to the following equation,

proposed by Mattews *et al*. [28].

$$\text{HOMA-IR} = \frac{\text{glycaemia (mMol/x insulin (U/mL)}}{22.5}$$

Values higher than 2.71 are considered as insulin resistance.

2.4 Data analysis (Statistical analysis)

Data obtained in the medical visits were regularly exported to Microsoft Excel spreadsheets. Descriptive statistics such as percentages and means with standard deviation (SD) were used to describe the baseline characteristics of the study population. The quantitative data were presented in mean and standard deviation and the categorized ones in frequency and percentage. Chi-square and ANOVA tests followed by Tukey's multiple comparison tests in case of normal distribution or symmetry were used to compare the differences in baseline pre-pregnancy, pregnancy, 6 weeks after delivery and 5-11 years postpartum for mother-infant considering four groups. For those who presented asymmetric distribution, the comparison between means was made using a generalized linear model fit with gamma distribution followed by the Wald multiple comparison test.

Relative risk with 95% confidence interval (CI) was used to estimate the risk for development of GDM and obesity, insulin

resistance and dyslipidemia over 5-11 years of follow-up. Considering *Diabetes mellitus*, insulin resistance and overweight as response variables at the present moment, a logistic regression model was obtained in function of previous variables with the attainment of the possible risk factors calculated by the odds ratio.

All statistical analyses were conducted using SAS for Windows, v.9.3 and program R, v.3.3.3. In all models, p value <0.05 was considered statistically significant and all were two sided.

3. Results

Table 1 describes the mother characteristics according to GDM status. At the index pregnancy, GDM patients had higher BMI either at pre-pregnancy (p <0.050) or 6 weeks postpartum (p <0.006) compared to non-GDM.

Table 1. Characteristics of mother by GDM status at pre-pregnancy, during pregnancy, at delivery, 6 weeks postpartum and 5-11 years postpartum.

	non-GDM (*n*= 41)	GDM (*n*=69)	*p*
Baseline			
Maternal pre-pregnancy characteristcs (2004-2011)			
maternal BMI (kg/m²)	25.7 ±6.2	27.8 ±6.8	**0.050**
hypertension (%)	9.75% (4)	18.6% (14)	0.239
Maternal pregnancy characteristcs (2004-2011)			
glycemic mean <120mg/dL (%)			
hypertension (%)	24.4% (10)	34.6% (26)	0.220
weight gain in pregnancy (kg)	13.1 ±6.1	11.5 ±7.6	0.279
Maternal characteristcs 6 weeks postpartum			
BMI (kg/m²)	24.2 ±3.4	28.9 ±5.9	**0.006**
Follow-up			
Maternal characteristcs 5-11 years postpartum (2016)			
age (years)	37.5 ±6.4	40.8 ±6.3	**0.0007**
BMI (kg/m²)	29.6 ±7.5	30.1 ±6.7	0.727
weight gain in current days (kg)	-1.8 ±8.1	-4.3 ±15.0	0.347
waist circumference (cm)	96.8 ±16.6	99.3 ±15.8	0.447
hip circumference (cm)	107.7 ±15.4	111.9 ±13.9	0.154
waist/hip index (cm)	0.9 ±0.1	0.9 ±0.1	0.394
physical activity (%)	39% (16)	40.58% (28)	1.00
hypertension (%)	17% (7)	26.08% (18)	0.392
fasting glucose (mg/dL)	88.2 ±8.4	155.6 ±92.3	**<0.0001**
HbA1c (%)	5.4 ±0.4	7.1 ±2.6	**<0.0001**
insulin (µUI/mL)	10.2 ±7.2	10.8 ±11.8	0.713
fasting glucose at OGTT (mg/dL)	89.7 ±8.6	101.7 ±24.1	**0.0002**
2 hours postload at OGTT (mg/dL)	102.6 ±30.7	129.4 ±51.2	**0.0007**
total cholesterol (mg/dL)	197.6 ±38.4	201.4 ±34.2	0.581
LDL (mg/dL)	121.7 ±32.6	122.8 ±25.8	0.844
HDL (mg/dL)	51.7 ±10.6	49.6 ±12.2	0.368
triglyceride (mg/dL)	119.6 ±60.3	152.1 ±92.9	**0.046**
red blood cells (million/mm³)	4.5 ±0.3	4.6 ±0.4	0.216

hemoglobin (g/dL)	13.2 ±0.8	12.8 ±1.2	0.080
hematocrit (%)	40.0 ±2.5	39.0 ±3.1	0.102
white blood cells (/mm³)	6501 ±1447	7902 ±7733	0.265

Data are mean ± SD or % (number).
Chi-square or ANOVA. Statistically significant *p* value < 0.050.
Gestational *Diabetes mellitus* (GDM), body mass index (BMI), glycosylated hemoglobin (HbA1c), oral glucose tolerance test (OGTT), hight density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), large gestational age (LGA).

Table 2 describes the infant characteristics according to maternal GDM status. At delivery,the newborn gestational age (*p* = 0.0004) and lenght (*p* = 0.031) were lower in GDM mothers and the ponderal index mean (*p* = 0.018) was higher in GDM group. GDM infant had higher BMI (*p* = 0.014), higher waist and hip circumferences, higher fasting glucose and HbA1c levels (*p* <0.050) compared to non-GDM infants5-11 years after . Other metabolic factors, including insulin, total cholesterol, LDL, HDL, triglyceride, red blood cells, hemoglobin, hematocrit and white blood cells, did not differ significantly between groups.

Table 2. Characteristics of infant by maternal GDM status.

INFANT	**non-GDM (*n*= 41)**	**GDM (*n*=69)**	***p***
At delivery			
Newborn characteristcs (2004-2011)			
gestation (days)	270.2 ±10.8	262.7 ±10.2	**0.0004**
weight (g)	3264.0 ±482.2	3230.9 ±517.8	0.731
length (cm)	48.7 ±2.2	47.8 ±2.3	**0.031**
ponderal index ($cm.kg^{-1/3}$)	2.78 ±0.24	2.92 ±0.31	**0.018**
male sex (%)	51.2% (21)	56% (42)	0.967
caucasian (%)	85.3% (35)	69.3% (52)	0.314

LGA (%)	12.2% (5)	21.7% (15)	0.317
macrosomic (%)	2.44% (1)	7.2% (5)	0.522
premature (%)	9.75% (4)	21.7% (15)	0.178
placental weight (g)	621.5 ±137.9	634.1 ±170.7	0.680
Follow-up			
Offspring characteristcs at age 5-11 years			
physical activity (%)	53.65% (22)	56% (42)	0.588
BMI (kg/m²)			
5-6 years	15.9 ±1.8	19.1 ±5.7	**0.014**
7-11 years	20.1 ±4.3	19.2 ±4.4	0.468
classification *z* score BMI (kg/m²)			
eutrophic	43.9% (18)	46.6% (31)	1,000
overweight	56.1% (23)	56.3% (38)	1,000
waist circumference (cm)			
5-6 years	54.1 ±4.0	63.2 ±13.0	**0.003**
7-11 years	67.9 ±11.9	65.3 ±11.8	0.464
hip circumference (cm)			
5-6 years	58.0 ±6.2	64.9 ±13.3	**0.046**
7-11 years	71.1 ±10.7	69.3 ±12.2	0.609
neck circumference (cm)			
5-6 years	26.24 ±1.61	26.97 ±2.99	0.382
7-11 years	28.83 ±4.19	27.81 ±2.76	0.350
fasting glucose (mg/dL)	87.6 ±7.4	90.4 ±6.5	**0.035**
HbA1c (%)	5.28 ±1.1	5.32 ±0.7	**0.012**
insulin (µUI/mL)	7.2 ±5.8	8.0 ±6.7	0.457
total cholesterol (mg/dL)	168.8 ±25.8	168.6 ±29.2	0.972
LDL (mg/dL)	99.7 ±23.5	101.4 ±24.0	0.717
HDL (mg/dL)	50.0 ±10.0	50.2 ±11.5	0.934
triglyceride (mg/dL)	88.4 ±43.4	83.9 ±45.6	0.539
red blood cells (million/mm³)	4.9 ±0.3	5.0 ±0.4	0.347
hemoglobin (g/dL)	13.5 ±0.8	13.2 ±0.8	0.144
hematocrit (%)	39.5 ±4.0	39.2 ±1.9	0.611
white blood cells (/mm³)	7552 ±2342	7213 ±2131	0.440

Data are mean ± SD or % (number).

Chi-square or ANOVA. Statistically significant *p* value < 0.050.

Gestational *Diabetes mellitus* (GDM), body mass index (BMI), glycosylated hemoglobin (HbA1c), hight density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), large gestational age (LGA).

On logistic regression analysis (Table 3), previous GDM 5-11 years before was significant predictor of type 2DM isolated [2.56 (95% C.I. 1.73- 3.79)] or associated to overweight [4.51 (95% C.I. 2.43- 8.34)], to dyslipidemia [4.06 (95% C.I. 1.81- 9.07)], to insulin resistance [5.46 (95% C.I. 2.56- 11.66)], to overweight + dyslipidemia [4.06 (95% C.I. 1.81- 9.07)] and to overweight + insulin resistance [4.94 (95% C.I. 2.33- 10.48)]. At the 5-11 years follow-up after index pregnancy 30.4% of GDM and 78% non-GDM, were normoglycemic (p <0.0001). Unlike, type 2DM was detected in 69.6% of previous GDM patients and in 22% of non-GDM women 5-11 years postpartum (p <0.0001). Type 2DM plus overweight as well as type 2DM plus overweight plus insulin resistance 5-11 years after index pregnancy were higher in women with previous GDM (p <0.0001). Surprisingly, maternal GDM environmental was not predictor of offspring characteristcs at age 5-11 years, including classification *z score* BMI, insulin resistance, dyslipidemia, overweight plus insulin resistance positive and overweight plus dyslipidemia.

