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Associação da Derivação Gastrojejunal em Y-de-Roux Prévia à Gestação com os Desfechos Perinatais, Obstétricos e o Desenvolvimento Cognitivo da Prole

Dissertação de Mestrado

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LISTA DE ABREVIATURAS

AGA	*Adequate for gestational age*
BMI	*Body mass index*
BW	*Birth weight*
CI	*Confidence interval*
GA	*Gestational age*
GDM	*Gestational diabetes mellitus*
GEE	*Generalized estimating equation*
GWG	*Gestational weight gain*
HPD	*Hypertensive pregnancy disorders*
IMC	Índice de massa corporal
IOM	*Institute of Medicine*
LGA	*Large for gestational age*
MPR	Matrizes Progressivas de Raven
MPCR	Matrizes Progressivas Coloridas de Raven
OR	*Odds ratio*
RCPM	*Raven's Colored Progressive Matrices*
RPM	*Raven's Progressive Matrices*
RYGB	*Roux-en-Y gastric bypass*
SD	*Standard deviation*
SE	*Standard error*
SGA	*Small for gestational age*
WC	*Waist circumference*
WHO	*World Health Organization*

Capítulo 1 - Introdução

A obesidade é uma doença multifatorial de proporções epidêmicas (1, 2). No Brasil, a prevalência aumentou de 11,4% em 2006 para 17,9% em 2014, mais frequente (18,2%; IC 95%: 17.2-19.1) entre as mulheres (3, 4). Durante a gestação, a obesidade materna, classificada através do índice de massa corporal (IMC) pré-gestacional maior ou igual a 30 kg/m² (5), associa-se a desfechos obstétricos adversos tais como diabetes mellitus gestacional (DMG), hipertensão arterial sistêmica, pré-eclâmpsia, prematuridade, macrossomia fetal, malformações congênitas, mortalidade fetal e infantil, além de apresentar associação com índice aumentado de parto cesáreo (6-11).

A obesidade gestacional está relacionada a um aumento da inflamação sistêmica e placentária (12). Um ambiente intrauterino (*milieu*) subótimo pode induzir, através do incremento de citocinas do plasma materno, a ativação da inflamação placentária, sugerindo modificações de funções endócrinas, imunes e influenciando o crescimento fetal (13, 14). Modelos experimentais e estudos clínicos com mães obesas têm demonstrado um possível papel da programação intrauterina sobre o metabolismo da prole (15, 16).

O conceito de programação metabólica indica que as exposições adversas durante o período fetal e neonatal, como a obesidade materna, o tabagismo, o excesso de peso ao nascer, o baixo peso ao nascer, o crescimento acelerado nos primeiros anos de vida, a ausência de aleitamento materno e os fatores ambientais influenciam diretamente o crescimento e o desenvolvimento de doenças tardiamente (17-24). Uma revisão sistemática apontou de forma consistente o aumento no risco de desenvolvimento de excesso de peso entre os filhos nascidos de mães que tinham sobrepeso (OR 1.95; IC 95%: 1.77-2.13) e obesidade (OR 3.06; IC 95%: 2.68-3.49) pré-gestacional em relação a mulheres com índice de massa corporal (IMC) normal (25).

Estudos têm demonstrado, ainda, associação negativa entre obesidade gestacional e neurodesenvolvimento da prole (26-28), sugerindo alterações estruturais e funcionais durante o período de desenvolvimento cerebral determinadas por um *milieu* subótimo (29, 30). Os mecanismos fisiopatológicos que relacionam a obesidade materna à disfunção cognitiva da prole ainda não são totalmente conhecidos. Contudo, o efeito pró-inflamatório da obesidade, provavelmente transmitido através da barreira hematoencefálica, constitui potencial fator (31).

A obesidade gestacional está associada à endotoxemia subclínica (12). Modelos experimentais demostram que a exposição fetal à inflamação e a endotoxinas intraútero pode desencadear a ativação microglial e a infiltração de macrófagos no cérebro fetal, possibilitando mudanças na arquitetura e lesão da substância branca cerebral durante o período perinatal (32-34).

