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

Fabiana Vieira Duarte De Souza Reis

Interação entre início precoce ou tardio do diabetes mellitus gestacional e obesidade pré-gestacional com desfechos neonatais adversos

Interaction between early and late diagnosis of gestational diabetes mellitus and pre-gestational obesity with neonatal adverse outcomes

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, como parte dos requisitos para obtenção do título de Doutora em Tocoginecologia.

Orientadora: Profa. Dra. Angélica Mércia Pascon Barbosa
Coorientadora: Dra. Juliana Ferreira Floriano

Botucatu
2023

Fabiana Vieira Duarte de Souza Reis

Interação entre início precoce e tardio do diabetes mellitus gestacional e obesidade pré-gestacional com desfechos neonatais adversos

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, como parte dos requisitos para obtenção do título de Doutora em Tocoginecologia.

Thesis presented to the Botucatu Medical School, São Paulo State University "Júlio de Mesquita Filho", as part of the requirements for obtaining the title of Doctor in Tocogynecology.

Orientadora: Profa. Dra. Angelica Mercia Pascon Barbosa
Coorientadores: Dra. Juliana Ferreira Floriano

Botucatu
2023

R375i

Reis, Fabiana Vieira Duarte De Souza
Interação entre início precoce ou tardio do diabetes mellitus gestacional e obesidade pré-gestacional com desfechos neonatais adversos / Fabiana Vieira Duarte De Souza Reis. -- Botucatu, 2023
96 p.

Tese (doutorado) - Universidade Estadual Paulista (Unesp), Faculdade de Medicina, Botucatu
Orientadora: Angélica Mércia Pascon Barbosa
Coorientadora: Juliana Ferreira Floriano

1. Gravidez. 2. Diabetes Melito Gestacional. 3. Neonato. 4. Obesidade. I. Título.

Sistema de geração automática de fichas catalográficas da Unesp. Biblioteca da Faculdade de Medicina, Botucatu. Dados fornecidos pelo autor(a).

Essa ficha não pode ser modificada.

Fabiana Vieira Duarte de Souza Reis

Interação entre início precoce e tardio do diabetes mellitus gestacional e obesidade pré-gestacional com desfechos neonatais adversos

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, como parte dos requisitos para obtenção do título de Doutora em Tocoginecologia

Orientadora: Profª. Dra. Angélica Mércia Pascon Barbosa

Banca Examinadora

_____

Prof.ª Dr.ª Angélica Mércia Pascon Barbosa
Faculdade de Medicina de Botucatu – FMB – UNESP

_____

Prof.ª Dr.ª Talita Domingues Caldeirão
Fundação Educacional do Município de Assis – FEMA

_____

Prof. Dr. Carlos Izaias Sartorão Filho
Fundação Educacional do Município de Assis – FEMA

_____

Prof.ª Dr.ª Caroline Baldini Prudencio
Faculdade de Medicina de Botucatu – FMB – UNESP

_____

Prof.ª Dr.ª Claudia Garcia Magalhães
Faculdade de Medicina de Botucatu – FMB – UNESP

Botucatu, de 11 de agosto de 2023

Dedicatória

Este trabalho é dedicado ao que há de mais precioso na minha vida: a Deus,

À meu esposo Luis e minha filha Rafaela, pela paciência, compreensão, apoio e por estarem sempre ao meu lado em todos os momentos, tornando mais fácil essa caminhada,

Aos meus Pais Nelson e Nadir, que são exemplos de dignidade, força e determinação, que sempre me apoiaram e me ensinaram o caminho da prosperidade, respeito pela vida e pelos nossos semelhantes, são a razão da minha existência.

Agradecimentos

AGRADECIMENTO ESPECIAL

À minha orientadora Profª. Angelica Mercia Pascon Barbosa, mulher sábia, forte, de excelente liderança e cheia de Fé.

Agradeço de coração pela orientação para a realização deste trabalho, incentivo, confiança, amizade e apoio.

Os seus ensinamentos fizeram engrandecer meus conhecimentos, contribuindo significativamente no atendimento dos meus pacientes que tanto amo.

AGRADECIMENTOS

Sou grata à **Deus**, por entender que a vida é um Dom Divino. E aceitar as bençõe s e também os opstáculos com coração aberto, sabendo que o tempo de Deus nem sempre é o nosso tempo. Ser grata à Deus é ter a certeza de que Ele está cuidando de nós e fazendo sempre o melhor.

À **Professora Marilza Vieira Cunha Rudge,** agradeço os seus ensinamentos por colocarem em minhas mãos as ferramentas com as quais posso abrir novos horizontes.

Ao **Professor Dr. Carlos Izaias Sartorão Filho,** por repartir seus conhecimentos, vivência, experiências e me fazer acreditar que somos capazes de transformar sonhos em realizadades.

À ***Diamater Study Group*** pela oportunidade integrar o grupo de pesquisa que tanto me acolheu carinhosamente tornando possível a realização desta tese.

À **Professora Drª. Juliana Floriano** pelo incentivo.

Ao **Professor Dr. Hélio** pela sua grande contribuição e ensinamentos nas análises estatísticas dos resultados experimentais.

Ao meu coloega **Rafael Guilen de Oliveira** pela generosidade, dedidacação e parceria com todo nosso trabalho.

Aos funcionários do **Programa de Pós-Graduação da Faculdade de Medicina de Botucatu,** e ao **Departamento de Tocoginecologia**, em especial à **Solange Sako**, por toda atenção e paciência.

À **Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES)** pelo apoio ao Programa de Pós-Graduação em Tocoginecologia.

À **Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP),** pelo financiamento do Projeto Temático processo 2016/01743-5, que possibilitou a execução deste doutorado.

Ao Escritório de Apoio à Pesquisa, **Cinthia** e **Cássia** por toda colaboração e competência dispensadas a mim e a este projeto.

Agradeço imensamente às **mães** e os seus recém-nascidos que participaram deste estudo e que nos permitiram acessar os seus dados pessoais e clínicos para geração de novos conhecimentos científicos.

Epígrafe

“A cura está ligada ao tempo e as vezes também a circunstância”

Hipócrates

Sumário

Seção 1

Resumos Expandidos

Resumo Tese

Introdução: A importância do momento no diagnóstico de hiperglicemia durante a gravidez e sua associação com resultados adversos para o recém-nascido é controversa. A literatura vem evoluindo na padronização do diagnóstico e da terminologia do diabetes mellitus gestacional (DMG). Artigo 1: nosso objetivo foi investigar a associação entre DMG de início precoce e desfechos adversos em recém-nascidos e neonatos, comparando-a com o modelo de DMG de início tardio. Artigo 2: Analisar a associação do diagnóstico de obesidade pré-gravidez com os resultados neonatais de curto prazo, tendo o diabetes gestacional como mediador, na população de mulheres grávidas. **Método:** Foi um estudo de coorte retrospectivo realizado no Centro de Pesquisa em Diabetes Perinatal-Núcleo afiliado a Assis da Faculdade de Medicina de Botucatu-UNESP, Brasil, entre 2016-2019. A composição do grupo foi de início precoce em relação aos participantes com glicemia de jejum ≥92 mg/dL. e <126 mg/dL antes de 20 semanas de gestação ou participantes de início tardio com triagem negativa no primeiro trimestre e 75g-OGTT positivo em 24-28 semanas. As características basais maternas incluíram: índice de massa corporal pré-gestacional (IMC; Kg/m2); o ganho de peso gestacional (Kg) calculado pela diferença entre o peso final da gestação (36 semanas gestacionais ou mais) e o peso materno pré-gestacional e classificado de acordo com o IMC pré-gestacional (8). Além disso, os desfechos perinatais avaliados neste estudo foram: idade gestacional (IG), peso ao nascer (PN) e situação do PN de acordo com a IG como adequado, grande ou pequeno, escores de Apgar no primeiro e no 5º minutos. **Resultados:** Artigo 1) Foram selecionadas 880 gestantes, sendo elegíveis 203 (23,07%) apresentando DMG no período de dezembro de 2016 a dezembro de 2021. De acordo com o momento de início do DMG, 89 (43,84%) estavam no grupo de início precoce e 114 (56,16%) %) no grupo de início tardio. os valores de GPJ no primeiro trimestre foram maiores no grupo de início precoce. Os valores de 75 gramas de TOTG foram maiores no grupo de início tardio. O IMC final foi maior no grupo de início tardio. Uma regressão linear univariada foi realizada para determinar a relação entre o início tardio de acordo com os diferentes desfechos, nenhuma relação significativa foi detectada. Artigo 2) Foram elegíveis 886 mulheres grávidas de dezembro de 2016 a dezembro de 2021. De acordo com o status de obesidade pré-gravidez, 709 (80%) foram classificadas como não tendo obesidade pré-gravidez e 177 (20%) no grupo de obesidade pré-gravidez. Houve um efeito atenuado da obesidade pré-gravidez, com o risco de complicações

neonatais de curto prazo ou escore de Apgar no 5º minuto < 7 sendo 4% maior entre aquelas com obesidade pré-gravidez. Além disso, os resultados expõem um efeito mediador do DMG durante a gravidez, com o risco de complicações neonatais de curto prazo ou escore de Apgar no 5º minuto < 7 sendo 5% maior na presença de DMG. **Conclusões:** Artigo 1) Gestantes com início precoce de DMG apresentaram maior IMC durante a gravidez, mas não houve diferença entre o início precoce ou tardio do DMG em relação aos resultados adversos neonatais. Artigo 2) Existe a necessidade de aconselhamento pré-gravidez para considerar o excesso de peso e a obesidade como fatores de risco cruciais para complicações durante a gravidez e neonatais e, principalmente, para propor estratégias às mulheres em idade reprodutiva para alcançarem um índice de massa corporal (IMC) apropriado antes da gravidez.

Palavras-chave: Diabetes mellitus gestacional, recém-nascido, complicações adversas.

Thesis Abstract

Introduction: The importance of timing in diagnosing hyperglycemia during pregnancy and its association with adverse outcomes for the newborn is controversial. The literature has been evolving in standardizing the diagnosis and terminology of gestational diabetes mellitus (GDM). Article 1: Our objective was to investigate the association between early-onset GDM and adverse outcomes in newborns and neonates, comparing it with the late-onset GDM model. Article 2: To analyze the association of pre-pregnancy obesity diagnosis with short-term neonatal outcomes, with gestational diabetes as a mediator, in the population of pregnant women. **Methods:** It was a retrospective cohort study conducted at the Perinatal Diabetes Research Center - Assis Branch of the Botucatu Medical School-UNESP, Brazil, between 2016-2019. The composition of the group was early onset in relation to participants with fasting blood glucose ≥92 mg/dL and <126 mg/dL before 20 weeks of gestation or late onset participants with negative screening in the first trimester and positive 75g-OGTT in 24-28 weeks. Maternal baseline characteristics included pre-gestational body mass index (BMI; Kg/m2), gestational weight gain (Kg) calculated by the difference between the final gestational weight (36 weeks gestational or more) and pre-gestational maternal weight and classified according to pre-gestational BMI (8). Furthermore, the perinatal outcomes assessed in this study were gestational age (GA), birth weight (BW), and BW status according to GA as appropriate, large, or small, Apgar scores at the first and 5th minutes. **Results:** Article 1) 880 pregnant women were selected, with 203 (23.07%) eligible for GDM from December 2016 to December 2021. According to the timing of GDM onset, 89 (43.84%) were in the early-onset group and 114 (56.16%) in the late-onset group. Fasting blood glucose values in the first trimester were higher in the early-onset group. The 75-gram OGTT values were higher in the late-onset group. The final BMI was higher in the late-onset group. Univariate linear regression was performed to determine the relationship between late onset and different outcomes, and no significant relationship was detected. Article 2) 886 pregnant women were eligible from December 2016 to December 2021. According to the pre-pregnancy obesity status, 709 (80%) were classified as non-prepregnancy obesity, and 177 (20%) in the pre-pregnancy obesity group. There was a softened effect of pre-pregnancy obesity, with the risk of short-term neonatal complications or 5th minute Apgar score < 7 being 4% higher among those with pre-pregnancy obesity. Furthermore, the results expose a mediating effect of GDM during pregnancy, with the

risk of short-term neonatal complications or 5th minute Apgar score < 7 being 5% higher in the presence of GDM. **Conclusions:** Article 1) Pregnant women with early-onset GDM had a higher BMI during pregnancy, but there was no difference between early and late-onset GDM in relation to neonatal adverse outcomes. Article 2) There is a need for pre-pregnancy counseling to consider overweight and obesity as crucial risk factors for pregnancy and neonatal complications and, primarily, to propose strategies to women of reproductive age to achieve an appropriate pre-pregnancy body mass index (BMI).

Keywords: Gestational diabetes mellitus, newborn, adverse complications.

Seção 2

Trajetória Acadêmica

Iniciei minha formação acadêmica no ano de 1994 na Faculdade de Medicina da Universidade do Oeste Paulista – UNOESTE na cidade de Presidente Prudente-SP e concluir o curso ano 2000.

Logo da minha formatura, cursei a Residência Médica em Pediatria entre os anos de 2001 a 2003 na Faculdade de Medicina de Marília – FAMEMA.

Entre os anos de 2005 a 2006, realizei a Especialização em Pediatria Neonatal no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

No ano de 2006 fui aprovada na prova de conhecimentos gerais sobre pediatria, onde obtive o Título de Especialista em Pediatria pela Sociedade Brasileira de Pediatria.

Entre os anos de 2012 a 2015, realizei a Especialização em Medicina Intensiva Pediátrica e Neonatal na Faculdade Redentor – FACREDENTOR.

No ano de 2015 fui aprovada na prova de conhecimentos gerais em UTI Pediátrica onde obtive o Título de Especialista em Medicina Intensiva Pediátrica pela Associação de Medicina Intensiva Brasileira – AMIB.

Entre os anos de 2015 a 2016 cursei a Especialização em Preciptoria de Residência Médica no SUS “Metodologias Ativas: Aprendendo a aprender” pelo Hospital Sírio Libanês – Instituto de Ensino e Pesquisa HSL, Brasil.

Entre os anos de 2015 a 2017 desenvolvi o Mestrado Profissional em Ensino em Saúde na Faculdade de Medicina de Marília – FAMEMA.

Minha atuação profissional como médica Pedriatra iniciou em 2002 onde atuo atualmente nas Santas Casas de Cândido Mota e Assis. No Hospital Regional de Assis atuo em cuidados de recém-nascidos de alto risco.

No ano de 2018 inicie como docente da Faculdade de Medicina na Fundação Educacional do Município de Assis – FEMA aonde atuo na recepção de recém-nascido

e conduta de berçário.

Fui apresentada à profa Angélica em 2019 por intermédio do Dr Carlos Sartorão, e consequentemente conheci o Projeto Temático Diamter, Como pediatra, dentre as investigações proposta neste Temático, me despertou especial atenção as análises sobre repercussões no neo-nato.

No ano de 2020 iniciei o Doutorado na Faculdade de Medicina de Botucatu, Prorgama de Pós-Graduação em Tocoginecologia, UNESP, no Grupo de Pesquisa “Diabetes e Gravidez: Clínico e Experimental” e *Diamater Study Group*.

Durante os 4 anos de doutorado cursei 8 disciplinas (Anexo 1) e publiquei 11 artigos como membro do *Diamater Study Group* (Anexos 2-12). Em 2022 obtive os Títulos de Especialista em Pediatria (Anexo 13) e Medicina Intensiva Pediátrica (Anexo 14). Participei de 6 eventos científicos (15-20).

Cumprir a etapa até aqui, foi processo de muitos desafios; conciliei as atividades da pós-graduação, consultório, filhos, família e pessoais, contudo foi de extrema gratificação e com valioso amadurecimento.

Seção 3

Contextualização

Os Grupos de Pesquisa “Diabetes e Gravidez: Clínico e Experimental” e *Diamater Study Group* realizam pesquisas multicêntricas nacionais e internacionais relacionadas à gravidez complicada pelo diabete; e de forma intrincada investiga repercussões e resultados maternos e fetais, perinatais e neonatais dos descendentes destas mulheres (1-8). Nos últimos quase 50 anos, os dois grupos juntos realizaram estudos clínicos e pré-clínicos. Importantes lacunas do conhecimento foram preenchidas ao longo destes anos. Estes resultados interferiram direta e profundamente em diferentes condutas e manejos obstétricos e clínicos com benefício à mulher, ao feto e ao recém-nascido (9-16). A internacionalização das pesquisas se evidencia com estudos pré-clínicos, que tomaram importante proporção com estudos sobre as repercussões a curto e longo prazo do diabete no desenvolvimento fetal embrionário (17-24).

O *diabetes mellitus* gestacional (DMG) (25,26) está associado ao risco aumentado de complicações para o binômio materno-fetal durante a gravidez, bem como no período após o nascimento (27-29). A literatura tem reforçado que a hiperglicemia gestacional de intensidade variada, independentemente do diagnóstico de DMG, está envolvida na determinação do peso ao nascimento (30,31), macrossomia fetal, hipoglicemia neonatal, hiperinsulinismo fetal (28), aumento dos índices de mortalidade fetal e perinatal (1,13), malformações congênitas (32), prematuridade e síndrome do desconforto respiratório (28).

As evidências revelam que a obesidade pré-gestacional e o excesso de ganho de peso durante a gestação conferem maior resistência insulínica e desequilíbrio hormonal ao longo da gestação. Outro fator de risco é a inatividade física, que se associa a maior resistência insulínica e também aumento do peso corporal [33].

Diversos fatores de risco aumentam a probabilidade de desenvolvimento de diabetes gestacional, dentre estes, destaca-se o consumo alimentar inadequado, caracterizado por maiores fontes de alimentos ricas em carboidratos simples, o que oferece maior produção e disponibilidade de glicose plasmática [33].

Segundo estudos realizados pela Organização Pan-Americana da Saúde OPAS (2016) [34], nas últimas décadas a prevalência variou de 1 a 37,7%, com um percentual médio de 16,2%. Mundialmente são mais de 150.000 casos dessa doença. Porém, no Brasil, estima-se que a prevalência seja de aproximadamente 18%. Sendo que a maior causa de incidência do diabetes gestacional está associada à obesidade [35].

Aumento no índice de massa corporal pré-gravidez (pBMI) foi observado nos últimos anos, o que resultou em um aumento simultâneo na carga associada à obesidade de resultados maternos e infantis, como grandes para idade gestacional (GIG) [36,37].

A obesidade pré-gestacional aumentou o risco de diabetes mellitus gestacional (DMG), cesariana, macrossomia e gigante para idade gestacional (GIG) [38, 39], que foram importantes fatores de risco para morbidade materna e neonatal e mortalidade. Além disso, o DMG pode mediar associações entre pIMC e outras complicações maternas ou infantis. A associação entre obesidade e DMG é biologicamente plausível: um metabolismo intermediário materno anormal causado pela obesidade, em que uma combinação de aumento da resistência à insulina, lipídios séricos mais altos e diminuição dos níveis de adiponectina foi associada ao desenvolvimento de DMG [40]. Existem também explicações biológicas para GHP e macrossomia/GIG devido ao DMG: remodelação vascular e hiperinsulinemia e hiperglicemia induzidas pela resistência à insulina resultam em aumento da resistência arterial periférica e

aumento do volume de fluido corporal, o que pode levar à hipertensão arterial [41]. O aumento da resistência à insulina da mãe resulta em mais glicose sendo passada através da placenta para o feto. Um feto que absorve GIG [42].

No entanto, alguns estudos sugerem que as relações entre IMC e infantis podem variar de acordo com a raça ou etnia da mulher, e se as relações são as mesmas entre as mulheres brasileiras não está claro [43,44].

Impacto da COVID-19 na pesquisa clínica

Os estudos de acompanhamento em longo prazo são desafiadores, particularmente em relação ao custo e ao planejamento em longo prazo. Além disso, ao mesmo tempo em que se esforça para aperfeiçoar continuamente o controle glicêmico antes e durante a gravidez é, sem dúvida, importante melhorar os resultados a curto e longo prazo para as crianças de mães com DMG.

Neste sentido, a proposta inicial desta tese foi a “Quantificação e caracterização de exossomos do sangue periférico e do cordão umbilical de gestantes com diabetes mellitus gestacional como potencial biomarcador para a doença cardíaca congênita dos descendente”.

Inesperadamente a proposta clínica teve importante impacto negativo do Covid-19 no desenvolvimento da pesquisa. O efeito foi devastador para humanidade e refletiu no desenvolvimento das pesquisas e no acesso aos serviços de saúde. Isso afetou substancialmente nossa pesquisa clínica. Embora todo esforço tenha sido realizado pela equipe Diamater não foi possível cumprir com todo objetivo inicial proposto. Cumprimos o compromisso do cronograma com a coleta de dados maternos, contudo, não foi possível avaliar e acompanhar os neonatos. Depois de discussão com a equipe, tomamos a decisão de avaliar os desfechos neonatais sob a

ótica do momento do início do DMG e avaliar a obsiddade pré-gestacional e os desfechos neonatais mediados peolo DMG.