Table 3. Relative risk (RR) of type 2DM by maternal GDM status 5-11 years after index pregnancy

	non-GDM	GDM (69)	*p*	RR (95% CI)
Follow-up				
Normoglycemic	78% (32)	30.4% (21)	**<0.0001**	1
Type 2 DM	22% (9)	69.6% (48)	**<0.0001**	**2.56 (1.73- 3.79)**
Type 2 DM + overweight	22% (9)	62.3% (43)	**<0.0001**	**4.51 (2.43- 8.34)**
Type 2 DM + dyslipidemia	12.2% (5)	30.4% (21)	**0.05**	**4.06 (1.81- 9.07)**

Type 2 DM + insulin resistance	14.6% (6)	52.2% (36)	**0.05**	**5.46 (2.56- 11.66)**
Type 2 DM + overweight + dyslipidemia	12.2% (5)	30.4% (21)	**0.05**	**4.06 (1.81- 9.07)**
Type 2 DM + overweight + insulin resistance	14.6% (6)	46.4% (32)	**0.001**	**4.94 (2.33- 10.48)**
INFANT	**non-GDM**	**GDM (69)**	***p***	**RR (95% CI)**
At delivery				
LGA (%)	12.2% (5)	21.7% (15)	0.209	1.25 (0.92- 1.69)
macrosomic (%)	2.4% (1)	7.2% (5)	0.283	1.35 (0.92- 2.00)
premature (%)	9.8% (4)	21.7% (15)	0.108	1.33 (1.00- 1.77)
Infant characteristics at age 5-11 years				
classification *z* score BMI (kg/m²)				
eutrophic	43.9% (18)	44.9% (31)	0.917	1.02 (0.76- 1.36)
overweight	56.1% (23)	55.1% (38)	0.917	0.98 (0.74- 1.31)
Insulin resistance	7.3% (3)	8.7% (6)	0.799	1.07 (0.66- 1.74)
Dyslipidemia	41.4% (17)	39.1% (27)	0.809	0.96 (0.72- 1.30)
physical activity (%)	53.6% (22)	55.1% (38)	0.885	1.02 (0.76- 1.37)
Overweight + insulin resistance	4.9% (2)	5.8% (4)	0.837	1.07 (0.59- 1.91)
Overweight + dyslipidemia	19.5% (8)	29% (20)	0.27	1.20 (0.89- 1.60)

Data are % (number) and RR (95% C.I.).

Logistic regression model. Statistically significant *p* value < 0.050.

Gestational *Diabetes mellitus* (GDM), type 2 *Diabetes mellitus* (type 2DM), large gestational age (LGA), body mass index (BMI).

4. Discussion

Our mothers-infant pairs long-term follow-up study showed that the onset of GDM during pregnancy was a significant risk factor for mother future development of type 2DM alone or combined with insulin resistance, overweight, dyslipidemia, overweight plus dyslipidemia and overweight plus insulin resistance. All these metabolic frameworks are steps envolved in the progression from GDM to type 2DM. Our results explicit that GDM, considered a transient unmasking of an underlying predisposition to type 2DM, due to the failure of beta-cells to compensate the insulin-resistance in late pregnancy [29-31], may be considered as a timely stage to predict type 2DM and confirm other reports [32-34].The literature has been showed that women with previous GDM are at significant risk to develop type 2DM [34]; however, the follow-up tests after delivery have been suboptimal [35,36], notwithstanding the current proposal including early postpartum diabetic screening at 6–12 weeks postpartum and further follow-up tests [37-39].

In the light of the findings discussed above, it is clear that GDM has a heavy impact on the mother-infant pairs, confirming the DOHaD theory that means the aphorism ‘‘diabetes begets diabetes”.

High levels of FPG and HbA1c testing detected in our GDM patients are in accordance with recent scientific publication suggesting

the use of both tests as a worthwhile step in the process of enrolling participants in a diabetes prevention program [40].

Patients with previous GDM are more likely to be insulin resistant 5-11 years after delivery than non-GDM. The impaired insulin secretion during pregnancy seems to be the key defect leading to the deterioration of hyperglycemia after GDM [33].

GDM exposure *in utero* associated with strict glycemic control was significantly associated with lower gestational age, higher newborn length and ponderal index. The classical findings of perinatal adverse outcome for GDM perinatal outcome as LGA, macrosomia and premature even being two to three times higher, no statistical difference was detected. The abnormal metabolic environment in GDM mother with strict glycemic control decrease the neonatal commitment, but the long-term infant metabolical abnormalities was met e.g. fasting glycemia, HbA1c, waist and hip circumference associated with high fasting glucose and HbA1c. These clinical and laboratory findings could be the first signals for type 2DM and obesity origin and may represent the widespread biological phenomena-developmental plasticity and compensatory growth described by Barker by inducing changes leading to the development of type 2DM in adulthood. Surprisingly, GDM environmental was not predictor of other infant characteristics at age 5-11 years, as *z score* BMI classification, insulin resistance, dyslipidemia, overweight plus insulin resistance positive

and overweight plus dyslipidemia. The results showing strongly association with greater adverse long-term repercussions for mother-infant pairs, that reflect the same GDM maternal environment on intrauterine compartment are noteworthy.

In addition, normal glycemic status during pregnancy represents a recognized healthy certificate in terms of Non-Communicable Disease (NCD) either for mother or infants. Our results confirm that pregnancy provides an effective opportunity to profile maternal risks and represent a vulnerable, but potentially modifiable period from prenatal life to adulthood [41]. The obstetrician caring for a GDM woman should be knowledgeable about the maternal and fetal risks during pregnancy as well as its long-term impact [42]. More recently, a thrifty ‘phenotype hypothesis’ of the aetiology of type 2DM suggested that these early changes powerfully determine susceptibility, additional factors such as obesity, ageing, physical inactivity, and possibly other processes leading to insulin resistance must also play a role in deciding the time of onset and severity of type 2DM [43]. Thus, our results confirm recent publications that GDM gives rise to a vicious cycle in which mothers with GDM have babies with epigenetic changes who are prone to develop metabolic disease later in life, which will give rise to a new generation of mothers with GDM. This trend of passing a disease from one generation to another through epigenetic changes, known as transgenerational transmission, is now widely accepted that

an adverse preconception and intrauterine environment is associated with epigenetic malprogramming of the fetal metabolism and predisposition to chronic, and in particular, metabolic disorders later in life [44,45].

GDM diagnosis (and tight glycemic control during pregnancy) were associated with high risk of later development of type 2DM confirming the reverse Barker hypothesis. Previous studies demonstrated that guidelines to improve GDM diagnosis represent an important key strategy and timely recognition to be developed and implemented in health system to prevent type 2DM. In Brazil, one of the top 10 countries/territories of number of people with diabetes [46] with high prevalence of DM by 2035, it is imperative that GDM diagnosis be followed by preventive postpartum care in the routine setting in order to decrease the global diabetic epidemy and the prevalence of NCD [47].

To the best of our knowledge, among many follow-up studies of GDM patients, this is the first follow-up study in mother-infant pairs of Brazilian women with a history of GDM, regarding the development of type2 DM at 5-11 years postpartum. Follow-up studies are complicated in a continental country as Brazil with a significant internal migration, associated with a complex mix of private and government health care providers, with patients moving easily from one to another health system, as well as the lack of interest from patient side. It is very

common the commitment and motivation of women for treatment to protect their health and thereby the health of the unborn baby, however behavior changes and compliance to treatment are associated with challenges with an identified number of barriers for long-term follow-up [9]. The most common excuse was that women with a history of GDM reported time pressure, lost requisition, dissatisfaction with health care services, logistics of accessing care, believing not to be in need of care, fear of receiving bad news, emotional stress, feeling overwhelmed, burden of child care, baby's health issues and recent delivery experiences as barriers for attending postpartum diabetes testing [48,49]. In our perspective this lack of motivation might be explained due to lack of knowledge about GDM impact on maternal as well as newborn health and future repercussions throughout the life.

The major strength of this study was a long-term follow-up, from early pregnancy until 5-11 years postpartum in Brazil. This has only been achieved due to the PDRC which has been created 21 years ago for research on GDM, sponsored by Fapesp (Sao Paulo State Foundation-Brazil) with relevant data which contributes to research on this area.

A new study protocol similar to our paper, to be developed in India one of the Top 10 countries/territories of number of people with diabetes as well as Brazil [46], was recently published. The authors considered that not only early diagnosis, proper management of GDM,

postpartum follow-up and preventive care is expected to reduce type 2 diabetes and metabolic abnormalities risk, but prospective studies needs to be done, particularly in undeveloped countries [47].

Our findings should be interpreted cautiously, as there are several limitations, as follows: 1-the diagnostic criteria of GDM vary worldwide [50,51]. Our results are based on two steps approach with 100g OGTT plus GP. For this study, GDM plus mild hyperglycemia was classified as GDM which may difficult to compare with other findings, although nowadays all hyperglycemic diagnostic during pregnancy is considered as GDM. 2- the study comprised a small number of patients; 3- high rate of lost to follow-up OGTT; 4- it was performed in a single center and in low income mothers, so we cannot be sure about its relevance in other parts of the world; postpartum dietary intake and physical activity during or after pregnancy were not estimate. These limitations could be overcome by a larger-scale prospective study in the future. Despite these limitations, we believe our findings offer an important contribution on this matter.

Women with GDM and their offspring are at increased risk of future type 2 diabetes and metabolic abnormalities confirming that the decreased of maternal functional pancreatic reserve during pregnancy is the underground basis for the long-term development of type 2DM. For offspring, the exposure to maternal GDM environmental *in utero* even though with tight glycemic control during pregnancy alter the

long-term offspring metabolic abnormalities with consequences that may be considered as risk factor for type 2DM and obesity development. Together, these findings suggest that the effect of GDM exposure in utero is strongly associated with greater risk for both maternal and offspring adverse long-term impact, increasing the risk of obesity and type2 DM later in life both in mother and offspring. Clinicians should be aware of the importance of these results in order to emphasize the importance of lifestyle changes after GDM not only for the mother but also for her offspring.

In the light of the findings discussed above, the current long-term maternal and perinatal outcomes in previous GDM women with strict glycemic control during pregnancy, reveal two metabolic windows for mother-infant pairs of GDM. For the mother, the GDM diagnosis and glycemic control during pregnancy were associated with increased risk of later development of type 2DM confirming that the decreased of maternal functional pancreatic reserve during pregnancy is responsible for the long-term development of type 2DM. For offspring the exposure to maternal GDM environmental *in utero* even though with tight glycemic control during pregnancy alter the long-term offspring metabolic abnormalities with consequences that may considered as first step to the development of type 2DM and obesity. Together, these findings suggest that the effect of GDM exposure in utero is strongly associated with greater risk for both maternal and

offspring adverse long-term impact, increasing the risk of obesity and type2 DM later in life both in mother and offspring. Clinicians should be aware of the importance of these results in order to emphasize the importance of lifestyle changes after GDM not only for the mother but also for her offspring.