Estudo recente avaliou 28 recém-nascidos a termo após duas semanas de nascimento e encontrou associação negativa entre obesidade materna, classificada através do IMC e do percentual de gordura corporal, e o desenvolvimento de substância branca cerebral (30). Casas et al. (35) observaram diminuição nos escores de avaliação cognitiva da prole no primeiro e segundo ano de vida paralelamente ao aumento do IMC pré-gestacional. Neggers et al. (36) avaliaram o desenvolvimento psicomotor e o quociente de inteligência (QI) em 355 crianças com idade média de 5 anos e, apesar da obesidade materna não estar relacionada a prejuízos no desenvolvimento motor da prole, em crianças nascidas de mães obesas, o escore no teste de QI foi 5 pontos menor do que o resultado encontrado entre crianças nascidas de mães com IMC pré-gestacional normal.

Em um estudo longitudinal que avaliou 11.025 e 9.882 crianças aos 5 e 7 anos de idade, respectivamente, o IMC materno pré-gestacional associou-se negativamente com o desempenho cognitivo tanto aos 5 quanto aos 7 anos de idade (26).

A derivação gastrojejunal em Y-de-Roux (DGYR) é a técnica cirúrgica mais amplamente realizada para o tratamento da obesidade em pacientes que não apresentam boa resposta ao tratamento clínico, promovendo perda sustentada de peso e redução da mortalidade geral (37, 38). Atualmente, os critérios para a indicação cirúrgica são: 1) IMC ≥ 40 kg/m²; 2) IMC ≥ 35 kg/m² com comorbidades associadas (39).

As mulheres representam 70% a 80% dos pacientes submetidos ao tratamento cirúrgico da obesidade e 49% encontra-se em idade reprodutiva (38, 40). Apesar de muitas mulheres não atingirem um peso ideal e ainda estarem com obesidade no momento da concepção, a cirurgia bariátrica está associada a menor incidência de DMG, pré-eclâmpsia e recém nascidos grandes para a idade gestacional (GIG) em comparação a mulheres obesas ou controles pareados de acordo com o IMC pré-gestacional, ambos não submetidos à cirugia bariátrica (41-43), sugerindo um *milieu* menos desfavorável, resultante de alterações induzidas pela cirurgia e/ou perda de peso.

Entretanto, as gestações que cursam após a cirurgia bariátrica materna estão relacionadas a um risco aumentado para recém-nascidos pequenos para a idade gestacional (PIG), parto prematuro, anemia materna e admissão em cuidados intensivos neonatais (40-42).

Uma revisão sistemática (42) com objetivo de avaliar os desfechos obstétricos e neonatais em gestantes previamente submetidas à cirurgia bariátrica incluiu 17 estudos observacionais e encontrou menor incidência de DMG (OR 0.47; IC 95%: 0.40-0.56; P<0.001), pré-eclâmpsia (OR 0.45; IC 95%: 0.25-0.80; P=0.007), bebês GIG (OR 0.46; IC 95%: 0.34-0.62; P<0.001) e maior incidência de parto prematuro (OR 1.31; IC 95%: 1.08-1.58; P=0.006), bebês PIG (OR 1.93; IC 95%: 1.52-2.44; P<0.001), admissão em cuidados intensivos neonatais (OR 1.33; IC 95%: 1.02-1.72; P=0.03) e anemia materna (OR 3.41; IC 95%: 1.56-7.44).

Gestantes com cirurgia bariátrica prévia apresentam maior frequência de deficiências nutricionais (44, 45). Apesar de ainda não existir consenso na literatura, a maioria dos autores recomenda um período de 12 a 18 meses entre a cirurgia e o início de uma gestação. Este intervalo tem como objetivo evitar que a mãe, o bebê, ou ambos, possam desenvolver prejuízos a sua saúde neste período de relativo estado de inanição, considerando que a rápida perda de peso imediatamente após a cirurgia é um risco potencial para o desenvolvimento de deficiências nutricionais (44-48).