A presente Tese, inédita, integra de modo complementar o Projeto Temático Diamater com os objetivos a saber:

1) Analisar a associação entre o início precoce ou tardio do *Diabetes Mellitus* Gestacional com desfechos adversos neonatais

2) Analisar a obesidade pre-gestacional e resultados ddversos neonatais de curto prazo tendo o *Diabetes Mellitus* Gestacional como Mediador

Os resultados obtidos estão apresentados em 2 artigos:

1 - Association Between the Early or Late Onset of Gestational Diabetes Mellitus with Neonatal Adverse Outcomes: A Retrospective Cohort Study

2 - Prepregnancy Obesity and short-term Neonatal Adverse Outcomes with gestational diabetes mellitus as a mediator: A Multicenter Retrospective Cohort Study in a Brazilian Population

REFERÊNCIAS

1. Rudge M, Calderon I, Ramos M, Peraçoli J. Avaliação da vitalidade dos fetos de gestantes diabéticas - Análise cardiotocográfica. Rev Ginecol e Obs USP. 1994;5(4):201–7.
2. Honorio-França A, Calderon I, Ramos M, Rudge M. Repercussões fetais da hiperglicemia materna decorrente de lesão pancreática de testes repetidos à glicose na prenhez de ratas. Rev Ginecol e Obs São Paulo. 1995;17(691–695).
3. Rudge M, Calderon I, Ramos M, Rodrigues M. Diabetes and experimental pregnancy in rats: course of maternal blood glucose levels and its repercussions on the blood glucose levels and pancreas of newborn pups. Brazilian J Med Biol Res. 1995;28:219–25.
4. Berezowski A, Suetake H, Missiato M, Rudge M. Mortalidade materna: análise dos últimos dez anos do Centro Médico-Universitário de Botucatu-UNESP. Rev Bras Ginecol e Obs. 1995;17(10):1001–7.
5. Rudge M, Calderon I, Ramos M, Maestá I, Souza L, Peraçoli J.Perspectiva perinatal decorrente do rígido controle pré-natal em gestações complicadas pelo diabete. Rev Bras Ginecol e Obs. 1995;17(1):26–32.
6. Maestá I, Rudge M, Calderon I, Ramos M, Peraçoli J, Henry M. Effects of insulin therapy on the mother. The newborn and the placenta of diabetic rats. Acta Obstet Gynecol Scand. 1997;76(167):97.
7. Group E (Estudo C para P da P com AC. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. BJOG An Int J Obstet Gynaecol [Internet]. 1996 Jan;103(1):39–47. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.1996.tb09513.x
8. Rudge MVC, Calderon I de MP, Ramos MD, Abbade JF, Rugolo LMSS. Perinatal Outcome of Pregnancies Complicated by Diabetes and by Maternal Daily Hyperglycemia Not Related to Diabetes. Gynecol Obstet Invest [Internet]. 2000;50(2):108–12. Available from: https://www.karger.com/Article/FullText/10293
9. Mascaro MS, Calderon I de MP, Costa RA de A, Maestá I, Bossolan G, Rudge MVC. Cardiotocografia Anteparto e Prognóstico Perinatal em Gestações

Complicadas pelo Diabete: Influência do Controle Metabólico Materno. Rev Bras Ginecol e Obs [Internet]. 2002 Oct;24(9):593–9. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-72032002000900005&lng=pt&nrm=iso&tlng=pt

10. Mascaro MS, Calderon I de MP, Rudge MVC. Análise dos Métodos Biofísicos de Avaliação Fetal Anteparto, em Gestações Complicadas pelo Diabete. Fem (Federação Bras das Soc Ginecol e Obs. 2003;31(3):259–63.
11. Rudge MVC, Nero U, Calderon I, Lima R. Prospective study of the influence of the placental weight, volume and density of pregnant women with high blood presure or diabete in the perinatal outcome. Hypertens Pregnancy. 2004;23:47.
12. Volpato GT, Damasceno DC, Miranda MRF, Sabbag Filho D, Calderon I de MP, Rudge MVC. Mixture of vitamin C, hesperidin and piperidol exposure in pregnancy: maternal-fetal repercussions. Rev Bras Ciências Farm [Internet]. 2006 Mar;42(1):77–82. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-93322006000100008&lng=en&nrm=iso&tlng=en
13. Basso NA de S, Costa RAA, Magalhães CG, Rudge MVC, Calderon I de MP. Insulinoterapia, controle glicêmico materno e prognóstico perinatal: diferença entre o diabetes gestacional e o clínico. Rev Bras Ginecol e Obs [Internet]. 2007 May;29(5):253–9. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-72032007000500006&lng=pt&nrm=iso&tlng=pt
14. Rudge MVC, Maestá I, Rudge CVC, Campanini F, Gomes M, Moraes V, et al. Dois níveis hierarquizados de atenção ao parto no modelo de maternidade segura: resultado materno e do recém-nascido. Rev La Div Ciencias la Salud la Univ del Norte. 2007;22:56–7.
15. Rudge MVC, Lima CAB, Paulette TAL, Jovanovic L, Negrato CA, Rudge CVC, et al. Influence of Lower Cutoff Values for 100-G Oral Glucose Tolerance Test and Glycemic Profile for Identification of Pregnant Women at Excessive Fetal Growth Risk. Endocr Pract [Internet]. 2008 Sep;14(6):678–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1530891X20412790
16. Braga A, Maestá I, Michelin OC, Delmanto LRG, Consonni M, Rudge MVC, et al. Maternal and perinatal outcomes of first pregnancy after chemotherapy for

gestational trophoblastic neoplasia in Brazilian women. Gynecol Oncol [Internet]. 2009 Mar;112(3):568–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0090825808009359

17. Iessi IL, Bueno A, Sinzato YK, Taylor KN, Rudge MV, Damasceno DC. Evaluation of neonatally-induced mild diabetes in rats: Maternal and fetal repercussions. Diabetol Metab Syndr [Internet]. 2010 Dec 8;2(1):37. Available from: https://dmsjournal.biomedcentral.com/articles/10.1186/1758-5996-2-37.
18. Saito FH, Damasceno DC, Kempinas WG, Morceli G, Sinzato YK, Taylor KN, et al. Repercussions of mild diabetes on pregnancy in Wistar rats and on the fetal development. Diabetol Metab Syndr [Internet]. 2010 Dec 23;2(1):26. Available from: https://dmsjournal.biomedcentral.com/articles/10.1186/1758-5996-2-26
19 Moreli JB, Morceli G, De Luca AKC, Magalhães CG, Costa RAA, Damasceno DC, et al. Influence of Maternal Hyperglycemia on IL-10 and TNF-α Production: The Relationship with Perinatal Outcomes. J Clin Immunol [Internet]. 2012 Jun 30;32(3):604–10. Available from: http://link.springer.com/10.1007/s10875-011-9634-3
20. Sinzato YK, Volpato GT, Iessi IL, Bueno A, Calderon I de MP, Rudge MVC, et al. Neonatally Induced Mild Diabetes in Rats and Its Effect on Maternal, Placental, and Fetal Parameters. Exp Diabetes Res [Internet]. 2012;2012:1–7. Available from: http://www.hindawi.com/journals/jdr/2012/108163/
21. Damasceno DC, Sinzato YK, Bueno A, Netto AO, Dallaqua B, Gallego FQ, et al. Mild Diabetes Models and Their Maternal-Fetal Repercussions. J Diabetes Res [Internet]. 2013;2013:1–9. Available from: http://www.hindawi.com/journals/jdr/2013/473575/
22. Bueno A, Sinzato YK, Sudano MJ, Alvarenga F da CL e, Calderon I de MP, Rudge MVC, et al. Short and long-term repercussions of the experimental diabetes in embryofetal development. Diabetes Metab Res Rev [Internet]. 2014 Oct;30(7):575–81. Available from: https://onlinelibrary.wiley.com/doi/10.1002/dmrr.2521
23. Moura PMSS, Maestá I, Rugolo LMSS, Angulski LFRB, Caldeira AP, Peraçoli JC, et al. Risk factors for perinatal death in two different levels of care: a case–control study. Reprod Health [Internet]. 2014 Dec 30;11(1):11. Available from: https://reproductive-health-journal.biomedcentral.com/articles/10.1186/1742-

4755-11-11

24. Gelaleti RB, Damasceno DC, Santos DP, Calderon IMP, Rudge MVC. Increased DNA Damage is Related to Maternal Blood Glucose Levels in the Offspring of Women With Diabetes and Mild Gestational Hyperglycemia. Reprod Sci [Internet]. 2016 Mar 2;23(3):318–23. Available from: http://journals.sagepub.com/doi/10.1177/1933719115602766
25. de Sousa Basso NA, Morceli G, Costa R, Dias A, Rudge MVC, Calderon IMP. Validation of a symphysis-fundal height chart developed for pregnancy complicated by diabetes and hyperglycemia: an observational study. Reprod Health [Internet]. 2016 Dec 3;13(1):89. Available from: http://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-016-0202-4
26. Vernini JM, Moreli JB, Magalhães CG, Costa RAA, Rudge MVC, Calderon IMP. Maternal and fetal outcomes in pregnancies complicated by overweight and obesity. Reprod Health [Internet]. 2016 Dec 27;13(1):100. Available from: http://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-016-0206-0
27. Sirimarco MP, Guerra HM, Lisboa EG, Vernini JM, Cassetari BN, de Araujo Costa RA, et al. Diagnostic protocol for gestational diabetes mellitus (GDM) (IADPSG/ADA, 2011): influence on the occurrence of GDM and mild gestational hyperglycemia (MGH) and on the perinatal outcomes. Diabetol Metab Syndr [Internet]. 2017 Dec 3;9(1):2. Available from: http://dmsjournal.biomedcentral.com/articles/10.1186/s13098-016-0200-2
28. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2012 Jan 1;35(Supplement_1):S64–71. Available from: https://diabetesjournals.org/care/article/35/Supplement_1/S64/26301/Diagnosis-and-Classification-of-Diabetes-Mellitus
29. Weinert LS. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care [Internet]. 2010 Jul 1;33(7):e97–e97. Available from: https://diabetesjournals.org/care/article/33/7/e97/39395/International-Association-of-Diabetes-and
30. Katz L, Amorim M, Coutinho I, Santos LC. Análise Comparativa de Testes

Diagnósticos para Diabete Gestacional. Rev Bras Ginecol e Obs [Internet]. 2002 Sep;24(8). Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-72032002000800005&lng=pt&nrm=iso&tlng=pt

31. Rudge M, Calderon I, Ramos M, Suetake H, Peraçoli J. Diabetes investigation during pregnancy. Rev Bras Ginecol e Obs. 1996;18(1):21–8.
32. The HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcomes. N Engl J Med [Internet]. 2008 May 8;358(19):1991–2002. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0707943
33. OPAS. *Diabetes Mellitus Rastreamento E Diagnóstico.* Vol 1.; 2016. http://www.diabetes.org.br/profissionais/images/pdf/diabetes-gestacional-relatorio.pdf%0Ahttp://iris.paho.org/xmlui/bitstream/handle/123456789/34278/9788579671180-por.pdf?sequence=1
34. Wang MC, Freaney PM, Perak AM, Greenland P, Lloyd-Jones DM, Grobman WA, et al. Trends in prepregnancy obesity and association with adverse pregnancy outcomes in the United States, 2013 to 2018. J Am Heart Assoc. 2021; 10 (Epub 2021/08/26): e020717 Available from: https://doi.org/10.1161/jaha.120.020717
35. Wang L, Zhou B, Zhao Z, Yang L, Zhang, Jiang Y, et al. Body-mass index and obesity in urban and rural China: findings from consecutive nationally representative surveys during 2004–18. Lancet. 2021; 398 (Epub 2021/07/05): 53-63. Available from: https://doi.org/10.1016/s0140-6736(21)00798-4
36. Lewandowska M. Maternal obesity and risk of low birth weight, fetal growth restriction, and macrosomia: multiple analyses.Nutrients. 2021; 13 (Epub 2021/05/01). Available from: https://doi.org/10.3390/nu13041213
37. Vats H, Saxena R, Sachdeva MP, Walia GK, Gupta V. Impact of maternal pre-pregnancy body mass index on maternal, fetal and neonatal adverse outcomes in the worldwide populations: A systematic review and meta-analysis.Obes Res Clin Pract. 2021; 15 (Epub 2021/11/17): 536-545. Available from: https://doi.org/10.1016/j.orcp.2021.10.005
38. Han Z, Mulla S, Beyene J, Liao G, McDonald SD. Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-

analyses. Int J Epidemiol. 2011; 40 (Epub 2010/11/26): 65-101. Available from: https://doi.org/10.1093/ije/dyq195

39. Li Z, Kim R, Vollmer S, Subramanian SV. Factors associated with child stunting, wasting, and underweight in 35 low- and middle-income countries. JAMA Netw Open. 2020; 3 (Epub 2020/04/23): e203386. Available from:https://doi.org/10.1001/jamanetworkopen.2020.3386
40. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese Biomed Pharmacother. 2021; 137 (Epub 2021/02/10)https://doi.org/10.1016/j.biopha.2021.111315
41. Ohishi M. Hypertension with diabetes mellitus: physiology and pathology. Hypertens Res. 2018; 41 (Epub 2018/03/21): 389-393. Available from: https://doi.org/10.1038/s41440-018-0034-4
42. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab. 2015; 66 (Epub 2015/06/06): 14-20. Available from: https://doi.org/10.1159/000371628
43. Lin X, Aris IM, Tint MT, Soh SE, Godfrey KM, Yeo GS, et al. Ethnic differences in effects of maternal pre-pregnancy and pregnancy adiposity on offspring size and adiposity. J Clin Endocrinol Metab. 2015; 100 (Epub 2015/07/23): 3641-3650. Available from: https://doi.org/10.1210/jc.2015-1728
44. Read SH, Rosella LC, Berger H, Feig DS, Fleming K, Ray JG, et al. BMI and risk of gestational diabetes among women of South Asian and Chinese ethnicity: a population-based study. Diabetologia. 2021; 64 (Epub 2021/01/25): 805-813. Available from: https://doi.org/10.1007/s00125-020-05356-5

Seção 4

Artigos

Artigo 1

Seção redigida como Artigo Original de acordo com as normas de publicação da revista Plos One para a qual está em processo de submissão.

Qualis A1 MED III – FI: 3,124 https://journals.plos.org/plosone/s/submission-guidelines.

Association Between the Early or Late Onset of Gestational Diabetes Mellitus with Neonatal Adverse Outcomes: A Retrospective Cohort Study

Fabiana Vieira Duarte de Souza Reis[1,2‡], Carlos Izaias Sartorao-Filho[1,2‡], Luis Sobrevia[1,3*], Caroline Baldini Prudencio[1,4*], Bruna Bologna[1*], Luana Favaro Iamundo[1*], Adriely Magyori[1*], Luis Takano[1*], Raissa Escandiussi Avramidis[1*], Rafael Guilen de Oliveira[1*], Marilza Vieira Cunha Rudge[1•], Angelica Mercia Pascon Barbosa[1,4 •], Diamater Study Group[#]

‡ FVDSR and CISF are the first authors of this work.
*These authors contributed equally to this work.
• MVCR and AMPB are the last authors of this work.
Diamater Study Group is provided in the Acknowledgments

[1] São Paulo State University (Unesp), Postgraduate Program on Tocogynecology, Botucatu Medical School, Botucatu, Brazil;
[2] Educational Foundation of the Municipality of Assis, FEMA, Medical School, Assis, Sao Paulo, Brazil.
[3] The University of Queensland, NHMRC Centre for Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, Brisbane, Australia.
[4] Department of Physiotherapy and Occupational Therapy, Universidade Estadual Paulista (UNESP), Brazil.

#Diamater Study Group: Rudge MVC, Barbosa AMP, Calderon IMP, Souza FP, Lehana T, Graeff CFO, Magalhães CG, Costa RAA, Lima SAM, Rodrigues MRK, Felisbino SL, Barbosa WF, Campos FJ, Bossolan G, Corrente JE, Nunes HRC, Abbade JF, Rossignoli PS, Pedroni CR, Atallah ÁN, Jármy-Di Bella ZI, Uchôa SMM, Duarte MAH, Mareco EA, Sakalem ME, Martinho NM, Bussaneli DG, Orlandi MIG, Pascon C, Dangió TD, Rudge CVC, Piculo F, Prata GM, Avramidis RE, Carvalho CNF, Magyori ABM, Nava GTA, Caldeirão TCD, Shetty RHL, Reyes DRA, Alves FCB, Marcondes JPC, Takemoto MLS, Prudencio CB, Pinheiro FA, Sartorao Filho CI, Quiroz SBCV, Pascon T, Nunes SK, Catinelli BB, Reis FVDS, Oliveira RG, Costa SMB, Menezes MO, Santos NJ, Enriquez EMA, Takano L, Carr AM, Garcia GA, Iamundo LF, Bassin HCM, Barbosa VP, Jacomin M, Silva AJB, Lourenço IO, Marostica de Sá J, Caruso IP, Rasmussen LT, Nogueira VKC, Ribeiro-Paes JT, França DCH, Bastos HVM, Heliodoro MLA, Kuroda MN, Carvalho, H.L.

* Corresponding Author: Angélica Mércia Pascon Barbosa; Botucatu Medical School, Univ Estadual Paulista (UNESP), Department of Gynecology and Obstetrics, Botucatu, Brazil. Email: angelicapascon@gmail.com.
Financial disclaimer: Supported by Sao Paulo Research Foundation protocol number 2016/01743-5 and 2021/10665-6. Brazilian Federal Agency for Support and Evaluation of graduate Education/SD (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES/DS). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background: The significance of timing in diagnosing hyperglycemia during pregnancy and its association with adverse outcomes for the newborn is controversial. The literature has been evolving in standardizing gestational diabetes mellitus (GDM) diagnosis and terminology. we aimed to investigate the association between early-onset GDM and adverse outcomes in newborns and neonates, comparing it with the late-onset GDM model.

Methods: It was a retrospective cohort study at the Perinatal Diabetes Research Center-Assis affiliated nucleus from Botucatu Medical School-UNESP, Brazil, between 2016- 2019. The group composition were, early-onset concerning participants with fasting glucose ≥92 mg/dL and <126 mg/dL before 20 weeks of gestation or late-onset participants with negative first-trimester screening and positive 75g-OGTT at 24-28 weeks. The maternal baseline characteristics included: pre-pregnancy body mass index (BMI; Kg/m^2); the pregnancy weight gain (Kg) calculated by the difference between final pregnancy weight (36 gestational weeks or more) and pre-pregnancy maternal weight and classified according to the pre-pregnancy BMI (8). In addition, the perinatal outcomes evaluated in this study were: gestational age (GA), birth weight (BW), and BW status according to GA as adequate, large or small, Apgar scores at the first and 5th minutes.

Results: Eight hundred eighty pregnant women were selected, 203 (23.07%) presenting GDM were eligible from December 2016 to December 2021. According to the timing onset of GDM, 89 (43.84%) were in the early-onset group and 114 (56.16%) in the late-onset group. the FPG values at the first trimester were higher in the early-onset group. The 75grams-OGTT values were higher in the late-onset group. The final BMI was higher in the late-onset group. A univariate linear regression was performed in order to determining relation between late-onset according different outcomes (Table 3), no significant relation was detected.

Conclusions: Pregnants with early-onset of GDM showed higher BMI during pregnancy, but there was no difference between the early or late-onset of GDM concerning neonatal adverser outcomes.

Keywords: Gestational diabetes mellitus, newborn, adverse complications.

Introduction

The significance of timing in diagnosing hyperglycemia during pregnancy and its association with adverse outcomes for the newborn is controversial (1). The literature has been evolving in standardizing gestational diabetes mellitus (GDM) diagnosis and terminology (2). Over the past years, studies have demonstrated that the GDM diagnosis strategy considers either first-trimester hyperglycemia or second-trimester 75g oral glucose tolerance test (75g-OGTT) screening and diagnosis (3,4). Currently, there is no consensus for the preferred testing approach or diagnostic glycemic thresholds for early GDM (5).

Recognizing the pregnancy risk factors related to the timing of GDM diagnosis may have a positive impact on the health of both the fetus and the newborn, mainly because there are divergences for in GDM screening and diagnosis protocols (1). However, insufficient data exist reporting the extent to which the first-trimester recognition of hyperglycemia or the conventional 24-28 weeks of gestation diabetes screening during pregnancy lead to unequal newborn adverse outcomes (6).

Therefore, we aimed to investigate the association between early-onset GDM and adverse outcomes in newborns and neonates, comparing it with the late-onset GDM model. We hypothesize that the early onset of hyperglycemia during pregnancy may lead to worse neonatal outcomes.