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Conflict of interest

None declared.

Author contribution

MAA and AMPB conducted data extraction, analyzed the data and co-drafted the manuscript. RAAC, JFA, GB and CAN provided study data and together with DCD contributed to interpretation of the data. LPC, BFNC, assisted with screening of data. MVCR and IMPC conceived the design of the study, co-drafted the final manuscript and are the guarantor of this work. All authors contributed to the critical revision of the manuscript.

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Seção 4

Artigo Científico 2

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The impact of "diabesity" (pre-pregnancy obesity with gestational diabetes) 5-11 years postpartum in pairs of mother and offspring outcomes in Brazil: descriptive study derives from a prospective cohort

The impact of "diabesity" in pairs of mother and offspring

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ABSTRACT

Objective: To investigate the conjoint effect of pre-pregnancy obesity with GDM "diabesity" on adverse long-term follow up of pairs of mother and offspring outcome in low income population in Brazil.

Design: descriptive study derives from a prospective cohort

Setting: Brazil, 2004- 2016.

Population: The study included 534 previously nondiabetic women screened between 2004-2011. 322 women were diagnosed in GDM group and 212 pregnant women with normal glucose tolerance. Based on prepregnancy weight, pregnant women were classified to BMI as lean (BMI between 18.5- 24.9kg/m^2) or overweight (BMI ≥ 25.0 kg/m^2). All women who performed a screening for GDM during pregnancy were invited to return for the follow-up study 5-11 years after delivery with their offspring.

Main outcomes: adverse long-term effect on previous “diabesity” women and her offspring outcomes.

Results: “Diabesity" were significantly risk factor for type 2DM development [6.00 (95% C.I. 2.42- 14.84)], overweight [2.37 (95% C.I. 1.56- 3.61)], insulin-resistance [3.14 (95% C.I. 1.79- 5.49)], and dyslipidemia [5.47 (95% C.I. 2.17- 13.76)]. Maternal "diabesity" environmental was not predictor of offspring characteristics neither at delivery nor at age 5-11 years.

Conclusion: “Diabesity” profile during pregnancy severely worsens the maternal and offspring long-term prognosis.

Keywords: Obesity, type 2 *Diabetes mellitus*, diabesity, gestational *Diabetes mellitus*, offspring obesity.

1. Introduction

This study was designed to investigate the conjoint effect of pre-pregnancy obesity with gestational *Diabetes mellitus* (GDM) ("diabesity") on adverse long-term follow up of pairs of mother and offspring outcome in low income population in Brazil.

The co-occurrence of GDM with obesity, nicknamed “diabesity”, is well known and the reciprocal effects of these two entities were recently reviewed. The "diabesity" epidemic is probably the major epidemic in human history and a huge problem for global health worldwide nowadays. In additionally, the reasons for this current high prevalence of "diabesity" is assigned to growth in the pathophysiological knowledge and clinical results supporting a link in the interaction between GDM and obesity [1].

Separatedely, GDM and maternal obesity has been accepted as responsible for adverse maternal and neonatal outcomes [2,3].

Examination of the combined association of these common metabolic problems with pregnancy outcomes is an important question [4].

The metabolic changes *in utero* may influence the physiological and structural patterns that “program” long-term health in adulthood [5,6]. Early studies by Barker *et al.* in the 1980s established that the prevalence of some diseases in adulthood, such as atherosclerosis, high blood pressure, stroke, type 2 *Diabetes mellitus* (type 2DM), and

dyslipidemia are related to intrauterine environment (“Barker hypothesis”) [7]. Actually, “diabesity” are strongly associated with altered fetal growth and development as well as with lifelong perturbations in metabolic tissues [8].

So, “diabesity“ during pregnancy could be a specific period either for the mother to detec her pancreatic reserve [9] or for the newborn to analyse the risk for the Developmental Origins of Health and adult Disease (DOHaD) [8]. The DOHaD concept puts pregnancy and its influences on the mother and on the developing fetus in the focus of the transgenerational transmission of “diabesity“ risk. This new concept may explain some aspects of fetal programming of childhood obesity in a close watch of maternal “diabesity“ [10].

It is well established that the physiologic adaptations during pregnancy reveals a woman’s predisposition to chronic diseases not only for her (reverse Barker hypothesis) but also for the offspring up to adulthood (Barker hypothesis). By the other side, the predictive role of pregnancy in asymptomatic hyperglycemic, mild hyperglycemia and GDM women that can be awaken temporarily during pregnancy or by the delivery of a macrosomic infant as well as that normoglycemic pregnant women are followed by lower rates of subsequent diseases than the general female population puts “pregnancy as a window for maternal and offspring future health” [4,11-14].

This long-term study tested the hypothesis that pre-existing

maternal overweight profile increase the risk for GDM and both for maternal long-term type 2DM, overweight and lipid abnormalities; this maternal environmental profile plays a role on risk of childhood growth patterns and altered metabolic profile, parameters involved in DOHaD in order to characterize that pre-pregnancy obesity plus GDM represents an underutilized opportunity to detect the maternal and infant long-term health.

2. Research design and methods

2.1 Data source and participants

Study design and subjects

The study population was obtained from an existing clinical pregnancy registry at the Perinatal Diabetes Research Center (PDRC), Botucatu University Hospital- Unesp-Brazil (mothers and newborn pairs). All women and newborn that completed the baseline survey were eligible for this study. Further, as inclusion criteria, these women needed to have had singleton pregnancy, underwent their GDM diagnosis between 24-28 weeks of gestation (n=534).

Ascertainment and treatment of GDM

All pregnant women with singleton pregnancy who had performed a 100g- oral glucose tolerance test (100g-OGTT) and glycemic profile (GP) at 24 and 28 gestation weeks, to confirm or not the diagnosis GDM between 2004 and 2011 were contacted by phone invitation for this long-term follow-up study of mother and offspring. These pairs of women and newbors that were followed at the PDRC at 6 weeks after delivery and postpartum were contacted and invited to participate in this long-term follow-up study (2016). Although, for different reasons, a substantial number of women and children did not accept the invitation to return to follow-up 5-11 years postpartum. For

the purpose of this study, we restricted our sample only to pairs of the mother and live-born children. Records were not kept for women who refused participation on follow-up. Exclusion criteria for pregnant women were known pre-gestational diabetes type 1 or type 2 diabetes, failed to report their prepregnancy weight or did not complete GDM diagnosis during the index pregnancy. At delivery, participants were excluded if birth data were missed.

The maternal diagnostic protocol for GDM included the 100-g OGTT, combined with the GP. The GDM diagnosis was based on the contemporary diagnosis: if two plasma glucose values exceed the following limits fasting >95 mg/dl, 1-hour >180 mg/dL ,2-hour >155 mg/dL and 3-hours >140 mg/dL. For mild gestational hyperglycemia the limits was fasting >90mg/dL and postprnadial >130 mg/ dL inthe glycemic profile [12]. All pregnant women with altered OGTT and or GP were considered as GDM [15]. A total of 534 previously nondiabetic women were screened between 2004-2011.

A total of 322 women previously nondiabetic women were diagnosed in GDM group and 212 pregnant women with normal glucose tolerance (normal 100g-OGTT and GP) as non-GDM group. Based on prepregnancy weight as self-reported during the first prenatal care visit, pregnant women were classified to BMI as lean (BMI between 18.5- 24.9kg/m^2 – n=272) [16] and overweight (BMI ≥25.0kg/m^2 – n=262). Data at delivery were obtained from labor and

delivery database at our Center and included total lenght of gestation, infant birth weight, macrosomia, sex, mode of delivery and Apgar scores. Based on these informations the ponderal index [(weight/lenght^3)*100], and classification according to weight/gestational age were calculated. The placentas were weighed immediately after childbirth.

Considering the pre-pregnancy weight classification and the hyperglycemia status during pregnancy, four groups of women were defined: lean+ non-GDM (n=137), lean+ GDM (n=135), overweight+ non-GDM (n=75) and overweight+ GDM (n=187). Pregnant women diagnosed with GDM received glucose-lowering treatment consisting firstly of diet and exercise, and antepartum insulin therapy if necessary. Glycemic control and management of diabetes were evaluated by 24h GP (fasting, pre and post-prandial glycemic levels) at 2-week intervals until week 32, and weekly until delivery. The glycemic means obtained in the GP, was used to classify the quality of maternal glycemic control in adequate (GM <120mg/dL) or inadequate (GM ≥120mg/dL). Pregnant women who were non-GDM, but overweight, received couseling about the importance of lifestyle changes to prevent GDM, and were promptly assigned to individualized nutritional guidance, walking for 30 min five times a week for weight control during pregnancy.

2.2 Data source and participants follow-up

All women who performed a screening for GDM during pregnancy were invited to return for the follow-up study 5-11 years after delivery with their offspring. Prior to the examination, subjects were briefed about the purpose of the study, methods to be adopted and written signed informed consent was obtained from parents or legal guardians, and child assent was also obtained as required by the local institute/ethical review boards before participation in the study. Data of all pregnancies were obtained with a proforma for data collection, including patients' identification details, socio-economic status, demographic characteristics, obstetric history, delivery and birth outcomes, perinatal and postnatal complications, neonatal morbidity, maternal and offspring long-term follow-up. To study the glucose tolerance after pregnancy, a 2-hour 75 g OGTT was performed in all women and plasma samples were obtained for all other metabolic assessments.

One hundred and forty-two mother-offspring pairs of mothers and newborn initially eligible returned for the 5-11 years follow-up visit and 32 were excluded from the analysis because of missing values for variables of interes (fasting glycemia, glycosylated hemoglobina (HbA1c), insulin, total cholesterol, high density lipoprotein cholesterol (HDL), triglycerides and 75g 2h OGTT).

A descriptive study derives from a prospective cohort with 110

mothers-offspring pairs were conducted considering the four established groups at pregnancy: lean+ non-GDM (n=26), lean+ GDM (n=30), overweight+ non-GDM (n= 15) and overweight+ GDM (n= 39). The study design i.e. the participant flow and data collection is depicted in Figure 1.