Os principais desfechos adversos neonatais relatados associando deficiências de micronutrientes após a cirurgia bariátrica foram complicações visuais por deficiência de vitamina A, defeitos do tubo neural por deficiência de folato, comprometimento neurológico por deficiência de vitamina B12 e hemorragia intracraniana por deficiência de vitamina K (47). Entretanto, a literatura disponível sobre desfechos adversos relacionados às deficiências nutricionais maternas após a cirurgia bariátrica é ainda limitada e permanece inconclusiva (47).

O estado nutricional materno antes e durante a gravidez é potencialmente um preditor da função cognitiva, considerando que a mãe é a única fonte de nutrição para o crescimento fetal, incluindo o desenvolvimento do cérebro. No entanto, os resultados de estudos observacionais que avaliaram esta relação, independentemente da cirurgia bariátrica materna prévia, foram inconclusivos (49). É possível que a associação entre estrutura cerebral e alterações funcionais determinadas por um *milieu* adverso (15,16) na obesidade possa estar relacionada a deficiências de micronutrientes induzidas pela obesidade *per se* ou pela perda de peso cirurgicamente induzida (25).

Considerando que as exposições precoces durante a vida intrauterina e pós-natal têm importância fundamental no crescimento e desenvolvimento da prole, que estudos sobre o desenvolvimento cognitivo de filhos que nasceram após a cirurgia bariátrica materna não

existem e que estudos que avaliaram o estado nutricional da prole são escassos nesta população, faz-se necessário o entendimento e acompanhamento destas crianças em longo prazo. Dessa forma, o objetivo deste estudo é avaliar a associação entre a DGYR prévia à gestação com o desenvolvivemento cognitivo tardio da prole em comparação a dois grupos controles não submetidos à cirurgia bariátrica e com diferentes categorias de IMC pré-gestacional, maior e menor do que 35 kg/m². Ademais, será avaliada a associação da DGYR com os desfechos perinatais e obstétricos e o estado nutricional atual da prole a partir de cinco anos de idade.

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Capítulo 2 – Artigo original – A ser submetido ao periódico JAMA Pediatrics

Does maternal bariatric surgery associate with obstetric outcomes and long-term cognition in the offspring?

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Abstract

Background: Maternal obesity is adversely associated to obstetric and perinatal outcomes and cognitive and neurodevelopment of the offspring. It is unclear whether bariatric surgery prior to pregnancy could affect long-term cognition in the offspring.

Objectives: To assess whether Roux-en-Y gastric bypass (RYGB) prior to pregnancy is associated with long-term cognition in the offspring. Additionally, we evaluated perinatal, obstetric, and long-term children nutritional status

Methods: Singleton births from women submitted to RYGB between 2000 and 2010 (BS) were matched to two control births by maternal age, delivery year and newborn gender. Control group 1 (CG1) and control group 2 (CG2) included women with pre-pregnancy body mass index (BMI) <35 kg/m² and ≥35 kg/m², respectively, without a history of bariatric surgery. Mothers and children attended a contemporaneous evaluation for cognition evaluation.

Results: Thirty-two children from each group (n=96) were analyzed, most female (59%), caucasian (82%), mean age of 7 ± 2y. Crude analyses disclosed a higher global cognitive score in the offspring from women with a mean pre-pregnancy BMI of 25 ± 4 kg/² compared to offspring from women with a mean pre-pregnancy BMI of 37 ± 2 kg/m², both without a history of bariatric surgery. However, adjusting for sociodemographic confounders, social class and maternal education, group effect disappeared. Family economic class was the strongest predictor (low: β= -20.57; P<0.001; middle: β= -9.34; P=0.019) of offspring global cognitive score and the only covariate remaining statistically significant in all analyses. Gestational diabetes mellitus (OR 0.06; 95% CI: 0.03;0.35) and hypertensive disorders (OR 0.09; 95% CI: 0.01;0.40) were less frequent in BS *vs.* CG2. Post-RYGB pregnancies were associated with lower gestational weight gain *vs.* CG1 (P=0.019), lower birth weight (P=0.021) compared to both control peers and reduced frequency for large for gestational age

vs. CG2 (OR 0.13 95% CI: 0.02;0.54). Long-term prevalence of overweight and obesity among children was higher (OR 4.59; 95% CI: 1.55; 13.61; P=0.006) in the CG2 (78%) *vs.* CG1 (44%) and similar to BS (65%).