Method

It is a retrospective cohort study at the Perinatal Diabetes Research Center-Assis affiliated nucleus from Botucatu Medical School-UNESP, Brazil, between 2016-2019. Pregnant women were followed during pregnancy and the neonatal period. The original study design was based on the primary goal of developing a predictive model for postpartum UI in women who had had GDM during their pregnancy (7). This ongoing study protocol includes all pregnant women who receive prenatal care in the obstetric and maternal-fetal medicine clinics at PDRC. We decided to retrospectively investigate the newborn outcomes in the GDM group in this cohort according to the onset period of hyperglycemia.

The current study is an ancillary analysis of GDM and the postpartum maternal and neonatal outcome of an ongoing cohort study entitled "Diamater" from PDRC,

financially supported by FAPESP (São Paulo Research Foundation-São Paulo - Brazil). (7) Diamater's study was reviewed and approved by the Institutional Review Board -Botucatu (Letter of approval 1.048.565 issued on Apr 28, 2015) and by the Institutional Review Board (IRB-Assis number 1.716.895). Before enrollment, each woman was fully explained about the study and signed an informed consent form.

The inclusion criteria: patients from the antenatal care service submitted to the GDM screening and diagnosis from WHO guidelines. The exclusion criteria: multiple pregnancies, fetal loss before 22 weeks of gestation, stillbirth, loss to follow-up before collecting data during the pregnancy or neonatal period, severe maternal or fetal comorbidities during pregnancy or perinatal period and not related to the GDM status, pre-pregnancy DM. Patient follow-up: According to WHO guidelines, all women included started prenatal care before 20 weeks of gestation and underwent a universal screening with fasting glucose (FG) in the first prenatal visit, and for those with negative screening, the 75g-OGTT in the second trimester (24-28 weeks of gestation), except those previously submitted to bariatric surgery. For this specific group, the screening was made with FG in the second trimester.

The group composition were:

Early-onset: Patients with FG ≥92 mg/dL and <126 mg/dL before 20 weeks of gestation.

Later-onset: Patients with negative first-trimester screening and positive 75g-OGTT at 24-28 weeks.

The outcome of interest: pre-term or term birth, fetal weight in grams, mode of delivery, the fetal weight adequacy for the gestational age at the birth, the Apgar score at first and the 5th minute, the Apgar Score less than 7; the adverse outcomes in the newborn requiring hospitalization in the first 28 days of the childbirth. Women in this study received prenatal care in our hospital's obstetric and maternal-fetal medicine clinics. Pregnant with GDM received nutritional counseling through a centralized office where they were given instructions regarding their diet and recommended weight gain based on their pre-pregnancy BMI. Self-monitoring of plasma glucose was recommended four times daily, and targets for plasma glucose included a fasting value of less than 95 mg/dL and two-hour post-meal values of less than 130 mg/dL. In addition, incomplete or missing antenatal and perinatal data were recovered from the

institutional medical record.

The maternal baseline characteristics included: age, parity, Caucasian or non-Caucasian ethnicity, higher or non-higher educational level; previous bariatric surgery, physical activity during pregnancy (considered positive when more than 150 minutes per week during the gestational period); pre-pregnancy body mass index (BMI; Kg/m2); the pregnancy weight gain (Kg) calculated by the difference between final pregnancy weight (36 gestational weeks or more) and pre-pregnancy maternal weight and classified according to the pre-pregnancy BMI (8). In addition, the perinatal outcomes evaluated in this study were: gestational age (GA), birth weight (BW), and BW status according to GA as adequate, large or small, Apgar scores at the first and 5th minute; presence or not of neonatal complications until 28 days. All reference parameters were used following the clinical protocol of the local perinatal unit.

The outcome of interest was the gestational age at the delivery, newborn weight, the adequacy of newborn weight according to the gestational age, the Apgar score at 1st and the 5th minute, the Apgar score less than seven at the 5th minute, and the necessity of neonate hospitalization during the first 28 days.

For the sample size, we assumed that the risk of an outcome event equal to 0.20 among the group with a prior diagnosis, increased risk of an event outcome to 0.35 in the group with a late diagnosis, ratio of the number of participants in the group with no and with previous obesity equal to 1:1, type I and II errors equal to 0.05 and 0.20, respectively, and the presence of a maximum of three other variables in the adjusted models, and it was estimated that 170 participants per group were necessary.

Confound variables considered: maternal age, parity, previous vaginal or C-section, ethnicity, educational level, physical activities during and after pregnancy, maternal weight, previous bariatric surgery, pre-pregnancy BMI, and final BMI at delivery. Data collection procedures and statistical analysis: According to the predefined period and the inclusion and exclusion criteria, data were input into a specific software spreadsheet, audited, and consistency checked.

The Mann-Whitney test for numerical variables and the Chi-square test for categorical variables were used to compare groups according to the outcomes. Univariate logistic regression was conducted to estimate the relative risks (RR) and their respective 95% CI for the newborn outcomes according to the clinical and

demographic characteristics. Finally, multivariate regression analysis was performed to identify which factors were independently associated with the newborn adverse outcomes and estimate the adjusted RR (adj RR).The variables were individually inserted, and those with a P-value under .05 were maintained. Lost to follow-up occurred entirely at random and were excluded. In addition, the missing data were sparse and occurred randomly, and the imputation method treated the few cases statistically. The SPSS version 23.0 (IBM, New York) was used for analysis. All statistical significances were two-sided and accepted at P<.05.

Results

Eight hundred eighty pregnant women were selected, 203 (23.07%) presenting GDM were eligible from December 2016 to December 2021. According to the timing onset of GDM, 89 (43.84%) were in the early-onset group and 114 (56.16%) in the late-onset group. Table 1 represents the baseline characteristics according to the period of GDM onset. Table 2 demonstrates the categorical baseline variables.

According with the results disposed in table 1, the FPG values at the first trimester were higher in the early-onset group. The 75grams-OGTT values were higher in the late-onset group. The final BMI was higher in the late-onset group.

According to table 2, the baseline characteristics did not differ between groups the timing of onset GDM in all studied variables.

Table 1. Baseline characteristics according to the timing GDM onset.

Variables	Early-onset (n=89) Med (IQR)	Late-onset (n=114) Med (IQR)	*p**
Number of gestations	2.0 (1.0-2.0)	2.0 (1.0-2.0)	*.196*
Number of vaginal delivery	0.0 (0.0-0.0)	0.0 (0.0-0.0)	*.996*
Number of C-sections	0.0 (0.0-1.0)	0.0 (0.0-1.0)	*.496*
Maternal age (years)	30.0 (26.0-34.5)	29.5 (25.0-33.3)	*.609*
First trimester FPG (mg/dL)	95.0 (93.0-97.0)	85.0 (80.0-89.0)	*.000*
75g OGTT (mg/dL) – fasting	83.0 (78.0-86.5)	91.7 (80.0-96.0)	*.000*
75g OGTT (mg/dL) - 1h	134.0 (113.0-150.0)	167.5 (144.0-184.0)	*.000*
75g OGTT (mg/dL) - 2h	117.0 (100.0-130.0)	140.0 (121.0-159.0)	*.000*
BMI (kg/m^2) pre-pregnancy	27.5 (24.1-32.1)	26.5 (23.8-29.7)	*.202*
BMI (kg/m^2) gestation	31.5 (28.1-36.8)	30.0 (27.4-33.7)	*.036*
Weeks of gestation	38.1 (37.3-38.9)	38.2 (37.4-38.9)	*.732*
Newborn weight at birth (grams)	3170 (2830-3490)	3150 (2855-3400)	*.728*
1-minute Apgar score	9.0 (9.0-9.0)	9.0 (9.0-9.0)	*.765*
5-minutes Apgar score	9.0 (9.0-10.0)	9.0 (9.0-10.0)	*.182*

n: sample; g: mg/dL: miligrams per deciliter; FPG: fasting plasma glucose; 75g OGTT: 75 grams oral glucose tolerance test; BMI: Body Mass Index; Data are presented in: Med (IQR): Median (interquartile range); p-values are based on *Mann–Whitney U. Significance $p < 0.05$.

Table 2. Baseline characteristics according to the GDM onset.

Variables	Early-onset (n=89) n (%)	Late-onset (n=114) n (%)	*p**
Non-Caucasian	14 (15.7%)	13 (11.4%)	*.409*
Higher educational level	55 (61.8%)	73 (64%)	*.771*
Previous bariatric surgery	0 (0%)	1 (0.9%)	*1.000*
Obesity pre-pregnancy	30 (33.7%)	26 (22.8%)	*.113*
Pre-term birth	12 (13.5%)	12 (10.5%)	*.662*
C-section	88 (98.9%)	112 (98.2%)	*1.000*
Fetal growth restriction	7 (7.9%)	8 (7%)	*1.000*
Adverse neonatal outcome	10 (11.2%)	12 (10.5%)	*1.000*
5-minutes Apgar < 7	1 (1.1%)	3 (2.6%)	*.633*

Data are presented in n(%): absolute frequency (n) and percentage (%); p-values are based on *Chi-square test. Significance $p < 0.05$.

A univariate linear regression was performed in order to determining relation between late-onset according different outcomes (Table 3), no significant relation was detected. It indicates that there is no difference regarding mother outcomes as gestational age on delivery, weight gain, c-section between the participants with late or early-onset of GDM. The same occurred related with newborn outcomes as weight on birth, apgar >7, pre-term birth and fetal growth restriction.

Table 3. Univariate linear regression according different models, regarding gestational age, weight gain, weight on birth and Apgar >7.

Variables	*B*	**95% CI**	***p****
	Investigation Model (Gestational Age)		
Late-onset GDM	-0.16	(-0.62-0.30)	*.502*
	Investigation Model (Weight Gain)		
Late-onset GDM	-22.18	(-157.46-113.09)	*.748*
	Investigation Model (Weight on birth)		
Late-onset GDM	-22.18	(-157.46-113.09)	*.748*
	Investigation Model (Apgar >7)		
Late-onset GDM	8.16	(0.16-417.97)	.296
	Investigation Model (Pre-term birth)		
Late-onset GDM	0.81	(0.36-1.85)	.617
	Investigation Model (C-section birth)		
Late-onset GDM	1.00	(0.75-1.33)	.976
	Investigation Model (Fetal growth restriction)		
Late-onset GDM	.94	(0.33-2.62)	.899

GDM: Gestational Diabeltes Mellitus; BMI: Body Mass Index; Data are presented in: β: Standardized regression Coefficient; SE: Standard error; 95% CI: 95% Coeficient Interval; p-values are based on *Univariate linear regression significance for investigation model $p < 0.2$.

Discussion

Our findings indicated that from the 203 GDM women, 43.84% were screened positive in the early-onset group and 56.16% in the late-onset group. The results are consonant with other similar studies. The GDM incidence in HAPO study cohort ranged from 9.3% to 25.5% depending on study site (9).

Early-onset of hyperglycemia during pregnancy refers to the occurrence of elevated blood glucose levels, typically indicative of gestational diabetes mellitus

(GDM), in the early stages of pregnancy, usually during the first trimester. In this context, "early-onset" suggests that the condition develops relatively early in the course of pregnancy, as opposed to later stages, such as the second or third trimester.

We observed in the early-onset GDM, a significant higher difference in the BMI calculated at the end of the prenatal care, compared with the late-onset group. We did not find diferences among the other variables studied. The relationship between early-onset GDM and obesity is complex. Obesity is a known risk factor for developing GDM, and individuals who are obese before becoming pregnant are at a higher risk of developing GDM during pregnancy. In fact, Weiss et al reported that the GDM risk was increased 3 to 4 fold in women with obesity (10).

Pregnant individuals with obesity are at a higher risk of experiencing complications during pregnancy and childbirth. These complications can sometimes affect the newborn's immediate health and Apgar score. For example, obese individuals are more likely to have babies with macrosomia (excessive birth weight), which can affect muscle tone and respiration in the newborn. Although our findings did not showed different between groups according timing of GDM diagnosis, it is important to consider this information for further studies.

It is essential to highlight the new emphasis on early GDM diagnosis to prevent perinatal morbidity and mortality and identify potential long-term maternal complications. Our results evokes the importance of the concern that GDM is a clinical entity starting before pregnancy, and the crutial early-onset diagnosis may be critical for reducing adverse outcomes.

Limitations include reduced precision due to the sampling design and implementation. We also assume that did not controlled how the disease and exposure variables were ascertained and recorded precisely in the pregnancy-span.

Although GDM is an entity with high prevalence worldwide and recognized association with adverse neonatal period, we can not fully generalize the results for different populations regarding ethnicity, socioeconomic status, parity, mode of delivery, and the plurality of variables influencing the outcome. No obstant, besides our parochial results, the presented results are critical to evoke new studies and discussions envolving the screening, diagnosis and treatment for the GDM during the entire pregnancy span.

Conclusion

Pregnant with early-onset of GDM showed higher BMI during pregnancy, but there was no difference between the early or late-onset of GDM concerning neonatal adverse outcomes.

Acknowledgments:

We are very thankful for the support from the Diamater Study Group.

Author contributions

Conceptualization: Rudge MVC, Barbosa AMP, and Calderon IMP Data curation: Sartorao Filho CI; Pinheiro FA; Takano L; Prudencio CB Formal analysis: Sartorao Filho CI, Hallur RLS, Supervision: Rudge MVC, Barbosa AMP, Calderon IMP Writing – original draft: Sartorao Filho CI, Calderon IMC; Nunes SK Writing – review & editing: Rudge MVC, Calderon IMP, Barbosa AMP, Hallur RLS. Diamater Study Group – data collection and analysis.

Conflicts of Interest Statement: The authors report no conflicts of interest.

References

1. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev. 2022 Sep;43(5):763–93.
2. González-González NL, González-Dávila E, Megía A, Pintado P, Vega B, Padrón E, et al. The NDDG criteria versus the IADPSG or the ADA criteria for diagnosing early-onset gestational diabetes mellitus or abnormal glucose tolerance. Int J Gynecol Obstet. 2023;160(3):906–14.
3. Djelmis J, Pavić M, Mulliqi Kotori V, Pavlić Renar I, Ivanisevic M, Oreskovic S. Prevalence of gestational diabetes mellitus according to IADPSG and NICE criteria. Int J Gynecol Obstet. 2016 Dec;135(3):250–4.
4. Erjavec K, Poljičanin T, Matijević R. Impact of the Implementation of New WHO Diagnostic Criteria for Gestational Diabetes Mellitus on Prevalence and Perinatal Outcomes: A Population-Based Study. J Pregnancy. 2016;2016:1–6.
5. Immanuel J, Simmons D. Screening and Treatment for Early-Onset Gestational Diabetes Mellitus: a Systematic Review and Meta-analysis. Curr Diab Rep. 2017

Oct;17(11):115.

6. Most OL, Kim JH, Arslan AA, Klauser C. Maternal and neonatal outcomes in early glucose tolerance testing in an obstetric population in New York city. J Perinat Med. 2009 Mar;37(2):114–7.

7. Rudge MVC, Souza FP, Abbade JF, Hallur RLS, Marcondes JPC, Piculo F, et al. Study protocol to investigate biomolecular muscle profile as predictors of long-term urinary incontinence in women with gestational diabetes mellitus. BMC Pregnancy Childbirth [Internet]. 2020 Dec 19;20(1):117. Available from: https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-020-2749-x

8. Martin KE, Grivell RM, Yelland LN, Dodd JM. The influence of maternal BMI and gestational diabetes on pregnancy outcome. Diabetes Res Clin Pract. 2015 Jun;108(3):508–13.

9. Sacks DA, Coustan DR, Hadden DR, Hod M, Maresh M, Oats JJN, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care. 2012 Mar;35(3):526–8.

10. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. Am J Obstet Gynecol. 2004 Apr;190(4):1091–7.

Artigo 2

Seção redigida como Artigo Original de acordo com as normas de publicação da revista Neurourology and Urodynamics para a qual está em processo de submissão.

Qualis A1 MED III – FI: 2,037 https://onlinelibrary.wiley.com/journal/15206777.

Prepregnancy Obesity and short-term Neonatal Adverse Outcomes with gestational diabetes mellitus as a mediator: A Multicenter Retrospective Cohort Study in a Brazilian Population

Fabiana Vieira Duarte de Souza Reis[1,2‡], Carlos Izaias Sartorao-Filho[1,2‡], Luis Sobrevia[1,3*], Caroline Baldini Prudencio[1*], Bruna Bologna[1*], Luana Favaro Iamundo[1*], Adriely Magyori[1*], Luis Takano[1*], Raissa Escandiussi Avramidis[1*], Rafael Guilen de Oliveira[1*], Marilza Vieira Cunha Rudge[1•], Angélica Mercia Pascon Barbosa[1,4 •], Diamater Study Group[#]

[‡] FVDR and CISF are the first authors of this work.
*These authors contributed equally to this work.
• MVCR and AMPB are the last authors of this work.

[1]São Paulo State University (UNESP), Botucatu Medical School, Department of Gynecology and Obstetrics, Botucatu, São Paulo, Brazil.
[2] Educational Foundation of the Municipality of Assis (FEMA), Medical School, Assis, Brazil.
[3] Cellular and Molecular Physiology Laboratory (CMPL), Department of Obstetrician, Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
[4] São Paulo State University (UNESP), School of Philosophy and Sciences, Department of Physiotherapy and Occupational Therapy, Marília, São Paulo, Brazil.

Corresponding Author: Angélica Mércia Pascon Barbosa
Department of Gynecology and Obstetrics, Botucatu Medical School, UNESP
Distrito de Rubião Jr s/n 18.618-000, Botucatu, São Paulo, Brazil
Phone: +55 (14) 3880-1631, email: angelica.pascon@unesp.br
Data Availability Statement: All relevant data are within the paper and its Supporting Information files.
Funding: The authors received a grant from Fapesp 2016/01743-5
Competing interests: The authors declare no competing interests.

[#] Membership of the Diamater Research Group is provided in the Acknowledgments.
[#] Rudge MVC, Barbosa AMP, Calderon IMP, Souza FP, Lehana T, Graeff CFO, Payao SLM, Rodrigues MRK, Felisbino SL, Barbosa WF, Bossolan G, Corrente JE, Nunes HRC, Abbade JF, Rossignoli PS, Pedroni CR, Jármy-Di Bella ZI, Uchôa SMM, Duarte MAH, Mareco EA, Sakalem ME, Martinho NM, Bussaneli DG, Orlandi MIG, Pascon C, Dangió TD, Rudge CVC, Piculo F, Prata GM, Avramidis RE, Carvalho CNF, Magyori ABM, Nava GTA, Caldeirão TCD, Shetty RHL, Reyes DRA, Alves FCB, Marcondes JPC, Takemoto MLS, Prudencio CB, Pinheiro FA, Sartorao Filho CI, Quiroz SBCV, Pascon T, Nunes SK, Catinelli BB, Reis FVDS, Oliveira RG, Costa SMB, Menezes MO, Santos NJ, Enriquez EMA, Takano L, Carr AM, Garcia GA, Iamundo LF, Bassin HCM, Barbosa VP, Jacomin M, Silva AJB, Lourenço IO, Marostica de Sá J, Caruso IP, Rasmussen LT, Nogueira VKC, Ribeiro-Paes JT, França DCH, Bastos HVM, Heliodoro MLA, Kuroda MN, Carvalho H.L., Mosele FC, Oliveira MA, Chaves MR, Laverde EA, de Oliveira BS, Ciconi TCT.

Abstract

Background: We aimed to analyze the association of prepregnancy obesity diagnosis with short-term neonatal outcomes, with gestational diabetes as a mediator, in the population of pregnant women **Methods:** We performed a retrospective study. The groups were stratified according pre-pregnancy weight which was reported by the pregnant woman during the interview, the pregnant which reported BMI ≥ 30 kg/m^2 were considered obese and the others were considered non-obese. The perinatal outcomes evaluated in this study were: gestational age at birth (GA), neonate weight in grams which was stratified according to GA as adequate or inadequate, apgar scores at the first and 5th minute, stratified as: score at the fifth minute below seven; presence or not of neonatal complications related to GDM until 28 days. The short-term neonatal adverse outcomes were established as the occurrence of admission to the neonatal intensive care unit until 28 days of childbirth, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, abnormal Apgar score at 5 min, neonatal death, neonatal sepsis, and/or birth trauma **Results:** 886 pregnant women were eligible from December 2016 to December 2021. According to the pre-pregnancy obesity status, 709 (80%) were allocated as non-prepregancy obesity and 177 (20%) in the prepregancy obesity group. There was a softened effect of prepregnancy obesity, with the risk of short-term neonatal complication or 5th minute Apgar score < 7 being 4% higher among those with prepregnancy obesity. Furthermore, the results expose a mediating effect of GDM during the pregnancy, with the risk of a short-term neonatal complication or 5th minute Apgar score < 7 being 5% higher in the presence of GDM. **Conclusions:** There is a necessity of prepregnancy counseling to consider overweight and obesity as a crucial risk factors for pregnancy and neonatal complications and, mainly, to propose strategies for women in their reproductive age period to achieve an appropriate BMI prepregnancy.

Keywords: Obesity, Newborn, newborn diseases, gestational dibetes.