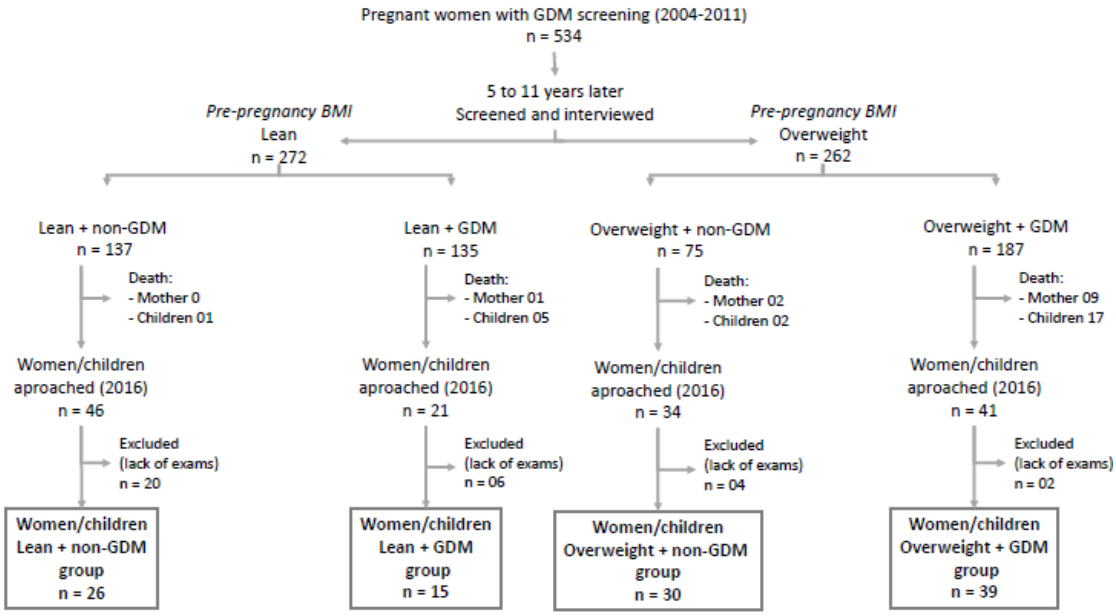

Fig. 1 Flow diagram of sample for the analysis of associations between prepregnancy overweight and GDM between 2004-2011 of pairs of mother and offspring 5-11 years after delivery.

2.2.1 Clinical registry

Obstetric history including pre-pregnancy weight, height, weight at the GDM diagnosis (24-28 weeks), pregnancy weight gain, maternal and perinatal outcomes and at 6 weeks postpartum data were retrieved from medical records. At 5-11years the mother and children anthropometric measurements and sampling of blood specimen were

collected according to the study protocol.

2.2.2 Clinical and metabolic measurements

Anthropometric measurements were taken for the mothers and their offspring. Height was measured without shoes. 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. The participant´s weight were measured, and all outer clothing and shoes were removed. Maternal pre-pregnancy BMI were calculated dividing weight in kilograms by the square of height in metres. Overweight was defined as a prepregnancy BMI ≥25.0kg/m^2. Offspring BMI were standardized for age and sex by conversion to a *z* score. This standardization was required because children were measured at different ages and BMI varies with age. To standardize BMI, *z* score was used, caused either by the normally distribution or the clearly convey magnitude of BMI difference between any two measurements at the extremes of the BMI distribution [17].

Blood fasting samples were collected for all the laboratory measurements to evaluate the metabolic assessment including fasting glycemia, HbA1c, serum lipid concentration (total cholesterol, HDL, triglycerides, and insulin was performed. HDL and triglycerides were measured by enzymatic colorimetric assay. HbA1c was determined by high performance liquid chromatography (HPLC) and insulin using a

especific radioimmunoassay kit. To study the glucose tolerance 5-11 years after pregnancy, a 2h 75g OGTT was performed in all women,with sample collection at 0 and 120 minutes for plasma glucose determination.

The HOMA-IR was calculated to determine the degree of insulin resistance, according to the following equation, proposed by Mattews *et al*. [18].

$$\text{HOMA-IR} = \frac{\text{glycaemia (mMol/L) x insulin (U/mL)}}{22.5}$$

Insulin resistance ≥ 2.71

2.4 Statistical analysis

Data obtained in the medical visits were regularly exported to Microsoft Excel spreadsheets. Descriptive statistics such as percentages and means with standard deviation (SD) were used to describe the baseline characteristics of the study population. The quantitative data were presented in mean and standard deviation and the categorized ones in frequency and percentage. Chi-square and ANOVA tests followed by Tukey's multiple comparison test in case of normal distribution or symmetry were used to compare the differences in baseline pre-pregnancy, pregnancy, 6 weeks after delivery and 5-11 years postpartum for mother to child considering four groups. For those who presented asymmetric distribution, the comparison between means was made using a generalized linear model fit with gamma

distribution followed by the Wald multiple comparison test.

Relative risk with 95% confidence interval (CI) was used to estimate the risk for development of type 2DM, obesity, insulin resistance and dyslipidemia over 5-11 years of follow-up. Considering type 2DM, insulin resistance and overweight as response variables at the present moment, a logistic regression model was obtained in function of previous variables with the attainment of the possible risk factors calculated by the odds ratio

All statistical analyses were conducted using SAS for Windows, v.9.3 and program R, v.3.3.3. In all models a p value <0.05 was considered statistically significant and all were two sided.

3. Results

A total of 534 women with GDM and newborn (based on an electronic code entry for GDM) were identified in the dataset of PRDC during the study period (2004-2011). From this, 322 new cases of GDM (60.3%) and 262 of overweight women classified during pregnancy (49.1%) were reported. In this GDM plus overweight longitudinal follow-up study at 5-11 years postpartum our sample of pairs of women and offspring showed similar proportion (62.7%) of GDM and (49.1%) of pre-pregnancy overweight women

Baseline characteristics of mothers and offspring pairs 5-11 years after index-pregnancy, according to pre-gestational BMI and GDM status ("diabesity") are presented in Table 1. Participants with "diabesity" in pregnancy (overweight+ GDM) had high pre-pregnancy BMI, high blood pressure levels at pre-pregnancy and during pregnancy and high BMI 6 weeks after delivery. At 5-11 years postpartum these "diabesity" women presented high BMI, high waist circumference, associated with altered fasting glucose at OGTT, higher 2 hours postload at OGTT, high levels of cholesterol and low levels of HDL. The newborn of "diabesity" mothers showed lower gestational age at delivery (p <0.050) and higher ponderal index mean (p <0.050). However, in the long-term follow-up study only at 5-6 years after delivery, the offsprings of "diabesity" mothers showed high waist

circumference without none significant altered anthropometric and metabolic parameters.

The clinical and metabolic parameters of overweight non-GDM mothers were very similar to "diabesity" women at pre-pregnancy and at 6 weeks postpartum. Although at 5-11 years postpartum, compared to "diabesity" women, the overweight non-GDM mothers were younger with higher levels of LDL cholesterol and normal glycemic levels at 2 hours postload OGTT (p <0.050). The newborn of non-GDM overweight mothers showed higher gestational age at delivery (p <0.050) compared to "diabesity" mothers.

By the other hand, the clinical parameters of lean+ GDM mothers were similar to control group (lean+ non-GDM) at pre-pregnancy, pregnancy and 6 weeks postpartum. However, compared to lean+ non-GDM group 5-11 years after delivery, the available results of metabolical parameters in lean GDM mothers reveal higher levels of 2h post load 75g OGTT and lower HDL cholesterol.

At 5-6 years the waist circumference is the unique offspring altered parameter either clinical or metabolical according to mothers groups with the highest value in the "diabesity" group. In the other two groups the offspring waist circumference showed intermediate values.

The lean+ non-GDM mother presented significant lower levels of quite all clinical and metabolical parameters, at pre-pregnancy, pregnancy, 6 weeks pospartum and 5-11 years postpartum except for

maternal age 5-11 years postpartum and higher HDL cholesterol levels. The newborn of lean+ non-GDM mother showed high gestational age at delivery with low ponderal index and the lowest waist circumference at 5-6 years.

Table 1. Baseline characteristics of women and offspring pairs 5-11 years postpartum according to pre-gestational BMI and GDM status

	Lean + non-GDM (*n*= 26)	Lean + GDM (*n*=30)	Overweight + non-GDM (*n*= 15)	Overweight + GDM (*n*=39)
Baseline				
Maternal pre-pregnancy characteristcs (2004-2011)				
maternal BMI (kg/m²)	21.9 ±2.3[a]	22.0 ±1.8[a]	33.3 ±6.1[b]	32.4 ±5.7[b]
hypertension (%)	3.85% (1)[a]	6.66% (2)[a]	20% (3)[b]	28.20% (11)[b]
Maternal pregnancy characteristcs (2004-2011)				
hypertension (%)	11.54% (3)[a]	20% (6)[a]	46.66% (7)[b]	46.15% (18)[b]
Maternal characteristcs 6 weeks postpartum				
BMI (kg/m²)	22.2 ±2.8[a]	23.3 ±1.8[a]	27.3 ±1.0[b]	31.7 ±5.2[b]
Follow-up				
Maternal characteristcs 5-11 years postpartum (2016)				
age (years)	40.1 ±7.5[a]	42.5 ±5.7[a]	36.4 ±5.8[b]	40.3 ±6.4[a]
BMI (kg/m²)	22.2 ±2.2[a]	22.6 ±1.9[a]	32.6 ±6.7[b]	32.3 ±5.9[b]
waist circumference (cm)	82.1 ±5.8[a]	81.1 ±6.0[a]	103.3 ±15.6[b]	104.13.9[b]
hip circumference (cm)	96.2 ±6.0[a]	98.7 ±5.9[a]	112.8 ±15.6[b]	115.2 ±13.4[b]
hypertension (%)	7.7% (2)[a]	10% (3)[a]	33.33% (5)[b]	33.33% (13)[b]
fasting glucose at OGTT (mg/dL)	86.5 ±6.4[a]	87.2 ±7.5[a]	91.0 ±9.1[b]	106.6 ±25.8[b]
2 hours postload at OGTT (mg/dL)	84.4 ±18.6[a]	111.2 ±18.0[b]	110.2 ±31.8[a]	135.5 ±57.3[b]
total cholesterol (mg/dL)	196.2 ±32.7[a]	194.2 ±26.3[a]	198.1 ±41.0[b]	203.5 ±36.1[b]
LDL (mg/dL)	114.2 ±31.7[a]	122.9 ±23.2[a]	124.8 ±33.0[b]	122.7 ±26.7[a]
HDL (mg/dL)	60.0 ±11.4[a]	51.2 ±10.1[b]	48.3 ±8.3[b]	49.2 ±12.8[b]
Offspring	**Lean + non-GDM (*n*= 26)**	**Lean + GDM (*n*=30)**	**Overweight + non-GDM (*n*= 15)**	**Overweight + GDM (*n*=39)**
At delivery				