Conclusions: RYGB prior to pregnancy did not associate with long-term cognition in the offspring. Pregnancy in women previously submitted to bariatric surgery is associated with less frequency of gestational diabetes mellitus and hypertensive disorders when compared to pregnancy in obese women (pre-pregnancy BMI ≥35 kg/m²) and with lower birth weight compared to both women with pre-pregnancy BMI higher and lower than 35 kg/m².

Keywords: Bariatric surgery; Roux-en-Y gastric bypass; Obesity; Children; Raven Colored Progressive Matrices; Raven Progressive Matrices; Intelligence; Cognition

Introduction

Maternal obesity is adversely associated with obstetric and perinatal outcomes by increasing risk for gestational diabetes mellitus, stillbirth, prematurity, congenital malformation, fetal and infant death (1-5)

A pro-inflammatory suboptimal *milieu* is associated to early pregnancy obesity, which can lead to increased insulin resistance compared to lean mothers (6, 7). Experimental models and clinical studies with obese mothers have shown a possible role of maternal programming over offspring metabolism (8, 9). Fetal growth could be influenced by inflammation generated by this obese intrauterine milieu (10). At second trimester pregnancy, increased maternal C-reactive protein, a systemic inflammation biormarker, was associated with childhood adiposity by the age at 7y to 10y (11). In addition, in the long term, studies have reported an association between maternal obesity and cognitive and neurodevelopment of the offspring (12-14), which could be related to brain structure and function derangements determined by the adverse intrauterine *milieu* (15, 16).

Roux-en-Y gastric bypass (RYGB) is a worldwide surgically induced weight loss technique and nearly 50% of women undergoing are of reproductive age (17, 18). Although most women fail to achieve an ideal body weight and are still obese at conception, pregnancies after maternal RYGB are associated with reduced incidence of gestational diabetes mellitus, preeclampsia, large for gestational age babies compared to obese or pre-pregnancy body mass index (BMI)-matched controls peers (19-21). These findings may suggest an improved intrauterine *milieu* resulting from changes induced by surgery and or weight loss. However, bariatric surgery prior to pregnancy is related with increased risk for maternal anemia, small for gestational age infants, preterm birth, and admission for neonatal intensive care (19-21). Limited data have described adverse neonatal outcomes due to

nutritional deficiencies during pregnancies following maternal surgically induced weight loss (22, 23).

Considering that the mother is the only source of nutrition for fetal growth including brain development, maternal nutritional status before and during pregnancy is potentially a predictor of offspring cognitive function. However, results from observational studies seeking for this relationship were inconclusive (24). It is possible that the association between brain structure and function derangements determined by adverse intrauterine *milieu* (15, 16) in obesity could be related to micronutrient status derangements induced by obesity *per se* or bariatric surgery induced weight loss (25).

The purpose of this study was to assess whether RYGB prior to pregnancy is associated with long-term cognition in the offspring compared with two different pre-pregnancy BMI category groups of women not submitted to bariatric surgical procedures. Additionally, we evaluated perinatal and obstetric outcomes and nutritional status in children from five years old.

Methods

Setting and study-subject characteristics

A nested case-control study was carried out. Women who underwent RYGB between January 2000 and December 2010 at Surgery Center of Obesity and Metabolic Syndrome, *Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul* (HSL PUCRS), Porto Alegre, Brazil and became pregnant after surgery were retrieved.