Introduction

Obesity is the abnormal or excessive fat accumulation that presents a health risk. A person with a body mass index (BMI) ≥ 30 is considered obese. (1) Obesity is a severe health problem, especially among young women who want to get pregnant. This is because the incidence of obesity in the population is high, as is the impact on adverse health maternal and offspring outcomes. (2,3)

In addition, obesity contributes to a series of morbidities for women during pregnancy, childbirth, and their offspring. The association of prepregnancy obesity with the development and diagnosis of gestational diabetes is common. Both entities have a recognized epidemiological correlation and pathophysiological mechanisms in common. (4)

The objective of our study is to analyze the association of prepregnancy obesity diagnosis with short-term neonatal outcomes, with gestational diabetes as a mediator, in the population of pregnant women. We hypothesize that prepregnancy obesity women who develop gestational diabetes mellitus have more remarkable short-term adverse neonatal outcomes.

Method

We performed a retrospective study at the Perinatal Diabetes Research Center-Assis affiliated nucleus from Botucatu Medical School-UNESP, Brazil, between 2016-2019. We included all pregnant women who received prenatal care at the Assis City affiliated nucleus. The inclusion criteria: patients from the antenatal care service submitted to the GDM screening and diagnosis from WHO guidelines. (5,6)

The current study is an ancillary analysis of GDM and the postpartum UI outcome of an ongoing cohort study entitled "Diamater" from PDRC, financially

supported by FAPESP (São Paulo Research Foundation-São Paulo - Brazil). (7) The study was reviewed and approved by the Institutional Review Board -Botucatu (Letter of approval 1.048.565 issued on Apr 28, 2015) and by the Institutional Review Board (IRB-Assis number 1.716.895).

The exclusion criteria are multifetal pregnancy, fetal loss before 22 weeks of gestation, stillbirth, loss to follow-up before collecting data during the pregnancy and 28 days after delivery, and prepregnancy Diabetes Mellitus.

The groups were stratified according pre-pregnancy weight which was reported by the pregnant woman during the interview, the pregnant which reported BMI ≥ 30 kg/m^2 were considered obese and the others were considered non-obese. The maternal baseline characteristics included: age at the first antenatal care visit, parity, caucasian or non-Caucasian ethnicity, higher or non-higher educational level, previous bariatric surgery, and the pregnancy wheigh gain calculated by the difference between final pregnancy and prepregnancy wheigh. In addition, the mode of delivery vaginal or C-section.

In addition to the pregnant characteristics the GDM classification was performed according to recommended by the American Diabetes Association (8) by the 75g oral glycemic tolerance test (75g-Oral glucose tolerance test (OGTT) at 24-30 weeks of gestation. The presence of GDM were confirmed if they presented fasting glycemic levels ≥92 mg/dL or 1 hour ≥180 mg/dL or 2 hours ≥153 mg/dL.

The perinatal outcomes evaluated in this study were: gestational age at birth (GA), neonate weight in grams which was stratified according to GA as adequate or inadequate, apgar scores at the first and 5th minute, stratified as: score at the fifth minute below seven; presence or not of neonatal complications related to GDM until 28 days. The short-term neonatal adverse outcomes were established as the

occurrence of admission to the neonatal intensive care unit until 28 days of childbirth, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, abnormal Apgar score at 5 min, neonatal death, neonatal sepsis, and/or birth trauma

Pregnant women received nutritional counseling regarding their diet and recommended weight gain based on their BMI. For the GDM group, self-monitoring of plasma glucose was recommended four times daily, and targets for plasma glucose included a fasting value of less than 95 mg/dL and two-hour post-meal values of less than 130 mg/dL.

Sample size estimation: we assumed the risk of an outcome event equal to 0.20 among the group of previously non-obese women, an increase in the risk of an outcome event to 0.30 in the group of pregnant women with prepregnancy obesity, the ratio of the number of participants in the non-obesity group and the obesity group equal to 1:0.2; type I and II errors equal to 0.05 and 0.20, respectively, and the presence of a maximum of three other variables in the adjusted models, it was estimated that 700 participants were needed in the group without obesity and 160 participants in the obesity group.

The SPSS version 23.0 (IBM, New York) was used for analysis. The Mann-Whitney test for numerical variables and the Chi-square test for categorical variables were used to compare the baseline group characteristics. The logistic regression was conducted to estimate the relative risks (RR) and their respective 95%CI for the outcomes according to the clinical and demographic characteristics. Finally, a Poisson multiple regression analysis was performed to identify which factors were independently associated with short-term neonatal adverse outcomes. The variables were inserted in the regression models, and those with a P-value under .05 were maintained. In addition, the missing data occurred randomly, and the imputation

method treated the few cases statistically. All statistical significances were two-sided and accepted at P< .05.

Results

886 pregnant women were eligible from December 2016 to December 2021. According to the pre-pregnancy obesity status, 709 (80%) were allocated as non-prepregancy obesity and 177 (20%) in the prepregancy obesity group. Table 1 represents the baseline characteristics according to the pre-preganacy obesity status. Table 2 demonstrates the categorical baseline variables.

We observed that pregnant women with prepregnancy obesity had more cesarean sections, higher fasting blood glucose in the first trimester, fasting plasma glucose at 24-28 weeks of gestation, 1 hour and 2 hours test 75grams-OGTT and higher final BMI compared to those who did not have prepregnancy obesity. We also observed that pregnant women with prepregnancy had, lower gestational age at delivery, a higher frequency of GDM, and a higher frequency of complications in the neonatal period (Table 1).

Table 1: Quantitative baseline characteristics of the overall population concerning the diagnosis of prepregnancy obesity.

	Non-prepregnancy Obesity (n=709)	Prepregnancy Obesity (n=177)	
Variable	**Med (IQR)**	**Med (IQR)**	***p***
Maternal age (years)	30 (26-34)	30 (26-35)	*.218*
First trimester FPG (mg/dL)	84 (78-89)	85 (79-92)	*.005*
75g OGTT (mg/dL) – fasting	79 (73-85)	81 (75-88)	*.013*
75g OGTT (mg/dL) - 1h	130 (105-150)	137 (117-154)	*.003*
75g OGTT (mg/dL) - 2h	112 (95-130)	120 (101-133)	*.005*
BMI (kg/m^2) pre-pregnancy	24.3 (22.1-26.5)	33.1 (31.3-35.9)	*.000*
BMI (kg/m^2) at 36-38 weeks	28.3 (26.2-30.5)	37 (35-39.3)	*.000*
Gestational age at birth	38.4 (37.7-39)	38.1 (37.4-38.8)	*.002*
Newborn weight at birth (g)	3145 (2900-3437.5)	3210 (2917.5-3430)	*.237*
1-minute APGAR score	9 (9-9)	9 (9-9)	*.281*
5-minutes APGAR score	9 (9-10)	9 (9-10)	*.532*

n: sample; g: mg/dL: miligrams per deciliter; FPG: fasting plasma glucose; 75g OGTT: 75 grams oral glucose tolerance test; BMI: Body Mass Index; Data are presented in: Med (IQR): Median (interquartile range); p-values are based on *Mann–Whitney U. Significance $p < 0.05$.

Table 2 shows a higher percentage of GDM and previous complications among pregnant women with prepregnancy obesity.

Table 2: Categorical baseline characteristics of the overall population concerning the diagnosis of prepregnancy obesity.

	Non-prepregnancy Obesity (n=709)	Prepregnancy Obesity (n=177)	
Variable	**n (%)**	**n (%)**	***p***
Non-Caucasian	96 (13.5%)	27 (15.3%)	*.627*
Higher educational level	420 (59.2%)	97 (54.8%)	*.307*
Previous bariatric surgery	7 (1.0%)	4 (2.3%)	*.244*
GDM	172 (24.3%)	72 (40.7%)	*<.001*
Pre-term birth	63 (8.9%)	21 (11.9%)	*.251*
Cesarian birth	692 (97.6%)	175 (98.9%)	*.395*
Large for Gestational age	37 (5.2%)	13 (7.3%)	*.276*
Adverse neonatal outcome	37 (5.2%)	18 (10.2%)	*.017*
5-minutes Apgar < 7	3 (0.4%)	2 (1.1%)	*.262*

GDM: Gestational Diabetes Mellitus; Data are presented in n(%): absolute frequency (n) and percentage (%); p-values are based on *Chi-square test. Significance $p < 0.05$.

Table 3 shows that GDM impacted the decrease in birth weight by 280 grams (95%CI: -0.50 - -0.06).

Table 3: Multiple linear regression to identify confounders to explain the birth weight outcome.

Model 1	β	**95% CI**	**SE**	**p***
Non-Caucasian	0.06	(-0.22-0.35)	0.15	.66
Higher level education	0.26	(0.06-0.46)	0.1	.012
Bariatric surgery	0.2	(-0.68-1.08)	0.45	.657
Parity	-0.15	(-0.36-0.05)	0.11	.148
Number of vaginal delivery	0.04	(-0.25-0.34)	0.15	.782
Number of C-sections	0.1	(-0.16-0.35)	0.13	.456
Maternal age	0	(-0.02-0.01)	0.01	.767
BMI (kg/m^2) pre-pregnancy	-0.04	(-0.09-0.01)	0.03	.145
BMI (kg/m^2) at 36-38 weeks	0.01	(-0.04-0.07)	0.03	.627
Model 2				
Prepregancy obesity	-0.08	(-0.47-0.31)	0.2	0.7
Higher level education	0.24	(0.04-0.44)	0.1	.016
Parity	-0.1	(-0.21-0.01)	0.06	.085
BMI (kg/m^2) pre-pregnancy	-0.02	(-0.05-0.01)	0.02	.188
Model 3				
GDM	-0.28	(-0.5--0.06)	0.11	.012
Higher level education	0.25	(0.06-0.45)	0.1	.012
Parity	-0.1	(-0.21-0.01)	0.06	.087
BMI (kg/m^2) pre-pregnancy	-0.02	(-0.04-0)	0.01	.04

BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; Data are presented in: β: Standardized regression Coefficient; SE: Standard error; 95% CI: 95% Coefficient Interval; p-values are based on *Multiple linear regression significance for investigation model $p < 0.2$.

Table 4 demonstrates the results. Neither prepregnancy obesity nor GDM was associated with the risk of preterm birth.

Table 4: Multiple linear regression to identify confounders to explain the preterm outcome.

Model 1	**RR**	**95%CI**	**p**
Non-Caucasian	0.938	(0.50-1.75)	.841
Higher education	0.666	(0.43-1.03)	.069
Previous bariatric surgery	0.696	(0.10-5.09)	.721
Parity	1.267	(0.86-1.87)	.23
Number of vaginal deliveries	0.828	(0.46-1.51)	.536
Number of C-sections	0.815	(0.50-1.34)	.421
Maternal age	1.019	(0.98-1.06)	.332
BMI (kg/m^2) pre-pregnancy	1.092	(0.97-1.23)	.135
BMI (kg/m^2) at 36-38 weeks	0.935	(0.83-1.05)	.262
Model 2			
Pre-pregnancy Obesity	0.99	(0.43-2.26)	.977
Higher level education	0.69	(0.45-1.06)	.093
BMI (kg/m^2) pre-pregnancy	1.03	(0.96-1.10)	.398
Model 3			
GDM	1.41	(0.89-2.22)	.141
Higher level education	0.68	(0.44-1.05)	.081

BMI (kg/m^2) pre-pregnancy	1.02	(0.98-1.06)	.293

BMI: Body Mass Index; Data are presented in: RR: Relative Risk; 95% CI: 95% Coefficient Interval; p-values are based on *Multiple Poisson Regression significance for investigation model p <0.2.

For the Birth Weight Inadequate outcome, multiple Poisson regression was used, as demonstrated in Table 5. Neither prepregnancy obesity nor GDM was associated with the risk of neonatal inadequate birth weight.

Table 5. Multiple linear regression to identify confounders to explain the birth weight inadequate outcome.

Model 1	**RR**	**95%CI**	**P**
Non-Caucasian	0.69	(0.27-1.76)	0.435
Higher level education	1.41	(0.77-2.58)	0.267
Bariatric surgery	1.82	(0.24-13.85)	0.563
Parity	1.04	(0.58-1.87)	0.887
Number of vaginal delivery	1	(0.46-2.19)	0.999
Number of C-sections	1.24	(0.62-2.48)	0.537
Maternal age	1	(0.95-1.05)	0.883
BMI (kg/m^2) pre-pregnancy	0.89	(0.78-1.03)	0.108
BMI (kg/m^2) at 36-38 weeks	1.16	(1.01-1.33)	0.037
Model 2			
Prepregancy obesity	1.34	(0.46-3.91)	0.59
BMI (kg/m^2) pre-pregnancy	0.89	(0.77-1.04)	0.145
BMI (kg/m^2) at 36-38 weeks	1.14	(1-1.3)	0.058
Model 3			
GDM	1.46	(0.81-2.64)	0.206
BMI (kg/m^2) pre-pregnancy	0.9	(0.79-1.03)	0.129
BMI (kg/m^2) at 36-38 weeks	1.14	(1-1.3)	.050

BMI: Body Mass Index; Data are presented in: RR: Relative Risk; 95% CI: 95% Coefficient Interval; p-values are based on *Multiple Poisson Regression significance for investigation model p <0.2.

Table 6 demonstrates Multiple Poisson regression considering the short-term neonatal outcome. We showed a mediating effect of GDM, as a significant effect of prepregnancy obesity in model 3 was annulled in model 5 when GDM was inserted into the model. Therefore, we concluded that there is no effect of prepregnancy obesity n the presence of the GDM variable as a mediator. Thus, that there is a significant

effect of GDM on the adverse short-term outcome, and the risk of neonatal complications increased by 99 % in the presence of GDM (RR 1.99; 95%CI 0.92-1.01).

Table 6, Multiple Poisson Regression to identify confounders to explain the short-term neonatal outcome.

Model 1	**RR**	**95%CI**	**p**
Non-Caucasian	0.9	(0.40-2.01)	.789
Higher education	1.24	(0.71-2.17)	.447
Previous bariatric surgery	1.4	(0.19-10.47)	.741
Parity	1.12	(0.66-1.88)	.676
Number of vaginal deliveries	1.09	(0.56-2.14)	.794
Number of C-sections	0.77	(0.40-1.50)	.447
Maternal age	0.96	(0.92-1.01)	.122
BMI (kg/m^2) pre-pregnancy	1.06	(0.92-1.21)	.421
BMI (kg/m^2) at 36-38 weeks	1.03	(0.90-1.19)	.642
Model 2			
Pre-pregnancy Obesity	1.98	(1.13-3.48)	.017
Maternal age	0.96	(0.92-1.01)	.122
Model 3			
Pre-pregnancy Obesity	1.68	(1.27-2.21)	,000
Model 4			
GDM	2.17	(1.27-3.69)	.004
Maternal age	0.97	(0.92-1.01)	.165
Model 5			
Pre-pregnancy Obesity	1.74	(0.98-3.09)	.057
GDM	1.99	(1.16-3.41)	.013
Maternal age	0.97	(0.92-1.01)	.148

BMI: Body Mass Index; Data are presented in: RR: Relative Risk; 95% CI: 95% Coeficient Interval; p-values are based on *Multiple Poisson Regression significance for investigation model p <0.2.

Apgar score at the fifth minute <7 was analyzed using Multiple Poisson regression, as seen in Table 7. Hence, a significant effect of GDM was observed. The risk of an Apgar score < 7 was ten times higher in the presence of GDM.

Table 7. Multiple Poisson regression models to identify the confounders variables for the Apgar 5th <7 outcome.

Model 1	**RR**	**95%CI**	**p**
Non-Caucasian	0	(0.00-.a)	1.000
Higher level education	2.45	(0.27-22.63)	.43
Previous bariatric surgery	0	(0.00-0.00)	
Parity	1.37	(0.28-6.64)	.694
Number of vaginal deliveries	1.17	(0.17-8.21)	.875
Number of C-sections	0.2	(0.02-2.65)	.225
Maternal age	1.05	(0.90-1.22)	.538
BMI (kg/m^2) pre-pregnancy	1.09	(0.73-1.63)	.682
BMI (kg/m^2) at 36-38 weeks	1.14	(0.73-1.77)	.558
Model 2			
Pre-pregnancy Obesity	2.67	(0.45-15.98)	.282
Model 3			
GDM	10.52	(1.18-94.16)	.035

BMI: Body Mass Index; Data are presented in: RR: Relative Risk; 95% CI: 95% Coefficient Interval; p-values are based on *Multiple Poisson Regression significance for investigation model p <0.2.

We analyzed the outcomes Apgar score at the 5th minute < 7 plus adverse short-term neonatal outcomes, Table 8. The risk of an score at the 5th minute < 7 plus adverse short-term neonatal outcomes was higher in the presence of GDM.

Table 8. Multiple Poisson regression models to identify the confounders variables for Apgar score at the 5th minute < 7 plus adverse short-term neonatal outcomes

Model 1	**RR**	**95%CI**	**P**
Non-Caucasian	.99	(0.94-1.04)	.670
Higher level education	1.02	(0.98-1.05)	.344
Previous bariatric surgery	1.02	(1.88-1.18)	.769
Parity	1.01	(0.97-1.04)	.720
Number of vaginal deliveries	1.01	(0.96-1.06)	.812
Number of C-sections	.98	(0.94-1.02)	.385
Maternal age	1.00	(0.99-1.00)	.084
BMI (kg/m^2) pre-pregnancy	1.00	(1.00-1.01)	.285
BMI (kg/m^2) at 36-38 weeks	1.00	(0.99-1.01)	.621
Model 2			
Pre-pregnancy Obesity	1.05	(1.05-1.09)	.015
Maternal age	1.00	(0.99-1.00)	.098
Model 3			
Pre-pregnancy Obesity	1.18	(1.18-1.27)	.000
Model 4			
GDM	1.06	(1.06-1.09)	.003
Model 5			
Pre-pregnancy Obesity	1.04	(1.04-1.09)	.043
GDM	1.05	(1.05-1.09)	.009
Maternal age	1.00	(0.99-1.00)	.117

BMI: Body Mass Index; Data are presented in: RR: Relative Risk; 95% CI: 95% Coeficient Interval; p-values are based on *Multiple Poisson Regression significance for investigation model p <0.2.

Discussion

We described a mediating effect of GDM and the risk for short-term neonatal adverse outcomes and Apgar score at the 5th minute under seven among women presenting prepregnancy obesity. Thus, the association of prepregnancy obesity in women affected by GDM during pregnancy appears to enhance four to five percent of having some degree of neonatal hypoxemia at birth or short-term complications. In our cohort, 19.97 of the pregnant women included presented with obesity. Furthermore, the group of prepregnancy obesity presented GDM diagnosis in 40.7% versus 24.3% in the non-obesity group, a significative difference (P<.001).

Pregnant women received nutritional counseling regarding their diet and recommended weight gain based on their BMI. For the GDM group, self-monitoring of plasma glucose was recommended four times daily, and targets for plasma glucose included a fasting value of less than 95 mg/dL and two-hour post-meal values of less than 130 mg/dL.

In a retrospective cohort study with 1064 women in São Paulo city, Brazil, patients were classified with hyperglycemia in the first trimester and GDM according to the OGTT screening. The group they called Diabetes in Pregnancy, having early-onset hyperglycemia in pregnancy, presented a higher prepregnancy BMI (Odds ratio 1.07; 95%CI 1.02-1.11) and a higher frequency of large for gestational age infants. (OR 2.78; 95%CI 1.23-6.27). (9)

In a systematic review from Wendland et al. in 2012, the WHO and the IADPSG criteria for GDM identified women at a small increased risk for adverse pregnancy outcomes, and the associations were of similar magnitude for both criteria. (10)

A prospective cohort study in Switzerland explored the impact of risk factors on perinatal outcomes in women presenting GDM. They demonstrated that prepregnancy, overweight, and obesity were primary predictors for perinatal and postpartum adverse outcomes. For the outcome large for gestational age, they described an Odds ratio of 1.32 (95%CI 1.05-1.64). They did not find differences after the statistical analyses for neonatal hypoglycemia and composite short-term neonatal complications. (11)

Recently, the American Diabetes Association recommendations were modified, and the categorization of overweight and obese women was added as a risk factor. In addition, prepregnancy obesity is a modifiable risk factor for a pregnant woman. Hence, it has a critical impact on most maternal neonatal outcomes. (11)

Simlilar results of our study were risks of the prematurity, macrosomia, and neonatal hypoglycemia higher in pregnant women with GDM(12) and increase of chance of large to gestational age newborns by 1.4 times, need for neonatal Intensive Care Unit by 1.7 times and low Apgar in the first minute by 1.7 times.(13)

Limitations of the study include the high risk of many research biases. In addition, we cannot control exposure or outcome assessment and must rely on others for accurate recordkeeping. Another limitation is the flaw of the BMI as a clinical marker for obesity and the controversial clinical protocols for screening and diagnosing GDM. Furthermore, the same difficulty in identifying the outcomes of interest.