Newborn characteristcs (2004-2011)				
gestation (days)	270.4 ±9.0[a]	266.9 ±10.5[b]	273.3 ±11.4[a]	262.1 ±10.8[b]
ponderal index (cm.kg$^{-1/3}$)	2.78 ±0.24[a]	2.83 ±0.23[ab]	2.80 ±0.26[ab]	3.00 ±0.5[b]
Follow-up				
Offspring characteristcs at age 5-11 years				
waist circumference (cm)				
5-6 years	52.60 ±3.06[a]	55.86 ±7.47[ab]	55.71 ±6.07[ab]	62.94 ±12.86[b]

Data are mean ± SD or % (number).
Chi-square or ANOVA. Statistically significant *p* value < 0.050.
Gestational *Diabetes mellitus* (GDM), Body mass index (BMI), Glycosylated hemoglobin (HbA1c), Oral glucose tolerance test (OGTT), Hight density lipoprotein cholesterol (HDL), Low density lipoprotein cholesterol (LDL), Large gestational age (LGA)

Table 2 presented the relative risk to develop type 2DM, overweight, insulin resistance and dyslipidemia 5-11 years after delivery. "Diabesity" were significantly risk factor for progression to type 2DM [6.00 (95% C.I. 2.42- 14.84)], overweight in the future [2.37 (95% C.I. 1.56- 3.61)], insulin-resistance [3.14 (95% C.I. 1.79- 5.49)], and dyslipidemia [5.47 (95% C.I. 2.17- 13.76)]. Surprisingly, maternal "diabesity" environmental was not predictor of offspring characteristics neither at delivery nor at age 5-11 years, including classification *z score* BMI, insulin resistance, dyslipidemia, overweight plus insulin resistance positive and overweight plus dyslipidemia.

Table 2. Relative risk (RR) of pre-gestational overweight plus GDM alone or combined of mother and offspring characteristics at delivery and at 5-11 years of follow-up study

	Lean + non-GDM (*n*= 26)	**Lean + GDM (*n*=30)**	**Overweight + non-GDM (*n*= 15)**	**Overweight + GDM (*n*=39)**
Mother				
Relative risk (RR)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Follow-up 5-11 years postpartum				
Type 2 DM	1	2.60 (0.95- 7.08)	2.16 (0.68- 6.87)	**6.00 (2.42- 14.84)**
Overweight	1	**3.33 (1.28- 8.67)**	-	**2.37 (1.56- 3.61)**
Insulin resistance	1	1.06 (0.48- 2.35)	1.63 (0.79- 3.37)	**3.14 (1.79- 5.49)**
Dyslipidemia	1	2.32 (0.83- 6.49)	1.20 (0.53- 2.71)	**5.47 (2.17- 13.76)**
Offspring				
Relative risk (RR)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
At delivery				
LGA (%)	1	-	1.25 (0.45- 3.47)	0.93 (0.33- 2.62)
macrosomic (%)	1	-	-	2.97 (0.37- 23.82)
premature (%)	1	0.50 (0.06- 4.39)	1.23 (0.31- 4.94)	2.05 (0.63- 6.62)
Offspring characteristcs at age 5-11 years				
classification *z* score BMI (kg/m²)				
overweight	1	1.58 (0.94- 2.65)	0.94 (0.52- 1.68)	1.38 (0.86- 2.23)
Insulin resistance	1	1.60 (0.18- 14.15)	1.52 (0.32- 7.31)	1.00 (0.15-6.25)
Dyslipidemia	1	1.36 (0.69- 2.67)	0.72 (0.35- 1.49)	1.30 (0.76- 2.22)
Overweight + insulin resistance	1	3.00 (0.22- 39.6)	1.57 (0.15- 15.79)	1.87 (0.18- 18.60)
Overweight + dyslipidemia	1	2.25 (0.74- 6.81)	0.86 (0.24- 2.94)	2.40 (0.95- 6.06)

Data RR (95% C.I.). Logistic regression model. Statistically significant *p* value < 0.050.

Gestational *Diabetes mellitus* (GDM), type 2 *Diabetes mellitus* (type 2DM), large gestational age (LGA), body mass index (BMI)

In the multivariate logistic model (Table 3), the maternal pre-pregnancy BMI, significantly increased the odds-ratio for type 2DM (OR 6.89; 95% C.I.: 2.52-18.82), insulin resistance (OR 10.71; 95% C.I.: 3.38- 34.04) and overweight (OR 9.02; 95% C.I.: 2.46- 32.98) at 5-11 years postpartum. GDM diagnosis (OR 9.22; 95% C.I.: 3.19- 26.65) was associated with an increase the risk for type 2DM development 5-11 years after pregnancy. The weight gain during pregnancy (OR 4.17; 95% C.I.: 1.31-13.03) was a risk factor for insulin resistance in the long-term follow-up.

Table 3. Multivariate analysis of maternal pre-pregnancy overweight, GDM and maternal weight gain on type2 DM, insulin resistance and overweight 5-11 years after delivery.

	Type 2DM 5-11 years after		
Variables	**OR**	**95% C.I.**	***p***
Maternal pre-pregnancy BMI	6.89	2.52- 18.82	0.0002
GDM	9.22	3.19- 26.65	<0.0001

	Insulin resistance 5-11 years after		
Variables	**OR**	**95% C.I.**	***p***
Maternal pre-pregnancy BMI	10.72	3.38- 34.04	<0.0001
Weight gain in pregnancy	4.17	1.31- 13.03	0.015

	Overweight 5-11 years after		
Variables	**OR**	**95% C.I.**	***p***
Maternal pre-pregnancy BMI	9.02	2.46- 32.98	0.0009

Odds ratio (OD), 95% confidence interval (95% C.I.) and *p*-value by adjusting the multivariate logistic model for investigating maternal type 2DM, insulin resistance and overweight 5-11 years after delivery.
Gestational *Diabetes mellitus* (GDM), Type 2 *Diabetes mellitus* (type 2DM)

4. Discussion

Main findings

The main finding of the study was that the impact of GDM and obesity alone as well the combination of these factors shows a greater risk of adverse pregnancy outcomes [19]. However, the combination of the two components of “diabesity”, has a greater impact than either one alone.

Strengths and limitations

This study has several strengths. First, the design study took into account that “diabesity” by its own definition involving two different medical complications overweight plus GDM during pregnancy, led us to design the project with 4 maternal groups: overweight+ GDM (study group) and 3 control groups: overweight+ non-GDM; lean+ GDM and lean+ non-GDM . With this study design, we were able to analyze the maternal and offspring long term adverse outcomes separately. Second, it was a long-term follow-up, from early pregnancy until 5-11 years postpartum. This has only been achieved due to the PDRC which has been created 21 years ago for research on GDM, sponsored by Fapesp (Sao Paulo State Foundation-Brazil) with relevant data which contributes to research on this area. Third, our study allow us to examine the conjoint impact of overweight and GDM in a continental country as Brazil with a significant internal migration as well as lack of interes from patient side. It is very common the commitment and motivation of women for treatment to protect their health and thereby the health of the unborn baby, however behavior changes and compliance to treatment are associated with challenges with an identified number of barriers for long-term follow-up.

Nonetheless, several limitations deserve comments. First, the relative small number of cases observed, which limited our ability to identify interactions between maternal BMI and GDM or control for potential cofounders. Second although not a population study, this is the largest prospective study following pairs of “diabesity” mother and offspring enabled a long-term analysis of the “diabesity” intrauterine environmental profile on mother and newborn. Recognize the limitations associated with observational study design and associated influence of measured and unmeasured covariates, we have used adjusted multivariate regression analysis to provide convincing and strong associations of pre-pregnancy BMI and GDM with perinatal outcomes and long-term health of mother and offspring.

Interpretation

“Diabesity” during pregnancy represents a significant health burden for both mother and newborn, placing women and their infants at increased risk of long-term adverse outcomes.

Consideration must be given to the significative high prevalence of type 2 DM, and insulin resistance in the “diabesity” mother 5-11 years after index pregnancy compared to lean+ non-GDM group and its increased risk to develop type 2DM, overweight, insulin resistance and dyslipidemia.

Our findings of heavier offspring based on high waist circumference at 5-6 years after delivery in “diabesity” probably indicates the first stage of offspring obesity since recent studies have established that the neonate born to a pregnancy with maternal “diabesity” is characterized by increased fat accumulation [10,18]. There are several mechanisms that may explain our severe maternal long-term associated with weaker offspring findings. First, our findings

support the idea that the guidelines for the treatment of "diabesity" pregnant women are based only on glucose-lowering treatment firstly of diet and exercise, and antepartum insulin therapy if necessary similar to GDM patients. This means that the overweight during pregnancy had not been treated and may be the reason for the severe maternal and weaker offspring long-term effect of “diabesity”. Our findings support the idea of a strong association between environmental exposures during early life and the conditioning of biological responses that define disease risk over the life course of the offspring. The physiological adaptive processes upon exposure to maternal obesity and diabetes during pregnancy affect fetal offspring resulting in adaptations across the cellular, tissue, and organ system levels. Furthermore, continued epigenetic changes throughout the life course in conjunction with postnatal diet and lifestyle factors lead to the development of metabolic disorders (e.g. obesity, type 2 diabetes and cardiovascular disease) in young adulthood which continue into adulthood and old age [8].

In 1990, David J. P. Barker first proposed that *in utero* metabolic adaptation defines a trajectory of growth that prepares the fetus for its likely adult environment [20]. What happens in utero to the fetus depends on the mother’s environmental during pregnancy. Based on this concept, our findings appear to largely reflect the tight glycemic control, routinely performed in PDRC during pregnancy, on the growth pattern of offspring.

It is well defined in the literature that maternal health prior to and at the time of conception has detrimental effects on pregnancy and on child health. In particular, obesity and insulin resistance during pregnancy have been consistently shown to negatively impact the metabolic health of the offspring [1].

Obesity and insulin resistance often co-exist and are common metabolic conditions of pregnancy with an estimated 33% of all pregnancies complicated by maternal obesity. The relationship between obesity and insulin resistance in pregnancy and the impact on obesity, type 2DM, and metabolic syndrome in the offspring may be due to permanent alterations in glucose-insulin metabolism in the offspring, causing reduced capacity for insulin secretion and insulin resistance [21].