For each birth to a mother submitted to RYGB prior to pregnancy (BS group), two control births selected from both HSL PUCRS and *Hospital de Clínicas de Porto Alegre* (HCPA), Rio Grande do Sul, Brazil were matched by maternal age (one year each way), delivery month and year (2000 to 2011) and newborn gender. Control group 1 (CG1) and

control group 2 (CG2) included women with pre-pregnancy BMI <35 kg/m² and ≥35 kg/m², respectively, without a history of bariatric surgery. Cutoff point of 35 kg/m² was used to select control groups since this is the current indication for bariatric surgery in Brazil and most countries (26, 27).

Subject's hospital records were initially assessed regarding matching characteristics for the control groups, which were selected by blinded researchers for pregnancy, obstetric and neonatal outcomes. Posteriorly, women were contacted by telephone and invited to participate. The three groups (mother-child) attended a contemporaneous evaluation at Clinical Research Center of HCPA between January 2015 and June 2016 for cognitive, anthropometric and clinical assessment. **Figure 1** shows identification and selection of the study participants.

Exclusion criteria were as follows: 1) Multiple-birth pregnancies; 2) Pregnancies that occurred after 2011, since the primary outcome was to assess global cognitive function in offspring aged 5y and older; 3) Children previously diagnosed with diseases that are known to alter cognitive development; 4) Refusal; 5) Non-attendance to contemporaneous clinical evaluation. The Ethical Committee of the HCPA and HSL PUCRS approved the study protocol and informed consent was obtained from all participants.

Sociodemographic, clinical and anthropometric measurements

Pregnancy, obstetric and neonatal outcomes were retrieved from all subjects (mother and child) included in the study using hospital registration, medical and exams reports. Standard questionnaires were used during face-to-face interview to collect sociodemographic status, present and previous health history from mothers and children in BS, CG1 and CG2. Data were retrieved from all groups, except laboratory assessment regarding nutritional status

during pregnancy, which was available only for the RYGB group. Household income in *reais* was converted to dollars (a minimum salary is equivalent to nearly U$267.00).

Measured or self-reported maternal weight and height in early and final pregnancy were used to estimate BMI and gestational weight gain (GWG). Pre-pregnancy BMI was calculated with the weight (kg)/height^2 (m) ratio and was classified as follows: underweight (<18.5 kg/m²); normal weight (18.5 to 24.9 kg/m²); overweight (25 to 29.9 kg/m²); obese (≥30 kg/m²). Gestational weight gain adequacy was classified based on the pre-pregnancy BMI: 12.5 to 18 kg for BMI <18.5 kg/m²; 11.5 to 16 kg for BMI 18.5-24.9 kg/m²; 7 to 11.5 kg for BMI 25-29.9 kg/m²; 5 to 9 kg for BMI ≥30 kg/m² (28).

Gestational age (GA) at delivery was estimated by ultrasound or registered date of last menstrual period. Preterm birth was considered as less than 37 weeks of gestation (29). Birth weight (BW) was classified as low (<2500g), macrosomia (>4000g) or adequate. Fetal growth considered BW, length (cm) and head circumference (cm) according to gestational age and sex. Small for gestational age was defined as BW below the 10th percentile and large for gestational age as higher than 90th percentile (30). Other outcomes included Apgar score and need for neonatal intensive care unit (NICU).

Contemporaneous maternal anthropometric status was assessed by BMI and waist circumference (WC) in centimeters. Children growth evaluation was based on height-for-age and BMI-for-age z-scores according to World Health Organization (WHO) growth charts (31) and WC was classified in percentiles by sex and age, whereas the cutoff value higher than 90th was considered at risk of developing obesity-related conditions (32). A digital scale (Toledo®) with 200 kg capacity and a harpenden stadiometer (Holtain Limited®, Crymych, Dyfed, U.K.) with 210 cm capacity assessed body weight (kg) and height (meters), respectively, from both mother and child, with subjects wearing light clothes and without

shoes on. Waist circumference from mother and child was measured at the midpoint between the last rib and the iliac crest with an inelastic tape.