Although our parochial results, we presume that the external validation for other populations might be considered. On this account, it is known that the pregnant population worldwide presents high rates of obesity and GDM, critical risk factors associated with adverse neonatal complications. (12)

Conclusion

There was a mediating effect of GDM positive screening, as the significant effect of prepregnancy obesity in model 3; was reduced in model 5 when GDM was inserted. Therefore, it is concluded that there is a softened effect of prepregnancy obesity, with the risk of short-term neonatal complication or 5th minute Apgar score < 7 being 4% higher among those with prepregnancy obesity. Furthermore, the results expose a mediating effect of GDM during the pregnancy, with the risk of a short-term neonatal complication or 5th minute Apgar score < 7 being 5% higher in the presence of GDM.

Prepregnancy obesity, when associated with a pregnancy complicated by GDM, is critical to elevate the rates of immediate neonatal morbidity and short-term neonatal adverse outcomes. These finds in a population study based in Brazil evoke the

necessity of prepregnancy counseling to consider overweight and obesity as a crucial risk factors for pregnancy and neonatal complications and, mainly, to propose strategies for women in their reproductive age period to achieve an appropriate BMI prepregnancy.

References

1. WHO Consultation on Obesity (1999: Geneva, Switzerland) & World Health Organization. (2000). Obesity : preventing and managing the global epidemic : report of a WHO consultation. World Health Organization. https://apps.who.int/iris/handle/10665/42330.
2. Yu C, Teoh T, Robinson S. Review article: Obesity in pregnancy. BJOG An Int J Obstet Gynaecol. 2006 Aug;113(10):1117–25.
3. Fuchs F, Senat M-V, Rey E, Balayla J, Chaillet N, Bouyer J, et al. Impact of maternal obesity on the incidence of pregnancy complications in France and Canada. Sci Rep. 2017 Sep;7(1):10859.
4. Pantham P, Aye ILMH, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta. 2015 Jul;36(7):709–15.
5. Rani PR. Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. J Clin DIAGNOSTIC Res. 2016;10(4):QE01-4.
6. McIntyre HD, Colagiuri S, Roglic G, Hod M. Diagnosis of GDM: A suggested consensus. Best Pract Res Clin Obstet Gynaecol. 2015;29(2):194–205.
7. Rudge MVC, Souza FP, Abbade JF, Hallur RLS, Marcondes JPC, Piculo F, et al. Study protocol to investigate biomolecular muscle profile as predictors of long-term urinary incontinence in women with gestational diabetes mellitus. BMC Pregnancy Childbirth [Internet]. 2020 Dec 19;20(1):117. Available from:

https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-020-2749-x

8. American Diabetes Association. Standards of Medical Care in Diabetes—2015. Diabetes Care [Internet]. 2015 Jan 1;38(Supplement_1):S1–2. Available from: http://care.diabetesjournals.org/cgi/doi/10.2337/dc15-S001
9. Zaccara TA, Paganoti CF, Mikami FCF, Francisco RP V., Costa RA. WHO criteria for diabetes in pregnancy: a retrospective cohort. BMC Pregnancy Childbirth. 2022 Dec;22(1):385.
10. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, et al. Gestational diabetes and pregnancy outcomes - a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth. 2012 Dec;12(1):23.
11. Corcillo A, Quansah DY, Kosinski C, Benhalima K, Puder JJ. Impact of Risk Factors on Short and Long-Term Maternal and Neonatal Outcomes in Women With Gestational Diabetes Mellitus: A Prospective Longitudinal Cohort Study. Front Endocrinol (Lausanne). 2022 Jun;13.
12. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022 Aug;133:155217.

Seção 5
Perspectivas Acadêmicas

Pensar nas perspectivas nesta fase final do doutorado, me fez rever todo o processo vivido até aqui e me estimulou ainda mais a cumprir esta etapa que é tão tensa e que exige dedicação, às vezes, até além da nossa capacidade. A formação no doutorado no Programa de Pós-Graduação em Tocoginecologia com o *Diamater Study Group*, fortaleceram e ampliaram a a carreira docente e de pesquisadora.

Para a continuidade da busca do conhecimento e na colaboração para melhorar a assistência à criança pela ótica da gestação, a proposta é permanecer como colaboradora do *Diamater Study Group* e desenvolver o Pós-Doutorado na mesma linha de pesquisa desta trajetória e continuar colaborando com o Grupo.

Espero poder levar o conhecimento e principalmente beneficiar diretamente as crianças, ao longo desta nova etapa da minha vida.

Seção 6
Diamater Study Group

Pesquisadores Reponsáveis	Pesquisadores Associados
Profa. Emérita Marilza Vieira Cunha Rudge Profa. Titular Iracema de Mattos Paranhos Calderon Profa. Dra. Angélica Mérica Pascon Barbosa Profa. Dra. Fátima Pereira de Souza **Pesquisadores Nacionais** Prof. Titular Carlos Frederico de Oliveira Graeff Prof. Titular Manoel João Batista Castello Girão Profa. Dra. Cláudia Garcia Magalhães Prof. Dr. Roberto Antonio de Araujo Costa Profa. Adjunto Silvana Andréa Molina Lima Profa. Dra. Meline Rossetto Kron Rodrigues Prof. Adjunto Sérgio Luis Felisbino Prof. Dr. Walnei Fernandes Barbosa Profa. Dra. Grasiela Bossolan Prof. Dr. José Eduardo Corrente Prof. Dr. Hélio Rubens de Carvalho Nunes Prof. Dr. Joelcio Francisco Abbade Profa. Dra Patrícia de Souza Rossignoli Profa. Dra. Cristiane Rodrigues Pedroni Prof. Titular Álvaro Nagib Atallah Profa. Dra. Zsuzsanna Ilona K. de Jarmy Di Bella Profa. Silvana Maria de Macêdo Uchôa Prof. Titular Marco Antonio Hungaro Duarte Prof. Dr. Edson Assunção Mareco Profa. Adjunta Marna Eliana Sakalem Profa. Dra. Natalia Miguel Martinho Fogaça Prof. Dr. Diego Girotto Bussaneli Profa. Titular Maeli Dal Pai Profa. Dra. Selma Maria Michelin Matheus Profa. Dra. Ana Karina Cristiuma De Luca Profa. Dra. Daisy Maria Fávero Salvadori Prof. Dr. Rondinelli Donizetti Herculano Prof. Dr. Spencer Luiz Marques Payao **Pesquisadores Internacionais** PhD Adonis Hijas PhD Luis Sobrevia Luarte PhD Bary Berghmans PhD Rob de Bie PhD Costanza Emanueli PhD Baerbel Junginger PhD Antonio Musàro PhD Lehana Thabane	PhD Raghavendra Hallur Lakshmana Shetty PhD David Rafael Abreu Reyes Dra Fernanda Cristina Bérgamo Alves Dr João Paulo de Castro Marcondes Dra Maíra Libertad Soligo Takemoto Dra Juliana Ferreira Floriano Dra. Fernanda Piculo Dra. Gabriela Marini Prata Dra Cibele Vieria Cunha Rudge Dr. Fabio Joly Campos Dr. Ícaro Putinhon Caruso Dr. Lucas Trevizani Rasmussen Dr Vinícius Krieger Costa Nogueira Ms. Caroline Baldini Prudencio Ms. Fabiane Affonso Pinheiro Ms. Carlos Izaias Sartorão Filho Ms. Sofia Beatriz Carolina Vega Quiroz Ms. Tawana Pascon Ms. Sthefanie Kenickel Nunes Ms. Bruna Bologna Catinelli Ms. Fabiana Vieira Duarte de Souza Reis Ms. Rafael Guilen de Oliveira Ms. Sarah Maria Barneze Costa Ms. Mariane de Oliveira Menezes Ms. Nilton José dos Santo Ms. Isabella Otenio de Lourenço Ms. Jéssica Maróstica de Sá Ms. Raissa Escandiusi Avramidis Ms Guilherme Thomaz de Aquino Nava Ms Talita Costa Domingues Eusebio Mario Amador Enriquez Jose Vitor Freitas Melo (*in memoriam)* Luiz Takano Aline Medolago Carr Gabriela Azevedo Garcia Adriely Bittencourt Morgenstern Magyori Carolina Neiva Frota de Carvalho Luana Fávaro Iamundo Henrique Caetano Mingoranci Bassin Carolina Neiva Frota de Carvalho Carolina Pascon Marques3 Michele Jacomin Ana Julia Bimbatti Silva Maiara Isabele Gonçalves Orlandi Tatiana Daniele Dangió **Apoio à Pesquisa** Rita de Cássia Athanázio Cinthia Scolastico Cecilio

Seção 7

Anexos

ANEXO 1

www.nature.com/scientificreports

scientific reports

OPEN

Reversal of diabetic-induced myopathy by swimming exercise in pregnant rats: a translational intervention study

Bruna B. Catinelli[1,37], Patrícia S. Rossignoli[2,37], Juliana F. Floriano[1], Aline M. Carr[1], Rafael G. de Oliveira[1], Nilton J. dos Santos[3,4], Lara C. C. Úbeda[5], Maria Angélica Spadella[6], Raghavendra L. S. Hallur[1,7], Luis Sobrevia[1,8,9,10,11], Sérgio L. Felisbino[3], Iracema M. P. Calderon[1], Angélica M. P. Barbosa[1,2,38], Marilza V. C. Rudge[1,38]✉ & The Diamater Study Group[1*]

Gestational diabetes mellitus (GDM) plus rectus abdominis muscle (RAM) myopathy predicts long-term urinary incontinence (UI). Atrophic and stiff RAM are characteristics of diabetes-induced myopathy (DiM) in pregnant rats. This study aimed to determine whether swimming exercise (SE) has a therapeutic effect in mild hyperglycemic pregnant rats model. We hypothesized that SE training might help to reverse RAM DiM. Mild hyperglycemic pregnant rats model was obtained by a unique subcutaneous injection of 100 mg/kg streptozotocin (diabetic group) or citrate buffer (non-diabetic group) on the first day of life in Wistar female newborns. At 90 days of life, the rats are mated and randomly allocated to remain sedentary or subjected to a SE protocol. The SE protocol started at gestational day 0 and consisted of 60 min/day for 6 days/week in a period of 20 days in a swim tunnel. On day 21, rats were sacrificed, and RAM was collected and studied by picrosirius red, immunohistochemistry, and transmission electron microscopy. The SE protocol increased the fiber area and diameter, and the slow-twitch and fast-twitch fiber area and diameter in the diabetic exercised group, a finding was also seen in control sedentary animals. There was a decreased type I collagen but not type III collagen area and showed a similar type I/type III ratio compared with the control sedentary group. In conclusion, SE during pregnancy reversed the RAM DiM in pregnant rats. These findings may be a potential protocol to consider in patients with RAM damage caused by GDM.

Gestational diabetes mellitus (GDM) is known as a serious global health problem[1]. GDM can cause damage to the skeletal muscle and extracellular matrix (ECM) health and function, i.e. maternal hyperglycemic myopathy[2–4].

The Diamater Study Group

M. V. C. Rudge[1], A. M. P. Barbosa[1,2], I. M. P. Calderon[1], L. Sobrevia[1,8,9,10,11], F. P. Souza[12], B. Berghmans[13], L. Thabane[14], B. Junginger[15], C. F. O. Graeff[16], C. G. Magalhães[17], R. A. Costa[1], S. A. M. Lima[18], M. R. Kron-Rodrigues[19], S. L. Felisbino[3], W. Barbosa[20], F. J. Campos[17], G. Bossolan[1], J. E. Corrente[21], H. R. C. Nunes[17], J. Abbade[17], P. S. Rossignoli[2], C. R. Pedroni[2], A. N. Atallah[22], Z. I. K. J. Di Bella[23], S. M. M. Uchoa[24], M. A. H. Duarte[25], E. A. Mareco[26], M. E. Sakalem[27], N. Martinho[28,29], L. S. R. Hallur[1,7], D. R. A. Reyes[1], F. C. B. Alves[1], J. P. C. Marcondes[1], C. B. Prudencio[1], F. A. Pinheiro[1], C. I. SartorãoFilho[1], S. B. C. V. Quiroz[1], T. Pascon[1], S. K. Nunes[1], B. B. Catinelli[1], F. V. D. S. Reis[1], R. G. Oliveira[1], S. Barneze[1], E. M. A. Enriquez[1], L. Takano[1], A. M. Carr[1], A. B. M. Magyori[1], L. F. Iamundo[1], C. N. F. Carvalho[1], M. Jacomin[1], R. E. Avramidis[1], A. J. B. Silva[2], M. I. G. Orlandi[1], T. D. Dangió[1], H. C. M. Bassin[1], M. L. S. Takemoto[1], T. D. Caldeirão[1], N. J. Santos[3,4], I. O. Lourenço[12], J. Marostica de Sá[12], I. P. Caruso[12], L. T. Rasmussen[30], G. A. Garcia[1], G. T. A. Nava[31], C. P. Marques[32], D. G. Bussaneli[33], V. K. C. Nogueira[33], C. V. C. Rudge[32], F. Piculo[34], G. M. Prata[35] & V. P. Barbosa[36]

ANEXO 2

International Urogynecology Journal
https://doi.org/10.1007/s00192-022-05245-y

ORIGINAL ARTICLE

Relaxin-2 during pregnancy according to glycemia, continence status, and pelvic floor muscle function

Caroline Baldini Prudencio[1] · Sthefanie Kenickel Nunes[1] · Fabiane Affonso Pinheiro[1] · Carlos Isaias Sartorão Filho[1] · Flávia Ignácio Antônio[2] · Guilherme Thomaz de Aquino Nava[3] · Marilza Vieira Cunha Rudge[1] · Angélica Mércia Pascon Barbosa[1,2] · Diamater Study Group

Received: 16 November 2021 / Accepted: 5 May 2022

Abstract

Introduction and hypothesis To investigate relaxin-2 concentration comparing gestational diabetes mellitus (GDM) and non-GDM patients during pregnancy according to urinary incontinence (UI) and pelvic function status.

Methods This is a cross-sectional study evaluating 282 pregnant women from 24 weeks of gestation. The participants were divided into two groups, non-GDM and GDM, according to American Diabetes Association's diabetes mellitus gestational threshold. In addition, according to subanalysis, both groups were subdivided according to the presence of pregnancy-specific urinary incontinence: non-GDM continent, non-GDM incontinent, GDM continent, and GDM incontinent. All participants filled in questionnaires on clinical, obstetric, and urinary continence status (International Consultation on Incontinence Questionnaire-Short Form, ICIQ-SF, and Incontinence Severity Index, ISI), followed by pelvic floor muscle evaluation by the PERFECT scheme in which strength, endurance, and speed of contractions were evaluated.

Results Serum relaxin-2 concentrations were significantly lower in pregnant women with pregnancy-specific urinary incontinence in both non-GDM and GDM patients, but GDM showed the lowest concentration. In addition, the stratification of the groups according to pelvic floor muscle strength showed that pregnant patients with GDM and modified Oxford scale 0–2 had significantly lower levels than those who were non-GDM and GDM with Modified Oxford Scale 3–5. Relaxin-2 level was much lower in GDM incontinent pregnant women with MOS 0–2 compared to the other three groups.

Conclusions Lower relaxin-2 concentration was associated with the presence of pregnancy-specific urinary incontinence, but the combination of GDM, pregnancy-specific urinary incontinence, and lower levels of pelvic floor strength led to lower levels of relaxin-2 compared to the other three groups.

Keywords Gestational diabetes · Obstetrics · Pelvic floor · Pregnancy · Relaxin-2

Diamater Study Group

Calderon IMP, Souza FP, Berghmans B, de Bie R, Thabane L, Junginger B, Graeff CFO, Magalhães CG, Costa RA, Lima SAM, Kron-Rodrigues MR, Felisbino S, Barbosa W, Campos FJ, Bossolan G, Corrente JE, Nunes HRC Abbade J, Rossignoli PS, Pedroni CR, Atallah AN, Di Bella ZIKJ, Uchoa SMM, Hungaro MA, Mareco EA, Sakalem ME, Martinho N, Hallur LSR, Reyes DRA, Alves FCB, Marcondes JPC, Quiroz SBCV, Pascon T, Catinelli BB, Reis FVDS, Oliveira RG, Barneze S, Enriquez EMA, Takano L, Carr AM, Magyori ABM, Iamundo LF, Carvalho CNF, Jacomin M, Avramidis RE, Silva AJB, Orlandi MIG, Dangió TD, Bassin HCM, Melo JVF, Takemoto MLS, Menezes MD, Caldeirão TD, Santos NJ, Lourenço IO, Marostica de Sá J, Caruso IP, Rasmussen LT, Garcia GA, Pascon C, Bussaneli DG, Nogueira VKC, Rudge CVC, Piculo F, Prata GM, Barbosa VP.

Published online: 03 June 2022

ANEXO 3

Received: 21 June 2021 | Accepted: 15 March 2022

DOI: 10.1002/nau.24927

CLINICAL ARTICLE

Neurourology Urodynamics ICS WILEY

Pelvic floor muscle dysfunction at 3D transperineal ultrasound in maternal exposure to gestational diabetes mellitus: A prospective cohort study during pregnancy

Fabiane A. Pinheiro[1] | Carlos I. Sartorão Filho[1,2] | Caroline B. Prudencio[1] | Sthefanie K. Nunes[1] | Tawana Pascon[1] | Ragavendra L. S. Hallur[1,3] | Luis Takano[1,2] | Eusébio M. A. Enriquez[1] | Bruna B. Catinelli[1] | Aline M. Carr[1] | Baerbel Junginger[4] | Marilza V. C. Rudge[1] | Angélica M. P. Barbosa[1,5] | The Diamater Study Group

[1]Postgraduate Program on Tocogynecology, Botucatu Medical School (FMB), São Paulo State University (UNESP), Botucatu, São Paulo State, Brazil

[2]Department of Medical Health, Medical School, Fundação Educacional do Município de Assis (FEMA, Assis Municipality Educational Foundation (FEMA), Assis, São Paulo State, Brazil

[3]Center for Biotechnology, Pravara Institute of Medical Sciences (Deemed to be University), Loni, Maharashtra, India

[4]Department of Gynecology, Pelvic Floor Center Charitè, Charitè University Hospital, Berlin, Germany

[5]Department of Physiotherapy and Occupational Therapy, School of Philosophy and Sciences, São Paulo State University (UNESP), Marília, São Paulo State, Brazil

THE DIAMATER STUDY GROUP

Rudge MVC, Barbosa AMP, Calderon IMP, Souza FP, Berghmans B, Thabane L, Junginger B, Graeff CFO, Magalhães CG, Costa RA, Lima SAM, Kron-Rodrigues MR, Felisbino S, Barbosa W, Campos FJ, Bossolan G, Corrente JE, Nunes HRC Abbade J, Rossignoli PS, Pedroni CR, Atallah AN, Di Bella ZIKJ, Uchoa SMM, Hungaro MA, Mareco EA, Sakalem ME, Martinho N, Hallur LSR, Reyes DRA, Alves FCB, Marcondes JPC, Prudencio CB, Pinheiro FA, Sartorão Filho CI, Quiroz SBCV, Pascon T, Nunes SK, Catinelli BB, Reis FVDS, Oliveira RG, Barneze S, Enriquez EMA, Takano L, Carr AM, Magyori ABM, Iamundo LF, Carvalho CNF, Jacomin M, Avramidis RE, Silva AJB, Orlandi MIG, Dangió TD, Bassin HCM, Melo JVF, Takemoto MLS, Menezes MD, Caldeirão TD, Santos NJ, Lourenço IO, Marostica de Sá J, Caruso IP, Rasmussen LT, Garcia GA, Nava GTA, Pascon C, Bussaneli DG, Nogueira VKC, Rudge CVC, Piculo F, Prata GM, and Barbosa VP.

Abstract

Aim: This study aimed to assess, for the first time, the dynamic morphometry of pelvic floor muscles (PFM) using three-dimensional transperineal ultrasound (3D-TPUS) and its progression at two-time points of gestation between women with and without gestational diabetes mellitus (GDM), and whether the PFM dysfunction is connected to GDM.

Methods: The study comprised 83 consecutive pregnant women with ($n = 38$) and without ($n = 45$) GDM screened at 24–30 and 38–40 weeks of gestation. 3D-TPUS and a mobility test were used to quantify PFM dynamic morphometry during maximum contraction and the Valsalva maneuver.

Results: When compared to the control group, GDM women had no significant variations in all levator hiatal dimensions at 24–30 weeks of gestation. Meanwhile, women with GDM experienced an increase in levator hiatal area (LHa) ($p < 0.000$) during PFM contraction and enlargement in LHa ($p < 0.001$) during Valsalva maneuver ($p = 0.010$) at 38–40 weeks of gestation.

Fabiane A. Pinheiro, Carlos I. Sartorão Filho, Marilza V. C. Rudge, and Angélica M. P. Barbosa contributed equally to this study.