The strategy outlined of having three control groups (overweight+ non-GDM; lean+ GDM and lean+ non-GDM) led to analyse one-by- one the “diabesity” components which is very important according to our findings.

The clinical and metabolic characteristics of women and offspring of lean+ non-GDM group with subsequent development of normal weight, normal glycemic and normal lipidic cutoff allow us to report the long-term standard profile after normal pregnancy and its usefulness in predicting long-term normality pregnancy-dependent.

The lean+ GDM group revealed similar long-term maternal and offspring patterns although with maternal higher long-term 2h post load OGTT and lower HDL compared to healthy controls. The newborn results demonstrate the GDM repercussion with lower gestational age at delivery and high ponderal index associated with long-term intermediate value at 5-6 years.

Many studies examined the impact of high gestational BMI on pregnancy risk. An associated increase risk of almost every pregnancy related complication [22,23] and the single greatest contributor to compromised health during pregnancy were found [24-26].

Furthermore, maternal overweight and obesity is well recognized as a contributor to high infant birth weight [22,23], which in turn is an independent risk factor for the development of obesity in both childhood and adulthood [27].

The “diabesity” epidemic is likely to be the biggest epidemic in human history. There has been comprehensive attention to the “traditional” risk factors for type 2DM i.e., genes, lifestyle and behavioral change. The spotlight is turning to the impact of the intra-uterine environment and epigenetics on future risk in adult life [9]. Our results highlights a novel approaches to prevent “diabesity” focusing on the conjoint short and long-term maternal and child health analysis that indirectly detect the epigenetic changes that could be transmitted intergenerationally, creating a vicious cycle that will continue to feed the diabetes epidemic.

This emphasizes the importance of lifestyle changes after “diabesity” pregnancy not only for women but also for the all family to avoid or prevent hyperglycemia and hyperinsulinemia, central obesity, dyslipidemia and type 2DM [10].

Current clinical recommendations of ACOG [7] indicate that, ideally, women should be counseled prior to conception about the increased pregnancy risks associated with obesity, and encouraged to lose weight prior to pregnancy to reduce the risk of complications [28]. Our results suggested that this ACOG guideline thereby enable the decrease of the vicious cycle of obesity affecting “diabesity” pregnant women and their offspring.

Conclusion

In conclusion, our results expand the knowledge in this area as we found that “diabesity” profile during pregnancy severely worsens the maternal and offspring long-term prognosis. The maternal “diabesity” is associated with adverse long-term follow-up effect on women and offspring outcomes.

Disclosure of interestS

None.

Details of ethics approval

This research using an existing clinical pregnancy registry at the Perinatal Diabetes Research Center - database has been ethically approved by the Institutional Review Board of Botucatu Medical School of- UNESP.

Supporting information

The following supplementary materials are available for this article

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Contribution to authorship

MAA and AMPB conducted data extraction, analyzed the data and co-drafted the manuscript. RAAC, JFA, GB and CAN provided study data and together with DCD contributed to interpretation of the data. LPC, BFNC, assisted with

screening of data. MVCR and IMPC conceived the design of the study, co-drafted the final manuscript and are the guarantor of this work. All authors contributed to the critical revision of the manuscript.

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Supplementary materials

Table 4. Baseline characteristics of womwn and offspring pairs 5-11 years postpartum according to pregestational BMI and GDM status

	Lean + non-GDM (*n*= 26)	Lean + GDM (*n*=30)	Overweight + non-GDM (*n*= 15)	Overweight + GDM (*n*=39)
Baseline				
Maternal characteristcs prepregnancy (2004-2011)				
maternal prepregnancy BMI (kg/m²)	21.9 ±2.3[a]	22.0 ±1.8[a]	33.3 ±6.1[b]	32.4 ±5.7[b]
maternal prepregnancy hypertension (%)	3.85% (1)[a]	6.66% (2)[a]	20% (3)[b]	28.20% (11)[b]
Maternal characteristcs pregnancy (2004-2011)				
maternal pregnancy hypertension (%)	11.54% (3)[a]	20% (6)[a]	46.66% (7)[b]	46.15% (18)[b]
Maternal characteristcs 6 weeks postpartum				
maternal BMI (kg/m²)	22.2 ±2.8[a]	23.3 ±1.8[a]	27.3 ±1.0[b]	31.7 ±5.2[b]
Follow-up				
Maternal characteristcs 5-11 years postpartum (2016)				
age (years)	40.1 ±7.5[a]	42.5 ±5.7[a]	36.4 ±5.8[b]	40.3 ±6.4[a]
maternal BMI (kg/m²)	22.2 ±2.2[a]	22.6 ±1.9[a]	32.6 ±6.7[b]	32.3 ±5.9[b]
weight gain in current days (kg)	-7.9 ±5.8	-5.0 ±26.3	0.5 ±7.8	-4.0 ±9.6
waist circumference (cm)	82.1 ±5.8[a]	81.1 ±6.0[a]	103.3 ±15.6[b]	104.13.9[b]
hip circumference (cm)	96.2 ±6.0[a]	98.7 ±5.9[a]	112.8 ±15.6[b]	115.2 ±13.4[b]
waist/hip index (cm)	0.9 ±0.1	0.8 ±0.0	0.9 ±0.1	0.9 ±0.1
physical activity (%)	38.46% (10)	46.66% (14)	40% (6)	25.64% (10)
hypertension (%)	7.7% (2)[a]	10% (3)[a]	33.33% (5)[b]	33.33% (13)[b]
fasting glucose (mg/dL)	84.9 ±5.1	143.1 ±105.7	89.6 ±9.2	159.1 ±88.8
HbA1c (%)	5.1 ±0.2	6.6 ±2.7	5.5 ±0.5	7.2 ±2.6
insulin (µUI/mL)	5.0 ±3.7	5.0 ± 1.6	12.4 ±7.2	12.4 ±12.9
fasting glucose at OGTT (mg/dL)	86.5 ±6.4[a]	87.2 ±7.5[a]	91.0 ±9.1[b]	106.6 ±25.8[b]

2 hours postload at OGTT (mg/dL)	84.4 ±18.6[a]	111.2 ±18.0[b]	110.2 ±31.8[a]	135.5 ±57.3[b]
total cholesterol (mg/dL)	196.2 ±32.7[a]	194.2 ±26.3[a]	198.1 ±41.0[b]	203.5 ±36.1[b]
LDL (mg/dL)	114.2 ±31.7[a]	122.9 ±23.2[a]	124.8 ±33.0[b]	122.7 ±26.7[a]
HDL (mg/dL)	60.0 ±11.4[a]	51.2 ±10.1[b]	48.3 ±8.3[b]	49.2 ±12.8[b]
triglyceride (mg/dL)	103.6 ±42.2	100.8 ±40.4	126.2 ±65.9	166.5 ±98.4
red blood cells (million/mm³)	4.6 ±0.3	4.6 ±0.3	4.5 ±0.3	4.6 ±0.4
hemoglobin (g/dL)	13.4 ±0.7	13.3 ±0.7	13.1 ±0.9	12.7 ±1.3
hematocrit (%)	40.7 ±2.7	39.8 ±2.2	39.7 ±2.6	38.8 ±3.3
white blood cells (/mm³)	5963 ±1076	10400 ±16002	6740 ±1542	7175 ±2001
Offspring	**Lean + non-GDM (*n*= 26)**	**Lean + GDM (*n*=30)**	**Overweight + non-GDM (*n*= 15)**	**Overweight + GDM (*n*=39)**
At delivery				
Newborn characteristcs (2004-2011)				
gestation (days)	270.4 ±9.0[a]	266.9 ±10.5[b]	273.3 ±11.4[a]	262.1 ±10.8[b]
weight (g)	3281.9 ±438.1	3265.0 ±481.1	3155.0 ±404.0	3258.0 ±577.1
length (cm)	49.0 ±1.9	48.6 ±2.5	48.3 ±2.1	47.6 ±1.2
ponderal index ($cm.kg^{-1/3}$)	2.78 ±0.24[a]	2.83 ±0.23[ab]	2.80 ±0.26[ab]	3.00 ±0.5[b]
male sex (%)	46.15% (12)	56.66% (17)	60% (9)	56.41% (22)
caucasian (%)	88.46% (23)	76.66% (23)	80% (12)	66.66% (26)
LGA (%)	7.7% (2)	23.33% (7)	0	20.51% (8)
macrosomic (%)	3.85% (1)	0	0	12.82% (5)
premature (%)	11.54% (3)	13.33% (4)	6.66% (1)	28.20% (11)
placental weight (g)	583.9 ±138.6	603.7 ±156.1	640.9 ±154.2	671.4 ±162.2
Follow-up				
Offspring characteristcs at age 5-11 years				
BMI (kg/m²)				
5-6 years	15.19 ±1.53	16.23 ±3.35	17.27 ±2.16	18.82 ±5.72
7-11 years	18.51 ±3.61	17.30 ±3.17	22.98 ±3.97	20.16 ±4.66
classification BMI (kg/m²)				

eutrophic	53.85% (14)	56.66% (17)	26.66% (4)	35.90% (14)
overweight	46.15% (12)	43.33% (13)	73.33% (11)	64.10% (25)
waist circumference (cm)				
5-6 years	52.60 ±3.06[a]	55.86 ±7.47[ab]	55.71 ±6.07[ab]	62.94 ±12.86[b]
7-11 years	64.00 ±11.49	61.67 ±7.69	76.00 ±12.10	67.48 ±12.74
hip circumference (cm)				
5-6 years	57.60 ±5.25	57.86 ±8.17	61.43 ±8.73	63.78 ±13.54
7-11 years	67.86 ±10.01	63.92 ±7.23	80.00 ±8.75	71.84 ±12.78
neck circumference (cm)				
5-6 years	25.75 ±1.32	25.71 ±2.16	26.92 ±2.01	27.94 ±3.28
7-11 years	27.50 ±1.32	27.54 ±2.18	30.70 ±2.59	27.98 ±3.09
fasting glucose (mg/dL)	85.8 ±6.2	90.5 ±8.4	88.3 ±7.9	89.6 ±6.0
HbA1c (%)	5.08 ±0.28	5.27 ±0.30	5.15 ±0.31	5.29 ±0.35
insulin (µUI/mL)	7.0 ±6.2	7.2 ±5.5	8.4 ±5.8	7.9 ±6.9
total cholesterol (mg/dL)	169.5 ±27.7	164.7 ±24.0	167.4 ±24.3	171.6 ±30.6
LDL (mg/dL)	99.4 ±25.6	98.7 ±20.9	98.1 ±21.9	103.3 ±25.4
HDL (mg/dL)	48.7 ±11.3	50.5 ±10.2	48.9 ±9.2	51.0 ±11.2
triglyceride (mg/dL)	90.4 ±39.2	77.2 ±44.2	102.3 ±46.7	85.5 ±46.0
red blood cells (million/mm³)	4.9 ±0.2	5.0 ±0.5	4.9 ±0.3	4.9 ±0.3
hemoglobin (g/dL)	13.4 ±0.6	13.3 ±0.9	13.5 ±0.7	13.2 ±0.8
hematocrit (%)	40.0 ±1.7	38.7 ±5.2	40.5 ±2.2	39.2 ±2.0
white blood cells (/mm³)	7775 ±2216	7599 ±2346	8395 ±2733	6691 ±1846

Data are mean ± SD or % (number).