Cognition assessment

Offspring cognitive function was assessed using the non-verbal Raven's Colored Progressive Matrices (RCPM) test (33) which is designed for use among children from 5y to 12y and consists of thirty-six items grouped into three sets (A, Ab and B). Each item represents a large colored figure with a missing piece, which is completed by selecting the correct part from six alternatives presented beneath the figure. Maternal cognition was evaluated as a potential predictor for children's score using the Raven's Standard Progressive Matrices (RSPM) test (34) which may be applied from the age of 12y and older. Raven's Standard Progressive Matrices consist of sixty elements (figures) grouped into five sets (A to E) with a missing part similar to RCPM, although the figures are not colored and the response options range from six to eight pictured inserts. A trained researcher blinded to exposure status, i.e. bariatric surgery prior to pregnancy and pre-pregnancy BMI, administered the tests. The purpose of Raven's tests is to assess non-verbal reasoning through the visual approach. Each set involves the principle of matrix transformation, thus, problems solving become increasingly more difficult. Both RCPM and RPM raw score were converted to percentile according to age range with results above 75^{th} indicating a higher cognition.

Statistical Analysis

The distribution of variables was explored using the Kolmogorov-Smimov test. Quantitative data are shown as mean and standard deviation (SD) or median and interquartile range according to variables distribution. Cognitive scores converted to percentiles are shown as mean and standard error (SE). Groups characteristics were compared using analysis of

variance (ANOVA) complemented with Tukey post-hoc or Kruskall-Wallis with Dunn post-hoc for variables with asymmetric distribution. Categorical data are presented as frequencies and their differences were analyzed using the χ^2 or Fisher's exact test. Odds ratios (OR) were estimated by logistic regression for pregnancy, obstetric and neonatal outcomes according to group by conditioned matching factors. Correlations between continuous variables were performed using Pearson or Spearman correlation coefficients. Generalized Estimating Equation (GEE) performed regression analyses with offspring cognition percentile as dependent variable. Potential confounders and mediators variables with P value <0.2 without multicollinearity on univariate analysis were further included on multivariate analysis. Linear and logistic GEE regression were used to evaluate differences between groups adjusted for variables that might, according to literature and univariate analysis, influence pregnancy, obstetric, neonatal outcomes and anthropometric status in children, such as maternal pre-pregnancy nutritional status, GWG, GA, interval from RYGB to conception and sociodemographic data. Data were analyzed using SPSS version 18.0 (IBM SPSS Statistics) and P values (two-tailed) of <0.05 were considered significant.

Results

Sociodemographic and clinical characteristics

Thirty-two children born after maternal RYGB and 64 matched controls were analyzed, most female (59%), white (82%) with a mean age of 7 ± 2 years old, ranging from 5y to 12y. Maternal preoperative BMI was 47 ± 10 kg/m², 25% classified from 35 to 39.9 kg/m², 44% from 40.0 to 49.9 kg/m² and 31% higher than 50 kg/m². Median interval from surgery to conception was 24 (13-43) months, whereas 22% of women conceived before 12 months. Compliance to vitamins and minerals supplementation during pregnancy in BS group was nearly 87%, and 69% of women attended at least two prenatal evaluation at referral

bariatric surgery center for adequate supplementation. Ninety-four, 97% and 100% of the subjects supplemented extra folic acid, B12 vitamin and iron, besides the routinely prescribed multivitamin. Prevalence of vitamin deficiencies at any time assessed during pregnancy were as follows: folic acid (12%), B12 vitamin (22%), iron (16%) and ferritin (53%).

Early pregnancy maternal age ranged from 19y to 41y and preexistent conditions included hypertension in 6%, 9% and 28% in BS, CG1 and CG2 (P=0.050), respectively, and diabetes mellitus in 6% of women from CG2 (P=0.320). Forty-four percent women in BS, 25% in CG1 and 22% in CG2 were nulliparous (P=0.120). The prevalence of maternal obesity was 41% in the low economic class (P=0.023). Maternal sociodemographic and clinical characteristics are summarized in **Table 1**.