Fabiane A. Pinheiro and Carlos I. Sartorão Filho are co-first authors.

Caroline B. Prudencio, Sthefanie K. Nunes, Tawana Pascon, Ragavendra L. S. Hallur, Luis Takano, Eusébio M. A. Enriquez, Bruna B. Catinelli, Aline M. Carr, and Baerbel Junginger contributed equally to this study.

Marilza V. C. Rudge and Angélica M. P. Barbosa are last authors of this study.

ANEXO 4

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 06 October 2022
DOI 10.3389/fendo.2022.958909

OPEN ACCESS

EDITED BY
Eric Siegel,
University of Arkansas for Medical Sciences, United States

REVIEWED BY
Luis Mercado,
University of Arkansas for Medical Sciences, United States
Diana Escalona-Vargas,
University of Arkansas for Medical Sciences, United States

*CORRESPONDENCE
Angélica Mércia Pascon Barbosa
angelicapascon@gmail.com

†These authors share first authorship

‡These authors share last authorship

§These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 01 June 2022
ACCEPTED 31 August 2022
PUBLISHED 06 October 2022

CITATION
Prudencio CB, Nunes SK, Pinheiro FA, Sartorão Filho CI, Nava GTA, Salomoni SE, Pedroni CR, Rudge MVC, Barbosa AMP and Diamater Study Group (2022) Gestational diabetes is associated with alteration on pelvic floor muscle activation pattern during pregnancy and postpartum: Prospective cohort using electromyography assessment. *Front. Endocrinol.* 13:958909. doi: 10.3389/fendo.2022.958909

Gestational diabetes is associated with alteration on pelvic floor muscle activation pattern during pregnancy and postpartum: Prospective cohort using electromyography assessment

Caroline Baldini Prudencio[1†], Sthefanie Kenickel Nunes[1†], Fabiane Affonso Pinheiro[1§], Carlos Izaias Sartorão Filho[1§], Guilherme Thomaz de Aquino Nava[2§], Sauro Emerick Salomoni[3], Cristiane Rodrigues Pedroni[4§], Marilza Vieira Cunha Rudge[1‡], Angélica Mércia Pascon Barbosa[1,4*‡] and Diamater Study Group

[1]São Paulo State University (Unesp), Postgraduate Program on Tocogynecology, Botucatu Medical School, Botucatu, Brazil, [2]Human Development and Technologies, Institute of Biosciences, São Paulo State University (UNESP), Rio Claro, Brazil, [3]Independent Researcher, Hobart, TAS, Australia, [4]São Paulo State University (Unesp), School of Philosophy and Sciences, Marília, Brazil

Background and objective: Gestational diabetes mellitus (GDM) is a comorbidity which may cause acute and lifelong disorders to mother and child. Alterations in muscular and connective tissues have been associated with GDM in translation studies, characterizing gestational diabetic myopathy. Pregnancy-specific urinary incontinence and sexual disabilities, disorders that depend on the pelvic floor muscle (PFM) integrity, are also associated with GDM both during and after pregnancy. The aim was to compare PFM activation patterns between GDM and non-GDM women from 24–30 gestational weeks 18–24 months postpartum during a standard clinical test during gestation d postpartum.

ethods: We conducted a prospective three-time-point cohort study from station (24–30 weeks—T1, and 36–38 weeks—T2) to 18–24 months stpartum (T3). PFM electromyography was recorded in primigravida or miparous women with one previous elective c-section with or without the gnosis of GDM according to the American Diabetes Association criteria. A reful explanation of the muscle anatomy and functionality of the PFM was en to participants before EMG assessment. The outcome measures were M activation patterns assessed during pregnancy and postpartum, mparing intra and between groups. PFM activation patterns were assessed

Diamater study group

Rudge MVC, Barbosa, AMP, Calderon IMP, Souza FP, Berghmans B, Thabane L, Junginger B, Graeff CFO, Magalhães CG, Costa RA, Lima SAM, Kron-Rodrigues MR, Felisbino S, Barbosa W, Campos FJ, Bossolan G, Corrente JE, Nunes HRC Abbade J, Rossignoli PS, Pedroni CR, Atallah AN, Di Bella ZIKJ, Uchoa SMM, Hungaro MA, Mareco EA, Sakalem ME, Martinho N, Hallur LSR, Reyes DRA, Alves FCB, Marcondes JPC, Prudencio CB, Pinheiro FA, Sartorão Filho CI, Quiroz SBCV, Pascon T, Nunes SK, Catinelli BB, Reis FVDS, Oliveira RG, Barneze S, Enriquez EMA, Takano L, Carr AM, Magyori ABM, Iamundo LF, Carvalho CNF, Jacomin M, Avramidis RF, Silva AJB, Orlandi MIG, Dangió TD, Bassin HCM, Melo JVF, Takemoto MLS, Menezes MD, Caldeirão TD, Santos NJ, Lourenço IO, Marostica de Sá J, Caruso IP, Rasmussen LT, Garcia GA, Nava GTA, Pascon C, Bussaneli DG, Nogueira VKC, Rudge CVC, Piculo F, Prata GM, Barbosa VP.

ANEXO 5

Research, Society and Development, v. 10, n. 5, e52710515370, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i5.15370

Evaluation of the knowledge of university students in the health area about sexually transmitted infections: A cross-sectional study

Avaliação do conhecimento dos estudantes universitários da área de saúde sobre infecções sexualmente transmissíveis: Estudo transversal

Evaluación del conocimiento de los estudiantes de salud sobre las infecciones de transmisión sexual: Estudio transversal

Received: 04/23/2021 | Reviewed: 05/01/2021 | Accept: 05/01/2021 | Published: 05/15/2021

Carlos Izaias Sartorão Filho
ORCID: https://orcid.org/0000-0003-4710-3392
Educational Foundation of the Municipality of Assis, Brazil
University of São Paulo State, Brazil
E-mail: carlos.sartorao@unesp.br
Carlos Izaias Sartorão Neto
ORCID: https://orcid.org/0000-0003-4057-1732
University of São Paulo State, Brazil
E-mail: neto.sartorao@usp.br
Carla Fabiana Souza Guazelli
ORCID: https://orcid.org/0000-0002-6124-8371
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Camila Rodrigues Avello
ORCID: https://orcid.org/0000-0002-2933-2936
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Ivana Geraldelli Neiva Rodrigues
ORCID: https://orcid.org/0000-0001-9219-8648
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Luana Durante Alvarez
ORCID: https://orcid.org/0000-0003-3377-4849
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Fabiana Vieira Duarte de Souza Reis
ORCID: https://orcid.org/0000-0001-5975-9917
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Vanessa Patrícia Fagundes
ORCID: https://orcid.org/0000-0003-1208-075X
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Luiz Takano
ORCID: https://orcid.org/0000-0002-8228-9295
Educational Foundation of the Municipality of Assis, Brazil
E-mail: lagofema@gmail.com
Caroline Baldini Prudêncio
ORCID: https://orcid.org/0000-0002-2070-3606
University of Sao Paulo State, Brazil
E-mail: caroline.baldini@unesp.br
Angélica Mércia Pascon Barbosa
ORCID: https://orcid.org/0000-0003-0817-9511
University of São Paulo State, Brazil
E-mail: angelicapascon@gmail.com
Marilza Vieira Cunha Rudge
ORCID: https://orcid.org/0000-0002-9227-832X
University of São Paulo State, Brazil
E-mail: marilzarudge@gmail.com

ANEXO 6

PLOS ONE

REGISTERED REPORT PROTOCOL

Effectiveness of the pelvic floor muscle training on muscular dysfunction and pregnancy specific urinary incontinence in pregnant women with gestational diabetes mellitus: A systematic review protocol

Angélica Mércia Pascon Barbosa[1☯‡*], Eusebio Mario Amador Enriquez[2☯‡], Meline Rossetto Kron Rodrigues[3☯], Caroline Baldini Prudencio[2☯], Álvaro Nagib Atallah[4☯], David Rafael Abreu Reyes[2☯], Raghavendra Lakshmana Shetty Hallur[2☯], Sthefanie Kenickel Nunes[2☯], Fabiane Affonso Pinheiro[2☯], Carlos Isaías Sartorão Filho[2☯], Gabriela Lopes Piemonte Andrade[5☯], Bary Berghmans[6☯], Rob de Bie[6☯], Silvana Andréa Molina Lima[7☯‡], Marilza Vieira Cunha Rudge[2☯‡], The Diamater Study Group[¶]

This is a Registered Report and may have an associated publication; please check the article page on the journal site for any related articles.

OPEN ACCESS

Citation: Barbosa AMP, Enriquez EMA, Rodrigues MRK, Prudencio CB, Atallah ÁN, Reyes DRA, et al. (2020) Effectiveness of the pelvic floor muscle training on muscular dysfunction and pregnancy specific urinary incontinence in pregnant women with gestational diabetes mellitus: A systematic review protocol. PLoS ONE 15(12): e0241962. https://doi.org/10.1371/journal.pone.0241962

Editor: Frank T. Spradley, University of Mississippi Medical Center, UNITED STATES

Received: April 20, 2020

Accepted: October 9, 2020

Published: December 7, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0241962

Acknowledgments

We thank the Diamater Study Group for making valuable comments.

The Diamater Study Group: Rudge MVC, Barbosa, AMP, Caldeiron IMP, Souza FP, Berghmans B, de Bie R, Thabane L, Junginger B, Graeff CFO, Magalhães CG, Costa RA, Lima SAM, Kron-Rodrigues MR, Felisbino S, Barbosa W, Campos FJ, Bossolan G, Corrente JE, Nunes HRC Abbade J, Rossignoli PS, Pedroni CR, Atallah AN, Di Bella ZIKJ, Uchoa SMM, Hungaro MA, Mareco EA, Sakalem ME, Martinho N, Hallur LSR, Reyes DRA, Alves FCB, Marcondes JPC, Prudencio CB, Pinheiro FA, Sartorão CI, Quiroz SBCV, Pascon T, Nunes SK, Catinelli BB, Reis FVDS, Oliveira RG, Barneze S, Enriquez EMA, Takano L, Carr AM, Magyori ABM, Iamundo LF, Carvalho CNF, Jacomin M, Avramidis RE, Silva AJB, Orlandi MIG, Dangió TD, Bassin HCM, Melo JVF, Takemoto MLS, Menezes MD, Caldeirão TD, Santos NJ, Lourenço IO, Marostica de Sá J, Caruso IP, Rasmussen LT, Garcia GA, Nava GTA, Pascon C, Bussaneli DG, Nogueira VKC, Rudge CVC, Piculo F, Prata GM.

Abstract

Background

There is ample evidence that gestational diabetes mellitus has a direct influence on urinary incontinence and pelvic floor muscles. There are no standardized pelvic floor muscle exercise programs in the literature for the physiotherapy and differ in the type of exercise, intensity, type and duration of application, and the frequency and duration of treatment sessions. The aim of this systematic review will be to investigate that Pelvic Floor Muscle Training can prevent and/or decrease the pregnancy specific urinary incontinence in women with gestational diabetes mellitus or gestational hyperglycemia.

Methods

We will perform a systematic review according to the Cochrane methodology of Randomized Controlled Trials. An overall search strategy will be developed and adapted for Embase, MEDLINE, LILACS, and CENTRAL databases, with the date of consultation until

ANEXO 7

Rudge *et al. BMC Pregnancy and Childbirth* (2020) 20:117
https://doi.org/10.1186/s12884-020-2749-x

BMC Pregnancy and Childbirth

STUDY PROTOCOL Open Access

Study protocol to investigate biomolecular muscle profile as predictors of long-term urinary incontinence in women with gestational diabetes mellitus

Marilza V. C. Rudge[1*], Fátima P. Souza[2], Joelcio F. Abbade[1], Raghavendra L. S. Hallur[1], João Paulo C. Marcondes[1], Fernanda Piculo[1,3], Gabriela Marini[1,4], Giovana Vesentini[1], Lehana Thabane[5,6], Steven S. Witkin[7,8], Iracema M. P. Calderon[1], Angélica M. P. Barbosa[1,9], and The Diamater Study Group

Abstract

Background: Pelvic floor muscles (PFM) and rectus abdominis muscles (RAM) of pregnant diabetic rats exhibit atrophy, co-localization of fast and slow fibers and an increased collagen type I/III ratio. However, the role of similar PFM or RAM hyperglycemic-related myopathy in women with gestational diabetes mellitus (GDM) remains poorly investigated. This study aims to assess the frequency of pelvic floor muscle disorders and pregnancy-specific urinary incontinence (PS-UI) 12 months after the Cesarean (C) section in women with GDM. Specifically, differences in PFM/RAM hyperglycemic myopathy will be evaluated.

Methods: The Diamater is an ongoing cohort study of four groups of 59 pregnant women each from the Perinatal Diabetes Research Centre (PDRC), Botucatu Medical School (FMB)-UNESP (São Paulo State University), Brazil. Diagnosis of GDM and PS-UI will be made at 24–26 weeks, with a follow-up at 34–38 weeks of gestation. Inclusion in the study will occur at the time of C-section, and patients will be followed at 24–48 h, 6 weeks and 6 and 12 months postpartum. Study groups will be classified as (1) GDM plus PS-UI; (2) GDM without PS-UI; (3) Non-GDM plus PS-UI; and (4) Non-GDM without PS-UI. We will analyze relationships between GDM, PS-UI and hyperglycemic myopathy at 12 months after C-section. The mediator variables to be evaluated include digital palpation, vaginal squeeze pressure, 3D pelvic floor ultrasound, and 3D RAM ultrasound. RAM samples obtained during C-section will be analyzed for ex-vivo contractility, morphological, molecular and OMICS profiles to further characterize the hyperglycemic myopathy. Additional variables to be evaluated include maternal age, socioeconomic status, educational level, ethnicity, body mass index, weight gain during pregnancy, quality of glycemic control and insulin therapy.

Discussion: To our knowledge, this will be the first study to provide data on the prevalence of PS-UI and RAM and PFM physical and biomolecular muscle profiles after C-section in mothers with GDM. The longitudinal design allows for the assessment of cause-effect relationships between GDM, PS-UI, and PFMs and RAMs myopathy. The findings may reveal previously undetermined consequences of GDM.

Keywords: Gestational diabetes mellitus, Hyperglycemic myopathy, Pelvic floor muscles, Rectus abdominis muscles, Urinary incontinence, Proteomics, Collagen, Electromyography, Transmission electron microscopy

Acknowledgments
We would like to thank the Perinatal Diabetes Research Center (PDRC) -Botucatu Medical School-UNESP, Brazil. We gratefully acknowledge the substantial contribution of all women who participated/participating in the Diamater study.
The Diamater Study Group: Rudge MV, Barbosa AMP, Calderon IMP, Souza FP, Abbade JF, Hallur LSR, Piculo F, Marini G, Vesentini G, Thabane L, Palma MS, Graeff CFO, Ami RK, Herculano RD, Salvadori DF, Mateus S, Dal Pai Silva M, Magalhães CG, Costa RA, Lima SAM, FelisbinoSL, Barbosa W, Atallah A, Girão MJB, Di Bella Z, Uchoa SM, Payão S, Hijas A, Berghman B, De Bie R, Sobrevia L, Junginger B, Alves FCB, Rossignoli PS, Prudencio CB, Orlandi MIG, Gonçalves MI, Nunes SK, Catineili BB, Quiroz S, Sarmento BV, Pinheiro FA, Sartorão CI, Lucas RR, Reyes DRA, Quiroz SBCV, Enriquez EMA, Oliveira RG, Floriano JF, Marcondes JPC, Rameze S, Dangió TD, Pascon T, Rossignoli P, Freitas JV, Takano L, Reis F, Caldeirão TD, Fernandes JN, Carr AM, Galtero MVC, Corrente JE, Nunes HRC, Candido AF, Sarmento, Costa SMB, Dangió TD, Pascon T, Melo JVF, Takano L, Reis FVDS, Caldeirão TD, Carr AM, Garcia GA,

* Correspondence: marilzarudge@gmail.com
[1]Department of Gynecology and Obstetrics, Botucatu Medical School (FMB), São Paulo State University (UNESP), CEP18618-687, Sao Paulo, Brazil
Full list of author information is available at the end of the article

ANEXO 8

Received: 27 March 2020 | Accepted: 10 August 2020
DOI: 10.1002/nau.24491

ORIGINAL CLINICAL ARTICLE

Neurourology Urodynamics ICS WILEY

Impact of gestational diabetes on pelvic floor: A prospective cohort study with three-dimensional ultrasound during two-time points in pregnancy

Carlos I. Sartorão Filho[1,2] | **Fabiane A. Pinheiro**[1] | **Caroline B. Prudencio**[1] | **Sthefanie K. Nunes**[1] | **Luiz Takano**[1] | **Eusebio M. A. Enriquez**[1] | **Maiara I. G. Orlandi**[1] | **Baerbel Junginger**[3] | **Raghavendra L. S. Hallur**[1] | **Marilza V. C. Rudge**[1] | **Angélica M. P. Barbosa PT, PhD**[1,4]

THE DIAMATER STUDY GROUP
Rudge MV, Barbosa AMP, Calderon IMP, Souza FP, Abbade JF, Rossignoli PS, L, Graeff CFO, Payão SL, Herculano RD, Salvadori DF, Matheus S, Silva MDP, Magalhães CG, Costa RA, Pedroni CR, Corrente JE, Nunes HRC, Lima SAM, Felisbino SL, Barbosa W, Atallah A, Girão MJB, Hijas A, Berghman B, De Bie R, Sobrevia L, Junginger B, Hallur LSR, Thabane L, Rudge CVC, Alves FCB, Prudencio CB, Orlandi MIG, Gonçalves MI, Nunes SK, Catinelli BB, Pinheiro FA, Sartorão Filho CI, Reyes DRA, Quiroz SBCV, Enriquez EMA, Oliveira RG, Floriano JF, Marcondes JPC, Dangió TD, Pascon T, Takano L, Caldeirão TD, Carr AM, Costa SMB, Melo JVF, Reis FVDS, Garcia GA, Bassin HCM, Avramidis RE, Takemoto MLS, Menezes MO, Sakalem ME, Jacomin M, Iamundo LF, Carvalho CNF, Lourenço IO, Marostica de Sá J, Megid RA, Caruso IP, Bussaneli DG, Nogueira VKC, Rasmussen LT, Prata GM, Piculo F, Vesentini G, Ferraz GAR, Kron MR, Rabadan GB, Suyama KS, Damasceno LN, Lima PR.

Funding information
Fundação de Amparo à Pesquisa do Estado de São Paulo,
Grant/Award Number: 2016/01743-5

Abstract

Aim: To evaluate the pelvic floor (PF) biometry using three-dimensional ultrasound (US) at two-time points of gestational in pregnant women with gestational diabetes mellitus (GDM).

Methods: A prospective cohort study conducted at the Perinatal Diabetes Research Center including 44 pregnant women with GDM and 66 pregnant women without GDM at 24 to 28 weeks of gestation. Three-dimensional transperineal US was performed at 24 to 28 and 34 to 38 weeks of gestation in the lithotomy position at rest. The axial plane of the minimal Levator hiatal dimensions was used to determine Levator ani muscle and Hiatal area (HA) biometry at 24 to 28 and 34 to 38 weeks of gestation.

Results: Of the 110 pregnant women, 100 (90.9%) completed the follow-up at 34 to 38 weeks of gestation. The evaluation by US showed a negative biometric change between the two-time points, during pregnancy in women with GDM; in the HA (β coefficient: estimative of effect in biometric progression according to GDM diagnosis, using the non-GDM group as reference = −6.76; $P = .020$), anteroposterior diameter ($\beta = -5.07$; $P = .019$), and Levator ani thickness ($\beta = -12.34$; $P = .005$).

Conclusions: Pregnant women with GDM had a significantly lower than expected percentage of changes in biometry of Levator ani thickness and HA from 24 to 28 to 34 to 38 weeks of gestation when compared with the group of pregnant women without GDM. GDM alters the morphology of PF structures assessed by three-

Carlos I. Sartorão Filho, Fabiane A. Pinheiro, Caroline B. Prudencio, Sthefanie K. Nunes, Luiz Takano, Eusebio M.A. Enriquez, Maiara I. Orlandi, Baerbel Junginger, Marilza V. C. Rudge, and Angélica M.P. Barbosa contributed equally to this work.

Carlos I. Sartorão Filho and Fabiane A. Pinheiro are the first authors on this work.

Angélica M.P. Barbosa and Marilza V. C. Rudge are the last authors on this work.