Chi-square or ANOVA. Statistically significant *p* value < 0.050.

Gestational Diabetes mellitus (GDM), Body mass index (BMI), Glycosylated hemoglobin (HbA1c), Oral glucose tolerance test (OGTT), Hight density lipoprotein cholesterol (HDL), Low density lipoprotein cholesterol (LDL), Large gestational age (LGA)

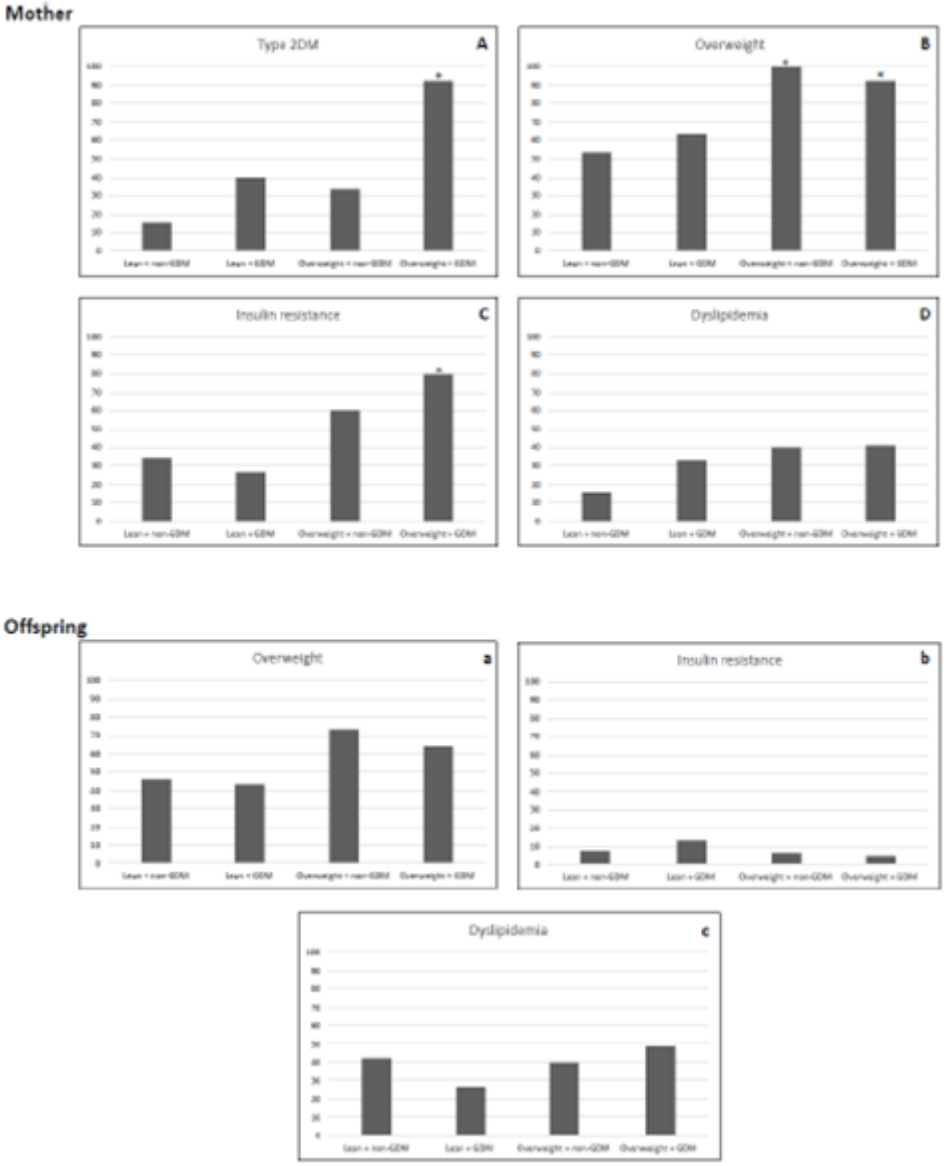


Figure 2. Prevalence in mother of type 2DM, overweight, insulin resistance and dyslipedemia according to pre-gestational BMI and GDM status at 5 to 11 years of follow-up study. ***A*** prevalence of type 2DM among the groups, ***B*** prevalence of overweight among the groups, ***C*** prevalence of insulin resistance among the groups, ***D*** prevalence of dyslipidemia among the groups.
Prevalence in offspring of overweight, insulin resistance and dyslipedemia according to pre-gestational BMI and GDM status at 5 to 11 years of follow-up study. ***a*** prevalence of overweight among the groups, ***b*** prevalence of insulin resistance among the groups, ***c*** prevalence of dyslipidemia among the groups.
Data are %. Chi-square or ANOVA. p <0.05: statistically significant difference compared to lean + non-GDM group.
Gestational *Diabetes mellitus* (GDM), type 2 *Diabetes mellitus* (type 2DM)

Seção 5
Anexos

Comitê de Ética em Pesquisa

Anexo 01

UNESP -FACULDADE DE MEDICINA DE BOTUCATU

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Follow-up metabólico e biométrico de pacientes com hiperglicemia na gestação e seus conceptos.

Pesquisador: Mariana Alvarez Arantes

Área Temática:

Versão: 2

CAAE: 56912316.1.0000.5411

Instituição Proponente: Departamento de Ginecologia e Obstetrícia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.641.871

Apresentação do Projeto:

Trata-se de projeto pendente no qual foi solicitado um novo TCLE em que não conste termos em língua estrangeira.

O TCLE foi reapresentado pelos pesquisadores referindo-se ao termo "follow up" como "seguimento", o que passa a ser mais compreensível para o sujeito de pesquisa e está de acordo com a resolução 466/2012.

Objetivo da Pesquisa:

constante do parecer 1.607.948

Avaliação dos Riscos e Benefícios:

constante do parecer 1.607.948

Comentários e Considerações sobre a Pesquisa:

constante do parecer 1.607.948

Considerações sobre os Termos de apresentação obrigatória:

O TCLE foi reapresentado agora explicitando o termo utilizado em inglês e tornando mais claro o objetivo da pesquisa

Endereço: Chácara Butignolli , s/n
Bairro: Rubião Junior **CEP:** 18.618-970
UF: SP **Município:** BOTUCATU
Telefone: (14)3880-1608 **E-mail:** capellup@fmb.unesp.br

Anexo 01

Continuação do Parecer: 1.641.871

Recomendações:

Recomenda-se que, mesmo com a reapresentação do novo TCLE, que se explique a cada indivíduo constante da pesquisa no momento da assinatura que do termo, o significado da palavra "follow up" para que não haja dúvidas a respeito do que se pretende com o presente projeto.

Conclusões ou Pendências e Lista de Inadequações:

Sugiro aprovação, sem necessidade de encaminhar à CONEP

Considerações Finais a critério do CEP:

Projeto de Pesquisa APROVADO, deliberado em reunião EXTRAORDINÁRIA do CEP de 20 de Julho de 2.016, sem necessidade de envio à CONEP.

O CEP, no entanto, solicita aos pesquisadores que após a execução do projeto em questão, seja enviado para análise o respectivo "Relatório Final de Atividades", o qual deverá ser enviado via Plataforma Brasil na forma de "NOTIFICAÇÃO".

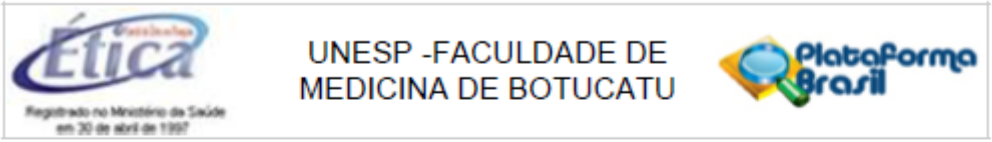
RECOMENDAÇÃO DO CEP: Para os participantes da pesquisa deve ser explicado de forma clara e objetivo o que significa a palavra "Follow-up"

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_701126.pdf	13/07/2016 11:51:06		Aceito
Outros	TALE.docx	13/07/2016 11:50:26	Mariana Alvarez Arantes	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	13/07/2016 11:49:30	Mariana Alvarez Arantes	Aceito
Cronograma	cronograma.docx	10/06/2016 11:12:34	Mariana Alvarez Arantes	Aceito
Declaração de Instituição e Infraestrutura	1617MarianaAlvarezArantes.pdf	09/06/2016 15:58:35	Mariana Alvarez Arantes	Aceito
Projeto Detalhado / Brochura Investigador	PROJETOFOLLOWUP.doc	09/06/2016 15:52:17	Mariana Alvarez Arantes	Aceito
Folha de Rosto	PlatBrasil1617MarianaAlvarezArantes.pdf	09/06/2016 15:48:37	Mariana Alvarez Arantes	Aceito

Endereço: Chácara Butignoli , s/n
Bairro: Rubião Junior **CEP:** 18.618-970
UF: SP **Município:** BOTUCATU
Telefone: (14)3880-1608 **E-mail:** capellup@fmb.unesp.br

Anexo 01



Continuação do Parecer: 1.641.871

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BOTUCATU, 20 de Julho de 2016

Assinado por:
SILVANA ANDREA MOLINA LIMA
(Coordenador)

Anexo 02

unesp Universidade Estadual Paulista
Faculdade de Medicina de Botucatu

Distrito Rubião Junior, s/nº - Botucatu – S.P.
CEP: 18.618-970
Fone/Fax: (0xx14) 3811-6143
e-mail secretaria: capellup@fmb.unesp.br

Registrado no Ministério da Saúde em 30 de abril de 1997

Botucatu , 08 de novembro de 2.004

OF 545/2004-CEP
MACAH/asc

Ilustríssima Senhora
Prof.ª Drª Marilza Vieira Cunha Rudge
Departamento de Ginecologia e Obstetrícia
Faculdade de Medicina de Botucatu

Prezada Drª Marilza,

De ordem da Senhora Coordenadora deste CEP, informo que o Protocolo de Pesquisa intitulado ***"Diabete e Hiperglicemia diária na gravidez – Pesquisa Clínica e Experimental para validação do grupo IB de Rudge", a ser conduzido por Vossa Senhoria com a participação da Profª Drª Iracema de Mattos Paranhos Calderon, Profª Drª Daisy Maria Fávero Salvadori, Profª Drª Débora Cristina Damasceno,*** *recebeu do relator parecer favorável, aprovado em reunião de 08 de novembro de 2.004*

O CEP esclarece que muito embora os subprojetos 2,3 e 8 envolvem Genética Humana, os mesmos não têm necessidade de envio à CONEP, pois cumpre as normas da Resolução 340 de 08/07/2004.