ANEXO 9

cells

MDPI

Review

Exosomes Could Offer New Options to Combat the Long-Term Complications Inflicted by Gestational Diabetes Mellitus

Juliana Ferreira Floriano [1], Gareth Willis [2], Francesco Catapano [3], Patrícia Rodrigues de Lima [1], Fabiana Vieira Duarte Souza Reis [1], Angélica Mercia Pascon Barbosa [1], Marilza Vieira Cunha Rudge [1,*] and Costanza Emanueli [3,*]

1 Botucatu Medical School, Sao Paulo State University, 18618687 Botucatu, Brazil; juliana.floriano@unesp.br (J.F.F.); patriciarl.lima@gmail.com (P.R.d.L.); fabianavdsreis@gmail.com (F.V.D.S.R.); angelicapascon@gmail.com (A.M.P.B.)
2 Division of Newborn Medicine/Children's Hospital, Harvard Medical School, Boston, MA 02115, USA; Gareth.Willis@childrens.harvard.edu
3 National Heart and Lung Institute, Imperial College London, London W12 0NN, UK; f.catapano@imperial.ac.uk
* Correspondence: marilzarudge@gmail.com (M.V.C.R.); c.emanueli@imperial.ac.uk (C.E.); Tel.: +44-2075943409 (C.E.)

Received: 4 January 2020; Accepted: 29 February 2020; Published: 10 March 2020

check for updates

Abstract: Gestational diabetes Mellitus (GDM) is a complex clinical condition that promotes pelvic floor myopathy, thus predisposing sufferers to urinary incontinence (UI). GDM usually regresses after birth. Nonetheless, a GDM history is associated with higher risk of subsequently developing type 2 diabetes, cardiovascular diseases (CVD) and UI. Some aspects of the pathophysiology of GDM remain unclear and the associated pathologies (outcomes) are poorly addressed, simultaneously raising public health costs and diminishing women's quality of life. Exosomes are small extracellular vesicles produced and actively secreted by cells as part of their intercellular communication system. Exosomes are heterogenous in their cargo and depending on the cell sources and environment, they can mediate both pathogenetic and therapeutic functions. With the advancement in knowledge of exosomes, new perspectives have emerged to support the mechanistic understanding, prediction/diagnosis and ultimately, treatment of the post-GMD outcomes. Here, we will review recent advances in knowledge of the role of exosomes in GDM and related areas and discuss the possibilities for translating exosomes as therapeutic agents in the GDM clinical setting.

Keywords: gestational diabetes mellitus; outcomes; urinary incontinence; therapy; exosomes; microRNAs

1. Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is an increasingly common condition, affecting approximately 8.3% of pregnancies [1] worldwide. GDM occurs when insulin resistance exceeds the capacity for insulin secretion. The resulting insulin imbalance leads to vascular inflammation [2,3] and predisposes women to the risk of developing more severe pathologies [4].

Currently, the mechanisms underpinning GDM development are poorly understood, as well as the concomitant complications caused by a GDM pregnancy in mother and offspring. The risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) rates, are rising alarmingly in the general population and is further increased for both mother and child after a GDM pregnancy [5–7]. Furthermore, for the mother, GDM is a strong predictor of urinary incontinence (UI) up to two years

ANEXO 10

PLOS ONE

RESEARCH ARTICLE

Alterations in the structural characteristics of rectus abdominis muscles caused by diabetes and pregnancy: A comparative study of the rat model and women

Giovana Vesentini[1,2]*, Angélica M. P. Barbosa[1,3], Débora C. Damasceno[2], Gabriela Marini[1,2,4], Fernanda Piculo[1,2], Selma M. M. Matheus[1,5], Raghavendra L. S. Hallur[1,2], Sthefanie K. Nunes[1,2], Bruna B. Catinelli[1,2], Claudia G. Magalhães[1,2], Roberto Costa[1,2], Joelcio F. Abbade[1,2], José E. Corrente[1,6], Iracema M. P. Calderon[1,2], Marilza V. C. Rudge[1,2], The DIAMATER Study Group¶

1 Perinatal Diabetes Research Center, University Hospital, Botucatu Medical School, Univ Estadual Paulista_UNESP, Botucatu, São Paulo, Brazil, **2** Department of Gynecology and Obstetrics, São Paulo State University (UNESP), Botucatu Medical School, Botucatu, São Paulo, Brazil, **3** Department of Physiotherapy and Occupational Therapy, São Paulo State University (UNESP), School of Philosophy and Sciences, Marília, São Paulo, Brazil, **4** Department of Health Sciences, Universidade Sagrado Coração, Bauru, São Paulo, Brazil, **5** Department of Anatomy, São Paulo State University (UNESP), Institute of Biosciences, Botucatu, São Paulo, Brazil, **6** Department of Biostatistics, São Paulo State University (UNESP), Bioscience Institute, Botucatu, São Paulo, Brazil

¶ Membership of the Termite Genome Working Group is listed in the Acknowledgments.
* gi.vesentini@hotmail.com

OPEN ACCESS

Citation: Vesentini G, Barbosa AMP, Damasceno DC, Marini G, Piculo F, Matheus SMM, et al. (2020) Alterations in the structural characteristics of rectus abdominis muscles caused by diabetes and pregnancy: A comparative study of the rat model and women. PLoS ONE 15(4): e0231096. https://doi.org/10.1371/journal.pone.0231096

Editor: Lingjun Li, National University Singapore Yong Loo Lin School of Medicine, SINGAPORE

Received: September 24, 2019

Accepted: March 16, 2020

Published: April 3, 2020

Data Availability Statement: All data is available at http://hdl.handle.net/11449/190666.

Funding: The financial support provided by the Brazilian Public Health System (SUS) supported the treatment of all pregnant women. The authors gratefully acknowledge funding by São Paulo Research Foundation (FAPESP) (Grant No: #2016/09710-9 and #2016/01743-5). GV received a FAPESP scholarship (Grant No: #2014/26852-6).

Abstract

Background and objective

In the present study, we compared the effect of diabetic pregnancy on the rectus abdominis muscle (RAM) in humans and rats. We hypothesized that our animal model could provide valuable information about alterations in the RAM of women with Gestational Diabetes (GDM).

Method

Newborns female rats (n = 10/group) were administered streptozotocin (100 mg/kg body weight) subcutaneously and were mated on reaching adulthood, to develop the mild hyperglycemic pregnant (MHP) rat model. At the end of pregnancy, the mothers were sacrificed, and the RAM tissue was collected. Pregnant women without GDM (non-GDM group; n = 10) and those diagnosed with GDM (GDM group; n = 8) and undergoing treatment were recruited, and RAM samples were obtained at C-section. The RAM architecture and the distribution of the fast and slow fibers and collagen were studied by immunohistochemistry.

Results

No statistically significant differences in the maternal and fetal characters were observed between the groups in both rats and women. However, significant changes in RAM

***The Diamater Study Group**: Rudge MVC (Universidade Estadual Paulista), Barbosa AMP (Universidade Estadual Paulista), Calderon IMP (Universidade Estadual Paulista), Souza FP (Universidade Estadual Paulista), Hijas A (Case Western Reserve University), Sobrevia L (Pontificia Universidad Catolica de Chile), Palma MS (Universidade Estadual Paulista), Graeff CFO (Universidade Estadual Paulista), Arni RK (Universidade Estadual Paulista), Herculano RD (Universidade Estadual Paulista), Salvadori DF (Universidade Estadual Paulista), Matheus S (Universidade Estadual Paulista), Dal Pai Silva M (Universidade Estadual Paulista), Magalhães CG (Universidade Estadual Paulista), Costa RA (Universidade Estadual Paulista), Lima SAM (Universidade Estadual Paulista), Emanueli C (Imperial College London), Felisbino S (Universidade Estadual Paulista), Barbosa W (Universidade Estadual Paulista), Atallah A (Universidade Federal de São Paulo), Girão MJB (Universidade Federal de São Paulo), Di Bella Z (Universidade Federal de São Paulo), Uchoa SM (Universidade Católica de Pernambuco), Payão S (Faculdade de Medicina de Marília), Berghman B (Maastrich University), De Bie R (Maastrich University), Junginger B (Charité Universitätsmedizin Berlin), Alves FCB (Universidade Estadual Paulista), Rossignoli PS (Universidade Estadual Paulista), Abbade J (Universidade Estadual Paulista), Prudencio CB (Universidade Estadual Paulista), Orlandi MIG (Universidade Estadual Paulista), Gonçalves MI (Universidade Estadual Paulista), Nunes SK (Universidade Estadual Paulista), Catinelli BB (Universidade Estadual Paulista), Sarmento BV (Universidade Estadual Paulista), Pinheiro FA (Universidade Estadual Paulista), Sartorão CI (Universidade Estadual Paulista), Quiroz SBCV (Universidade Estadual Paulista), Reyes DRA (Universidade Estadual Paulista), Enriquez EMA (Universidade Estadual Paulista), Oliveira RG (Universidade Estadual Paulista), Floriano JF (Universidade Estadual Paulista), Marcondes JPC (Universidade Estadual Paulista), Costa SMB (Universidade Estadual Paulista), Dangió TD (Universidade Estadual Paulista), Pascon T (Universidade Estadual Paulista), Hallur LSR (Universidade Estadual Paulista), Melo JVF (Universidade Estadual Paulista), Takano L (Universidade Estadual Paulista), Reis FVDS (Universidade Estadual Paulista), Caldeirão TD (Universidade Estadual Paulista), Carr AM (Universidade Estadual Paulista), Garcia GA (Universidade Estadual Paulista), Rabadan GB (Universidade Estadual Paulista), Bassin HCM (Faculdade de Medicina de Marília), Suyama KS (Universidade Estadual Paulista), Damasceno LN (Universidade Estadual Paulista), Takemoto MLS (Universidade Estadual Paulista), Menezes MD (Universidade Estadual Paulista), Bussaneli DG (Universidade Estadual Paulista), Nogueira, VKC (Universidade Estadual Paulista), Lima PR (Universidade Estadual Paulista), Lourenço IO (Universidade Estadual Paulista), Marostica de Sá J (Universidade Estadual Paulista), Megid RA (Universidade Estadual Paulista), Caruso IP (Universidade Estadual Paulista), Rasmussen LT (Faculdade de Medicina de Marília), Prata GM (Universidade do Sagrado Coração), Piculo F (Faculdades Integradas de Bauru), Vesentini G (Universidade Estadual Paulista), Arantes MA (Universidade Estadual Paulista), Ferraz GAR (Universidade Estadual Paulista), Camargo LP (Universidade Estadual Paulista), Kron MR (Universidade Estadual Paulista), Corrente JE (Universidade Estadual Paulista), Nunes HRC (Universidade Estadual Paulista).

ANEXO 11

DIABETES RESEARCH AND CLINICAL PRACTICE 166 (2020) 108315

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Deleterious effects of gestational diabetes mellitus on the characteristics of the rectus abdominis muscle associated with pregnancy-specific urinary incontinence

Giovana Vesentini [a,b], Angélica M.P. Barbosa [c], Juliana F. Floriano [a,b], Sérgio L. Felisbino [d], Sarah M.B. Costa [a,b], Fernanda Piculo [a,b], Gabriela Marini [a,b,e], Sthefanie K. Nunes [a,b], David R.A. Reyes [a,b], João P.C. Marcondes [a,b], Raghavendra L.S. Hallur [a,b], Ariane L. Rozza [d], Cláudia G. Magalhães [a,b], Roberto Costa [a,b], Joelcio F. Abbade [a,b], José E. Corrente [f], Iracema M.P. Calderon [a,b], Selma M.M. Matheus [g], Marilza V.C. Rudge [a,b,*], The Diamater Study Group [1]

[a] Perinatal Diabetes Research Center, University Hospital, Botucatu Medical School, Univ Estadual Paulista_UNESP, São Paulo State, Brazil
[b] São Paulo State University (UNESP), Botucatu Medical School, Department of Gynecology and Obstetrics, Botucatu, Sao Paulo, Brazil
[c] São Paulo State University (UNESP), School of Philosophy and Sciences, Department of Physical Therapy and Occupational Therapy, Marília, São Paulo State, Brazil
[d] São Paulo State University (UNESP), Institute of Biosciences, Department of Morphology, Botucatu, São Paulo State, Brazil
[e] Universidade Sagrado Coração, Department of Health Sciences, Bauru, São Paulo, Brazil
[f] São Paulo State University (UNESP), Institute of Biosciences, Biostatistics Department, Botucatu, São Paulo, Brazil
[g] São Paulo State University (UNESP), Institute of Biosciences, Department of Anatomy, Botucatu, São Paulo State, Brazil

ARTICLE INFO

Article history:
Received 7 February 2020
Received in revised form
5 June 2020
Accepted 7 July 2020
Available online 15 July 2020

Keywords:
Pregnancy-specific urinary incontinence
Urinary incontinence
Gestational diabetes mellitus
Skeletal muscle

ABSTRACT

Aims: To evaluate the effects of gestational diabetes mellitus (GDM) on the structural characteristics of the rectus abdominis muscle (RAM) and its indirect effects on pregnancy-specific urinary incontinence (PSUI).

Methods: A total of 92 pregnant women were divided into four groups, according to their clinical conditions: non-GDM continent, non-GDM associated PSUI, GDM continent and GDM associated PSUI. The muscle morphometry (histochemistry and immunohistochemistry) for the fiber types and collagen fiber distribution, the ultrastructural analysis (transmission electron microscopy), the protein expression of fiber types and calcium signaling (Western blotting), and the content of types I and III collagen fiber (ELISA) in RAM collected at delivery were assessed.

Results: The GDM groups presented a significantly increased number of slow fibers and slow-twitch oxidative fiber expression; decreased fiber area, number of fast fibers, and area of collagen; an increase in central nuclei; ultrastructural alterations with focal lesion areas such as myeloid structures, sarcomere disorganization, and mitochondrial alteration. The

* Corresponding author at: Univ Estadual Paulista (UNESP), Department of Gynecology and Obstetrics, Distrito de Rubião Júnior, s/n, Botucatu, SP 18618-970, Brazil.
E-mail address: marilzarudge@gmail.com (M.V.C. Rudge).
[1] DIAMATER Study Group Department of Gynecology and Obstetrics, School of Medicine of Botucatu, Univ Estadual Paulista_UNESP, São Paulo State, Brazil.

https://doi.org/10.1016/j.diabres.2020.108315

Acknowledgments

The authors wish to thank the patients who donated their RAM tissue within the context of this study. The authors are also grateful to all medical staff at the Maternity of University Hospital Botucatu Medical School UNESP for excellent patient care.

** **The Diamater Study Group:** Rudge Mvc, Barbosa, AMP, Caldeiron IMP, Souza FP, Hijas A, Sobrevia L, Palma MS, Graeff CFO, Arni RK, Herculano RD, Salvadori DF, Mateus S, Dal Pai Silva M, Magalhães CG, Costa RA, Lima SAM, Emanueli C, Felisbino SI, Barbosa W, Atallah A, Girão MJB, Di Bella Z, Uchoa SM, Payão S, Berghman B, De Bie R, Junginger B, Alves FCB, Rossignoli PS, Abbade J, Prudencio CB, Orlandi MIG, Gonçalves MI, Nunes SK, Catinelli BB, Quiroz S, Sarmento BV, Pinheiro FA, Sartorão CI, Quiroz SBCV, Reyes DRA, Enriquez EMA, Oliveira RG, Floriano JF, Marcondes JPC, Sarmento, Costa SMB, Dangió TD, Pascon T, Hallur LSR, Melo JVF, Takano L, Reis FVDS, Caldeirão TD, Carr AM, Garcia GA, Rabadan GB, Bassin HCM, Suyama KS, Damasceno LN, Takemoto MLS, Menezes MD, Bussaneli DG, Nogueira, VKC, Lima PR, Lourenço IO, Marostica de Sá J, Megid RA, Caruso IP, Rasmussen LT, Prata GM, Piculo F, Vesentini G, Arantes MA, Ferraz GAR, Camargo LP, Kron MR, Corrente JE, Nunes HRC.

ANEXO 12

Aluno: TOC190251 - Fabiana Vieira Duarte de Souza Reis | Tocoginecologia - Doutorado

Disciplinas Cursadas no Programa	Calendário	Conceito	Frequência	Créditos	Carga Horária	Sigla Programa	Situação
A captação de Recursos Externos para Pesquisa	1º / 2020	A	100%	2	30	TOC	Aprovado
Estrutura e Redação do Trabalho Científico	1º / 2020	A	100%	2	30	TOC	Aprovado
Seminários de Projetos de Teses	1º / 2020	B	100%	3	45	TOC	Aprovado
Medicina Baseada em Evidências	2º / 2020	A	100%	2	30	TOC	Aprovado
Revisões Sistemáticas da Literatura e metanálise	2º / 2020	A	100%	2	30	TOC	Aprovado
Seminars in maternal and offspring health	2º / 2020	***	***	4	60	TOC	Matriculado
A captação de Recursos Externos para Pesquisa	1º / 2021	J	***	2	30	TOC	Cancelado
Redação de projeto de pesquisa	1º / 2021	J	***	4	60	TOC	Cancelado
Tópicos Especiais: Diabetes and Obesity in Pregnancy: From Patients to Molecular Mechanisms	1º / 2021	A	100%	3	45	TOC	Aprovado
Seminars in maternal and offspring health	2º / 2021	A	100%	4	60	TOC	Aprovado
Tópicos Especiais: “Previsões com Inteligência Artificial por Aprendizado de Máquina pelo método N2N4K orientado pela coorte Diamater para geração do conhecimento”	2º / 2022	A	100%	3	45	TOC	Aprovado
Disciplinas Aproveitadas	**Calendário**	**Conceito**	**Frequência**	**Créditos**	**Carga Horária**	**Sigla Programa**	**Situação**
Metodologia Científica	1 / 2018	B	93%	7	105.0	***	Aproveitamento de crédito em disciplina externa portador de título de Mestre
Planejamento em Saúde	1 / 2018	A	100%	6	90.0	***	Aproveitamento de crédito em disciplina externa portador de título de Mestre
Seminários de Pesquisa em Ensino em Saúde	1 / 2018	A	100%	5	75.0	***	Aproveitamento de crédito em disciplina externa portador de título de Mestre

Total de Créditos Cumpridos : 39.0	Total de Créditos Matriculados : 4.0

Título Projeto :

QUANTIFICAÇÃO E CARACTERIZAÇÃO DE EXOSSOMOS DO SANGUE PERIFÉRICO E DO CORDÃO UMBILICAL DE GESTANTES COM DIABETES MELLITUS GESTACIONAL COMO POTENCIAL BIOMARCADOR PARA A DOENÇA CARDÍACA CONGÊNITA DOS DESCENDENTES

Situação Pesquisa : Coleta dos dados; Processamento dos dados; Análise dos dados; Processamento de dados e análise estatística;

Data Última Matrícula : 30/11/2022

ANEXO 13

CFM-CRM

Conselho Federal e Regional de Medicina

CERTIFICADO

A Comissão de Especialidades Médicas do Conselho Regional de Medicina do Estado de São Paulo, certifica que analisou e aprovou, conforme as normas em vigor, o registro de qualificação de especialista do(a) médico(a) abaixo:

Dr(a).: **FABIANA VIEIRA DUARTE DE SOUZA REIS - CRM 100944**

Especialidade: **PEDIATRIA**
RQE: **101917**
Data de Aprovação: **07/06/2022**

São Paulo, 23 de junho de 2022.

Dra. Irene Abramovich
Presidente

Dr. Angelo Vattimo
Diretor 1º Secretário

CFM-CRM

ANEXO 14

CFM-CRM

Conselho Federal e Regional de Medicina

CERTIFICADO

A Comissão de Especialidades Médicas do Conselho Regional de Medicina do Estado de São Paulo, certifica que analisou e aprovou, conforme as normas em vigor, o registro de qualificação de especialista do(a) médico(a) abaixo:

Dr(a).: **FABIANA VIEIRA DUARTE DE SOUZA REIS - CRM 100944**

Especialidade: **PEDIATRIA**
RQE: **101917**
Data de Aprovação: **07/06/2022**

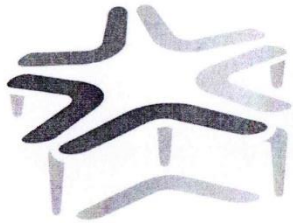
Área de Atuação: **MEDICINA INTENSIVA PEDIÁTRICA**
RQE: **1019171**
Data de Aprovação: **06/07/2022**

São Paulo, 13 de julho de 2022.

Dra. Irene Abramovich
Presidente

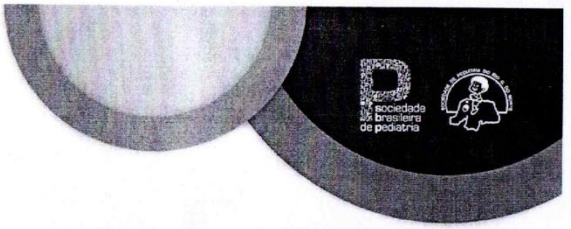
Dr. Angelo Vattimo
Diretor 1º Secretário

CFM-CRM



40º Congresso Brasileiro de Pediatria

Consolidando as conquistas em todo o Brasil



CERTIFICADO

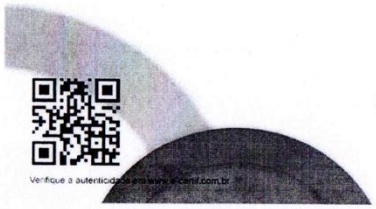
Certificamos que

FABIANA REIS

Participou do 40° Congresso Brasileiro de Pediatria, realizado em Natal-RN, como aluno(a) do Curso: PRÉ-CONGRESSO DERMATOLOGIA PEDIÁTRICA - DIAGNÓSTICO TOPOGRÁFICO E CONFORME A FAIXA ETÁRIA, com carga horária de 4 horas.