SITUAÇÃO DO PROJETO: APROVADO.

Atenciosamente,

Alberto Santos Capelluppi
Secretário do CEP

Termo de Consentimento

Anexo 03

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
(Participante maior de 18anos)

"Follow-up (seguimento) metabólico e biométrico de pacientes com hiperglicemia na gestação e seus conceptos"

Pesquisador – Responsável: Profa. Dra. Marilza Vieira Cunha Rudge, Departamento de Ginecologia e Obstetrícia – Faculdade de Medicina de Botucatu, UNESP, Botucatu – SP. (014 3880-1631).

I. EXPLICAÇÕES DO PESQUISADOR AO PACIENTE

Convido, o Senhor (a),_____ para participar do Projeto de Pesquisa intitulado "Follow-up(seguimento) metabólico e biométrico de pacientes com hiperglicemia na gestação e seus conceptos" ,que será desenvolvido por mim Mariana Alvarez Arantes – biomédica, com orientação do profissional e Professora Dra. Marilza Vieira Cunha Rudge da (Faculdade de Medicina de Botucatu –UNESP).

O objetivo deste estudo é avaliar o nível de glicose (açúcar), em pacientes, que foram diagnosticadas durante a gestação com hiperglicemia e avaliar a incidência do desenvolvimento de *diabete mellitus* tipo 2, de 2 a 10 após a gestação e seus filhos. Determinar a associação entre os níveis de glicose na gestação de mulheres com hiperglicemia, o desenvolvimento de diabete e a dislipidemia de seus filhos nos primeiros anos de vida.

Desta forma, solicitamos sua autorização para coleta de dados pessoais através de um questionário, para obtenção dos dados clínicos e obstétricos, que levará aproximadamente 15 minutos de duração. Avaliações como aferição de peso corporal, estatura, níveis pressóricos (pressão arterial sistólica e diastólica) e colheita de sangue, por punção venosa (cerca de 15 mL), para as dosagens laboratoriais.

Solicito também seu consentimento para levantar o seu prontuário médico para coletar informações lá contidas como evolução da gestação e dados do parto referentes a consultas feitas durante o pré-natal.

Exames de sangue como Teste Tolerância a Glicose 75g (TTG75g) serão agendadas e realizadas no Laboratório Clínico Central e no Centro de Avaliação do Bem Estar Fetal, nas dependências do Hospital de Clínicas da FMB/UNESP

Esclarecemos que, a não ser o pequeno desconforto no momento da picada da agulha, a coleta do sangue não tem risco, pois será feita por profissional qualificado e utilizando material descartável. A senhora pode, a qualquer momento, se recusar em contribuir com o estudo sem ser prejudicada no seu tratamento e acompanhamento médico, ou pode, também, ter acesso aos resultados. Sua identidade não será revelada e será mantido o caráter confidencial de todas as informações obtidas.

Os resultados deste estudo serão divulgados em congressos científicos e publicados em revistas especializadas, preservando sua identidade. Os resultados do estudo não trarão benefícios imediatos a sua pessoa, mas poderão contribuir, no futuro, para redução dos efeitos adversos causados por essa patologia.

Este Termo de Consentimento Livre e Esclarecido será elaborado em 2 vias de igual teor, o qual 01 via será entregue ao Senhor (a) devidamente assinada, e a outra via será arquivada e mantida pelos pesquisadores por um período de 5 anos após o término da pesquisa.

Os pesquisadores responsáveis por este estudo, sempre que solicitados, estarão à sua disposição para o esclarecimento de qualquer questão relacionada à pesquisa.

Qualquer dúvida adicional você poderá entrar em contrato com o Comitê de Ética em Pesquisa através dos telefones (14) 3880-1608 ou 3880-1609 que funciona de 2ª a 6ª feira das 8.00 às 11.30 e das 14.00 às 17 horas, na Chácara Butignolli s/nº em Rubião Júnior – Botucatu - São Paulo.

Ressaltamos que nem os pesquisadores e nem o paciente receberá qualquer remuneração financeira por participar desta pesquisa.

II. CONSENTIMENTO PÓS-INFORMADO

Eu, _____ abaixo assinado, declaro que fui esclarecido sobre o objetivo do presente estudo e sobre os eventuais desconfortos que poderei sofrer, assim como os benefícios do estudo.
Concordo, portanto, em participar, na qualidade de voluntário, do referido Projeto de Pesquisa, sob livre e espontânea vontade.

Botucatu, _____ de_____ de_____

_____
Paciente

_____
Pesquisadora: Mariana Alvarez Arantes
Endereço: UNIPEX, Faculdade de medicina de Botucatu, Rubião Júnior s/nº
telefone contato: (14) 99117-0937
mariana.alvarantes@gmail.com
Orientadora: Profa. Marilza Vieira Cunha Rudge
Endereço: UNIPEX, Faculdade de medicina de Botucatu, Rubião Júnior s/nº
telefone contato: (14) 3880-1631
marilzarudge@gmail.com

Anexo 04

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
(Participante 0 a 10 anos)

"Follow-up metabólico e biométrico de pacientes com hiperglicemia na gestação e seus conceptos"

Pesquisador – Responsável: Profa. Dra. Marilza Vieira Cunha Rudge, Departamento de Ginecologia e Obstetrícia – Faculdade de Medicina de Botucatu, UNESP, Botucatu – SP. (014 3880-1631).

III. EXPLICAÇÕES DO PESQUISADOR AO PACIENTE

Convido, o Senhor (a),_____ responsável pelo menor _____ para participar do Projeto de Pesquisa intitulado "Follow-up(seguimento) metabólico e biométrico de pacientes com hiperglicemia na gestação e seus conceptos" ,que será desenvolvido por mim Mariana Alvarez Arantes – biomédica, com orientação do profissional e Professora Dra. Marilza Vieira Cunha Rudge da (Faculdade de Medicina de Botucatu –UNESP).

O objetivo deste estudo é avaliar o nível de glicose (açúcar), em pacientes, que foram diagnosticadas durante a gestação com hiperglicemia e avaliar a incidência do desenvolvimento de *diabete mellitus* tipo 2, de 2 a 10 após a gestação e seus filhos. Determinar a associação entre os níveis de glicose na gestação de mulheres com hiperglicemia, o desenvolvimento de diabete e a dislipidemia de seus filhos nos primeiros anos de vida.

Solicito também seu consentimento para levantar o prontuário médico do seu filho(a) para coletar informações lá contidas como dados de nascimento referentes a consultas feitas anteriormente.

Desta forma, solicitamos sua autorização para coleta de dados pessoais através de um questionário, para obtenção dos dados clínicos e obstétricos, que levará aproximadamente 15 minutos de duração. Avaliações como aferição de peso corporal, estatura, níveis pressóricos (pressão arterial sistólica e diastólica) e colheita de sangue, por punção venosa (cerca de 15 mL), para as dosagens laboratoriais.

Esclarecemos que, a não ser o pequeno desconforto no momento da picada da agulha, a coleta do sangue não tem risco, pois será feita por profissional qualificado e utilizando material descartável. A senhora pode, a qualquer momento, se recusar em contribuir com o estudo sem ser prejudicada no seu tratamento e acompanhamento médico, ou pode, também, ter acesso aos resultados. Sua identidade não será revelada e será mantido o caráter confidencial de todas as informações obtidas.

Os resultados deste estudo serão divulgados em congressos científicos e publicados em revistas especializadas, preservando sua identidade. Os resultados do estudo não trarão benefícios imediatos a sua pessoa, mas poderão contribuir, no futuro, para redução dos efeitos adversos causados por essa patologia.

Este Termo de Consentimento Livre e Esclarecido será elaborado em 2 vias de igual teor, o qual 01 via será entregue ao Senhor (a) devidamente assinada, e a outra via será arquivada e mantida pelos pesquisadores por um período de 5 anos após o término da pesquisa.

Os pesquisadores responsáveis por este estudo, sempre que solicitados, estarão à sua disposição para o esclarecimento de qualquer questão relacionada à pesquisa.

Qualquer dúvida adicional você poderá entrar em contrato com o Comitê de Ética em Pesquisa através dos telefones (14) 3880-1608 ou 3880-1609 que funciona de 2ª a 6ª feira das 8.00 às 11.30 e das 14.00 às 17 horas, na Chácara Butignolli s/nº em Rubião Júnior – Botucatu - São Paulo.

Ressaltamos que nem os pesquisadores e nem o paciente receberá qualquer remuneração financeira por participar desta pesquisa.

IV. CONSENTIMENTO PÓS-INFORMADO

Eu, _____ abaixo

assinado, declaro que fui esclarecido sobre o objetivo do presente estudo e sobre os eventuais desconfortos que poderei sofrer, assim como os benefícios do estudo.
Concordo, portanto, em participar, na qualidade de voluntário, do referido Projeto de Pesquisa, sob livre e espontânea vontade.

Botucatu, _____ de_____ de_____

_____
Responsável

Pesquisadora: Mariana Alvarez Arantes
Endereço: UNIPEX, Faculdade de medicina de Botucatu, Rubião Júnior s/nº
telefone contato: (14) 99117-0937
mariana.alvarantes@gmail.com
Orientadora: Profa. Marilza Vieira Cunha Rudge
Endereço: UNIPEX, Faculdade de medicina de Botucatu, Rubião Júnior s/nº
telefone contato: (14) 3880-1631
marilzarudge@gmail.com