Natal, 7 de maio de 2022.

Código de Autenticação: XPZS24



LUCIANA RODRIGUES SILVA
Presidente da Sociedade Brasileira de Pediatria

KÁTIA CORREIA LIMA
Presidente do 40º Congresso Brasileiro de Pediatria e da Sociedade de Pediatria do Rio Grande do Norte

Nº 134339 e
Nº 134341

ANEXO 15

40º Congresso Brasileiro de Pediatria
CBP
Consolidando as conquistas em todo o Brasil

sociedade brasileira de pediatria

CERTIFICADO

Certificamos que

FABIANA REIS

Participou do 40° Congresso Brasileiro de Pediatria, realizado em Natal-RN, como aluno(a) do Curso: PRÉ-CONGRESSO NUTROLOGIA PARA O PEDIATRA (CASOS CLÍNICOS E DISCUSSÕES), com carga horária de 4 horas.

Natal, 7 de maio de 2022.

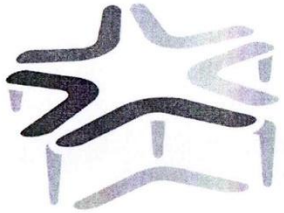
Código de Autenticação: XPZS24

Verifique a autenticidade em www.eventil.com.br

LUCIANA RODRIGUES SILVA
Presidente da Sociedade Brasileira de Pediatria

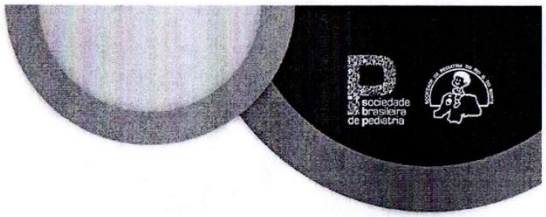
KÁTIA CORREIA LIMA
Presidente do 40º Congresso Brasileiro de Pediatria e da Sociedade de Pediatria do Rio Grande do Norte

CNA
Nº 134339 e Nº 134341



40º Congresso Brasileiro de Pediatria

Consolidando as conquistas em todo o Brasil



CERTIFICADO

Certificamos que

FABIANA REIS

Participou do 40° Congresso Brasileiro de Pediatria, realizado em Natal/RN no período de 3 a 7 de maio de 2022, com carga horária total de 43 horas.

Natal, 7 de maio de 2022.

Código de Autenticação: XPZS24

LUCIANA RODRIGUES SILVA
Presidente da Sociedade Brasileira de Pediatria

KÁTIA CORREIA LIMA
Presidente do 40º Congresso Brasileiro de Pediatria e da Sociedade de Pediatria do Rio Grande do Norte

CNA
Nº 134339 e Nº 134341

ANEXO 17


DEFESA DA PEDIATRIA
sociedade brasileira de pediatria
CERTIFICADO
· Biênio 2020/2021 ·
A Sociedade Brasileira de Pediatria reconhece o (a) Dr.(a)
FABIANA VIEIRA DUARTE DE SOUZA REIS, SÃO PAULO
como pediatra associado (a) atuante na promoção da saúde
e qualidade de vida de crianças e adolescentes do Brasil.
Rio de Janeiro, 17 de junho de 2020
Luciana Rodrigues Silva

ANEXO 18

fema

Fundação Educacional do Município de Assis
Instituto Municipal de Ensino Superior de Assis
Campus "José Santilli Sobrinho"

Certificado

Certificamos que **Fabiana Vieira Duarte** participou da mesa redonda *"Adolescência: crescimento, desenvolvimento e seus aspectos emocionais"*, para alunos do Curso de Medicina, promovida pela Coordenadoria do Curso de Medicina do Instituto Municipal de Ensino Superior de Assis (IMESA), unidade de ensino da Fundação Educacional do Município de Assis (FEMA), no dia 24 de abril de 2019, perfazendo um total de 3 horas.

Assis, abril de 2019.

Prof. Dr. Jairo Cesar dos Reis
Coordenador do Curso de Medicina

Av. Getúlio Vargas, 1200 - Vila Nova Santana - Assis - SP
CEP 19807-634 - Fone/Fax: (18) 3302-1055 - http://www.fema.edu.br

Fundação Educacional do Município de Assis
Instituto Municipal de Ensino Superior de Assis
Campus "José Santilli Sobrinho"

Certificado

Certificamos que **Fabiana Vieira Duarte de Souza Reis** participou da Mesa Redonda com o tema *"Hebiatria"*, realizada para alunos do IESC da 3ª Etapa, promovida Coordenadoria do Curso de Medicina do Instituto Municipal de Ensino Superior de Assis (IMESA), unidade de ensino da Fundação Educacional do Município de Assis (FEMA), no dia 05 de novembro de 2019, perfazendo um total de 2 horas.

Assis, novembro de 2019.

Prof. Dr. Jairo Cesar dos Reis
Coordenador do Curso de Medicina

Av. Getúlio Vargas, 1200 - Vila Nova Santana - Assis - SP
CEP 19807-634 - Fone/Fax: (18) 3302-1055 - http://www.fema.edu.br

ANEXO 20

Axeno 21

Aprovação do projeto pelo CEP

UNESP -FACULDADE DE MEDICINA DE BOTUCATU

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: QUANTIFICAÇÃO E CARACTERIZAÇÃO DE EXOSSOMOS DO SANGUE PERIFÉRICO E DO CORDÃO UMBILICAL DE GESTANTES COM DIABETES MELLITUS GESTACIONAL COMO POTENCIAL BIOMARCADOR PARA A DOENÇA CARDÍACA CONGÊNITA DOS DESCENDENTES

Pesquisador: Fabiana Vieira Duarte de Souza Reis

Área Temática:

Versão: 2

CAAE: 43176920.9.0000.5411

Instituição Proponente: Departamento de Ginecologia e Obstetrícia

Patrocinador Principal: CONSELHO NACIONAL DE DESENVOLVIMENTO CIENTIFICO E TECNOLOGICO-CNPQ

DADOS DO PARECER

Número do Parecer: 4.671.886

Apresentação do Projeto:

As informações elencadas nos campos "Apresentação do projeto", "Objetivo da pesquisa" e "Avaliação de riscos e benefício", foram retiradas do arquivo "Informações básicas da Pesquisa"

O Diabetes Mellitus Gestacional (DMG), está associado a cardiopatia fetal e alterações da estrutura vascular e funcional, e descendentes de mães diabéticas do tipo 1 e tipo 2, tem o risco aumentado para malformação cardíaca congênita e hipertrofia cardíaca. As malformações cardíacas nos filhos de mães diabéticas são cinco vezes maiores que nas gestações normais. O exame de ecocardiografia (ECO) é padrão outro para avaliar e identificar miopatia cardíaca congênita, tanto no feto quanto no neonato. A concentração e o conteúdo dos exossomos circulantes podem representar novos aspectos clínicos biomarcadores e adicionalmente expandem o conhecimento da fisiopatologia das doenças, inclusive em mulheres com DMG. Justificativa: O estudo de todos estes fatores pode ser a chave para o entendimento dos mecanismos que levam ao desenvolvimento da DCC, como também forma de diagnóstico precoce, menos invasivo e seguro, prognóstico mais assertivo, assim como subsidiar novas perspectivas terapêuticas que permitirão tratamento individualizado, efetivo e poderão minimizar efeitos deletérios a longo prazo. Está claro que os estudos dos exossomos é extremamente promissor,

Endereço: Chácara Butignolli , s/n
Bairro: Rubião Junior **CEP:** 18.618-970
UF: SP **Município:** BOTUCATU
Telefone: (14)3880-1609 **E-mail:** cep@fmb.unesp.br

novas publicações sobre os benefícios de sua utilização como biomarcador e como terapia são publicados mensalmente por grupos de pesquisas relevantes internacionais, mostrando o potencial dessa tecnologia e os benefícios de sua utilização. Hipótese Nossa hipótese é que serão identificados os exossomos como biomarcadores da DCC em filhos de mães com DMG.

Metodologia: Estudo longitudinal. Este projeto será desenvolvido imbricado com o projeto "Quantificação e caracterização de exossomos placentários, do sangue periférico e do cordão umbilical de gestantes hiperglicêmicas: Potencial aplicabilidade como biomarcadores e agente terapêutico livre de células para a miopatia diabética gestacional e incontinência urinária", em que as coletas de sangue materno e sangue do cordão descritas no presente projeto, estão aprovadas sob CAAE: 23868619.9.0000.5411 no Comitê de Ética em Pesquisa (CEP) da Faculdade de Medicina de Botucatu UNESP/Botucatu.

As análises propostas neste estudo coletarão dados somente das participantes e seus respectivos descendentes que forem incluídos no projeto previamente aprovado e ressaltamos que não serão incluídas nenhuma outra participante além das incluídas no referido projeto aprovado. Este estudo está vinculado e terá suporte do Projeto Temático Diamater (Processo Fapesp 2016/01743-5/ Sprint Fapesp - Imperial College London 2018/22406-2) e dos Projetos ExInnova (CNPq Process: 409902/2018-7 e Research England Global Challenges Research Fund 2019/20) com importante colaboração internacional da PhD Costanza Emanueli, do Imperial College London, London, UK. Serão compostos dois grupos, sendo um com gestantes não diabéticas (37 participantes) e outro com gestantes com diagnóstico de DMG (37 participantes) que tiveram sangue coletado no projeto "Quantificação e caracterização de exossomos placentários, do sangue periférico e do cordão umbilical de gestantes hiperglicêmicas: Potencial aplicabilidade como biomarcadores e agente terapêutico livre de células para a miopatia diabética gestacional e incontinência urinária" (CAAE: 23868619.9.0000.5411). Levantamento da amostra (aprovado sob CAAE: 23868619.9.0000.5411): Gestantes: O levantamento da amostra de gestantes e coleta de dados será realizado no Ambulatório de Obstetrícia da Maternidade do Hospital das Clínicas da Faculdade de Medicina de Botucatu; Neonatos: A avaliação do neonato destas gestantes será realizada no Serviço de Neonatologia da FMB. As coletas respeitarão os protocolos técnicos do hospital e dos serviços envolvidos. Etapas I - Coleta de sangue periférico materno - (aprovado sob CAAE: 23868619.9.0000.5411): II - Exame de Ecocardiografia fetal III - Coleta de sangue de cordão no parto - (aprovado sob CAAE: 23868619.9.0000.5411): IV - Exame de Ecocardiografia neonatal - Coleta de sangue do RN (no momento do exame do "pezinho" terá coletada uma gota do sangue no cartão Novaplex, sem que seja necessário realizar qualquer outro procedimento para coleta

deste sangue. O sangue terá a análise do perfil exossomal) V- Acompanhamento do descendente entre 2-3 meses de idade com Ecocardiografia (Neste mesmo momento também serão realizadas as medidas antropométricas) VI- Acompanhamento do descendente entre 18-24 meses de idade com Ecocardiografia e coleta de sangue (A coleta de sangue será obtida no mesmo momento de exame de rotina de acompanhamento, e não será necessário realizar outra punção na criança. Será coletado em torno de 4 mL de sangue para avaliação dos exossomos e do perfil lipídico e glicêmico). O exossomo será quantificado e caracterizado. Para o presente estudo, serão utilizados os resultados das análises de quantificação e caracterização dos exossomos das gestantes participantes do projeto citado anteriormente, além de convidá -las a realizar as etapas II a VI, para a realização dos exames de Ecocardiografia fetal, neonatal, 2-3 meses e 18-24 meses de vida. Dessa forma, não haverá recrutamento de participantes além das previstas no tamanho amostral do Projeto Mãe Coleta a ser apreciada pelo CEP Exame de Ecocardiografia Neonatal: entre 2 e 7 dias de vida. Serão avaliados na Unidade Neonatal do HC da FMB e terão os seguintes dados coletados: Apagar, Peso (P), Comprimento (C), Perímetro cefálico (PC), Perímetro braquial (PB), Índice ponderal (IP), Dobras cutâneas (Pg), Área muscular do braço (AM), Área de gordura do braço (AG) e Ecocardiografia. Exame de sangue Neonatal: O neonato participante, no momento do exame do "pezinho" terá coletada uma gota do sangue no cartão Novaplex, sem que seja necessário realizar qualquer outro procedimento para coleta deste sangue. O sangue terá a análise do perfil exossomal (mesma análise de sangue materno). Exame de Ecocardiografia entre 2- 3 meses de idade + coleta de sangue Exame de Ecocardiografia e coleta de sangue entre 18-24 meses de idade + coleta de sangue Devolutiva para participantes: Todas as participantes serão informadas dos resultados do exame de Ecocardiografia fetal e neonatal bem como dos exames de sangue e variáveis antropométricas, as que apresentarem sinais de alteração, serão encaminhadas para o atendimento especializado da FMB para que a conduta e protocolo estabelecidos sejam aplicados. Análise Estatística: A análise estatística, bem como a escolha dos testes de comparação, será executadas respeitando os pressupostos determinados pelos resultados, características e comportamento das variáveis de estudo obtidas para todos os grupos. Para todas as comparações estatísticas, será considerado limite mínimo de confiança de 95% (limite de significância $p<0,05$).

Critério de Inclusão: Serão incluídas as gestantes entre 24ª e 30ª semana gestacional que realizarem assistência pré-natal no HC da FMB, com idade igual ou acima de 18 anos, com e sem diagnóstico de Diabetes Mellitus Gestacional, e que concordarem em participar da pesquisa e assinarem o termo de consentimento livre e esclarecido.

Endereço: Chácara Butignolli , s/n
Bairro: Rubião Junior **CEP:** 18.618-970
UF: SP **Município:** BOTUCATU
Telefone: (14)3880-1609 **E-mail:** cep@fmb.unesp.br

Critério de Exclusão: Não serão incluídas no presente estudo mulheres que não respeitarem os critérios de inclusão e apresentarem diagnóstico de Diabetes mellitus Tipo I e Tipo II (DM I e II); e doenças neuromusculares.

Tamanho da amostra: 74 participantes.

Objetivo da Pesquisa:

Objetivo: Associar a quantificação e caracterização dos exossomos do sangue periférico e do cordão umbilical de gestantes com diabetes mellitus gestacional como potencial biomarcador para a doença cardíaca congênita dos seus descendentes. Objetivos específicos: 1 - Identificar possíveis biomarcadores para a doença cardíaca congênita do descendente de mães com DMG; e validar e patentear nova metodologia de diagnóstico para DCC. 2 - Acompanhar a evolução das condições cardíacas, lipídicas e glicêmicas do descendente ao longo de anos do nascimento.

Avaliação dos Riscos e Benefícios:

Riscos: O exame de Ecocardiograma é realizado utilizando sistema de ultrassom, que é indolor porque se trata de coletar imagens do coração e não traz nenhum desconforto à mãe ou ao feto/neonato. A coleta de sangue pode causar desconforto por decorrência da perfuração pela agulha.

Benefícios: Este trabalho apresenta metodologias extremamente inovadores e com alto potencial de validar novo biomarcador extremamente efetivo e precoce para diagnóstico, que pode beneficiar o entendimento do prognóstico a longo prazo, maximizando as chances futuras de terapias precoces e efetivas, evitando efeitos deletérios na vida adulta. Além disso, este estudo abre caminho para novos conhecimentos sobre aspectos que não estão claros sobre a fisiopatologia da DCC.

Comentários e Considerações sobre a Pesquisa:

Estudo nacional e unicêntrico, longitudinal. Caráter acadêmico, realizado para a obtenção do título de doutor. Patrocinador: Conselho Nacional de Desenvolvimento Cientifico e Tecnológico -CNPQ. País de Origem: Brasil. Número de participantes incluídos: 74. Previsão de início e encerramento do estudo: junho de 2021 a dezembro de 2023. Local da pesquisa: Hospital e Ambulatórios da Faculdade de Medicina de Botucatu/SP A coleta do material biológico será realizada no

ambulatório da maternidade, no Centro Obstétrico da maternidade do HCFMB e no ambulatório de pediatria, de acordo coma respectiva coleta. A coleta está dividida em etapas a saber: I - Coleta de sangue periférico materno, II - Exame de Ecocardiografia fetal, III - Coleta de sangue de cordão no parto, IV - Exame de Ecocardiografia neonatal e coleta de sangue no RN, V - acompanhamento do descendente entre 2-3 meses de idade com ECO e, VI - Acompanhamento do descendente entre 18-24 meses de idade com ECO e coleta de sangue. O material coletado para este projeto não será armazenado uma vez que serão processados após a coleta, portanto, dispensa o regulamento de biorrepositório. As etapas I e III, referentes às coletas de sangue materno e do cordão umbilical, estão contempladas dentro do projeto de pesquisa "Projeto Mãe" intitulado "Quantificação e caracterização de exossomos placentários, do sangue periférico e do cordão umbilical de gestantes hiperglicêmicas: Potencial aplicabilidade como biomarcadores e agente terapêutico livre de células para a miopatia diabética gestacional e incontinência urinária" (CAAE: 23868619.9.0000.5411), de responsabilidade da Profa. Marilza Vieira Cunha Rudge, orientadora do presente projeto de doutorado. Para o presente estudo, serão utilizados os resultados das análises de quantificação e caracterização dos exossomos das gestantes participantes do projeto citado anteriormente, além de convidá-las a realizar as etapas II, IV, V e VI, para a realização dos exames de Ecocardiografia fetal e neonatal, além da coleta de sangue neonatal. Dessa forma, não haverá recrutamento de participantes além das previstas no tamanho amostral do Projeto Mãe.

Os pesquisadores atenderam as pendencias apontadas quanto aos critérios de inclusão e exclusão; e a readequação do TCLE para atendimento da Resolução 466/2012.

Considerações sobre os Termos de apresentação obrigatória:

Apresentados os termos: folha de rosto, projeto de pesquisa, anuências institucionais, TCLE aos participantes da pesquisa.

Não foi apresentado biorrepositório, pois não haverá armazenamento de amostras biológicas humanas.

Recomendações:

-

Conclusões ou Pendências e Lista de Inadequações:

Após análise em REUNIÃO ORDINÁRIA, o Colegiado deliberou APROVADO o projeto de pesquisa apresentado.

Considerações Finais a critério do CEP:

Conforme deliberação do Colegiado, em REUNIÃO ORDINÁRIA do Comitê de Ética em Pesquisa FMB/UNESP, realizada em 20/04/2021, o Projeto de Pesquisa encontra-se APROVADO.

A coleta de dados deverá ser iniciada após data de aprovação do CEP.

Apresentar relatório final de atividades após finalização da pesquisa.

Att.

CEP-FMB

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_652097.pdf	29/03/2021 19:09:35		Aceito
Outros	Carta_resposta.docx	29/03/2021 19:07:11	Fabiana Vieira Duarte de Souza Reis	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	29/03/2021 19:06:25	Fabiana Vieira Duarte de Souza Reis	Aceito
Folha de Rosto	Folha_de_rosto.pdf	18/01/2021 11:04:06	Fabiana Vieira Duarte de Souza Reis	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_Ciencia_e_Anuencia_Maternidade.pdf	18/11/2020 17:31:31	Fabiana Vieira Duarte de Souza Reis	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_Ciencia_e_Anuencia_Institucional.pdf	18/11/2020 17:31:21	Fabiana Vieira Duarte de Souza Reis	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_Ciencia_e_Anuencia_HCFMB.pdf	18/11/2020 17:31:02	Fabiana Vieira Duarte de Souza Reis	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_Ciencia_e_Anuencia_Ambulatorio.pdf	18/11/2020 17:30:41	Fabiana Vieira Duarte de Souza Reis	Aceito
Declaração de Instituição e Infraestrutura	Termo_de_Ciencia_e_Anuencia_Neonatologia.pdf	18/11/2020 17:29:51	Fabiana Vieira Duarte de Souza Reis	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_de_doutorado_Fabiana_Reis.pdf	18/11/2020 17:27:48	Fabiana Vieira Duarte de Souza Reis	Aceito

Endereço: Chácara Butignolli , s/n
Bairro: Rubião Junior **CEP:** 18.618-970
UF: SP **Município:** BOTUCATU
Telefone: (14)3880-1609 **E-mail:** cep@fmb.unesp.br

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BOTUCATU, 26 de Abril de 2021

Assinado por:
Trajano Sardenberg
(Coordenador(a))

Endereço: Chácara Butignolli , s/n
Bairro: Rubião Junior **CEP:** 18.618-970
UF: SP **Município:** BOTUCATU
Telefone: (14)3880-1609 **E-mail:** cep@fmb.unesp.br