Gestational weight gain was lower in the BS *vs.* CG2 (P=0.004) and similar to CG1 (P=0.428) after adjustment for early pregnancy BMI (β= -0.739; P=0.002). In the BS, besides pre-pregnancy BMI (β= -0.754; P<0.001), interval from surgery to conception (in months) was associated with GWG (β=0.252; P<0.001). For each additional year from surgery to conception, there was an increase of 3.16 kg in GWG.

Pregnancy, obstetric and neonatal outcomes

Pregnancy, obstetric and neonatal outcomes according to group are shown in **Table 2**. Mean GA was 38 ± 2 weeks without difference among groups (P=0.217). Birth weight in the BS (3044 ± 405 g) was lower compared to both CG1 (3331 ± 450 g; P=0.016), and CG2 (3344 ± 561 g; P=0.045). However, after adjustment for pre-pregnancy BMI (β= 36; P=0.002) and GWG in kg (β= 22; P<0.001), BW remained statistically lower only in the BS compared to CG1 (mean difference = -348.09 g; 95% CI: -602.47; 93.70; P=0.003). Interval from surgery to conception was not predictor for low BW in the BS group. No infant was diagnosed with congenital malformation.

Birth length (48 ± 2 cm) and head circumference (34 ± 2 cm) were similar among groups, P=0.599 and P=0.257, respectively. Median breastfeeding length was 3 (1-11) months in BS, 15 (5-30) months in CG1 and 6 (1-22) months in CG2, lower in the BS *vs.* CG1 (P<0.001). Seventy-two percent of children in BS, 28% in CG1 and 47% in CG2 were breastfed for less than 6 months, lower in the BS *vs*. both controls (P=0.002).

Contemporary mother-child anthropometric evaluation

Mean mother's BMI was 35 ± 8 kg/m² in BS, 29 ± 5 kg/m² in CG1 and 38 ± 6 kg/m² in CG2 (P<0.001), whereas 62%, 56% and 87% were classified with obesity, respectively, greater in CG2 compared to BS (P=0.034) and CG1 (P=0.016). Women submitted to RYGB gained weight overtime (7 ± 2y) similarly to CG1 (P=0.798) and higher than CG2 (mean difference = 10.46 kg; 95% CI: 1.52; 19.18; P=0.015).

Children's height-for-age z-score was similar between groups (P=0.170) and no subject presented height deficit. BMI-for-age z-score was lower in CG1 compared to BS (P=0.024) and CG2 (P=0.003), while BS was similar to CG2 (P=0.846). Likewise, median WC classified in percentiles by sex and age was lower among children from CG1, compared to BS (P=0.027) and CG2 (0.012). Forty-seven percent of children in BS, 34% in CG1 and 59% in CG2 were classified with WC above 90th (P=0.134). Stratifying by sex, 33% of girls and 29% of boys from the entire sample were classified as overweight or obese (P=0.138). Overweight prevalence was 31%, 22% and 25% and obesity was 34%, 22% and 53% in BS, CG1 and CG2, more frequent in CG2 *vs.* CG1 (OR 4.59; 95% CI: 1.55; 13.61; P=0.006).

Cognitive assessment

The mean percentile of RCPM by age was 73 [95% CI: 63-82] in BS, 81 [95% CI: 76-87] in CG1, and 69 [95% CI: 61-77] in CG2 (P=0.032). Unadjusted analysis showed

difference between the controls, where children from CG1 presented higher mean percentile compared to CG2 (mean difference = 12.31; 95% CI: 0.20; 24.22; P=0.045). Seventy-two percent of children in BS, 69% in CG1 and 62% in CG2 scored higher than 75th (P=0.716), indicating above-average intelligence. Maternal cognition percentile assessed by RSPM was better in BS *vs*. CG2 (P=0.007), however, groups were similar when adjusted for education (P=0.704).

Household income (r=0.537; P<0.001), early pregnancy age (r=0.348; P<0.001), maternal education (r=0.223; P=0.029) and maternal RSPM score in percentile (r=0.201; P=0.040) were positively correlated to global cognition in children, while pre-pregnancy BMI (r= -0.272; P=0.007), and children's WC in cm (r= -0.255; P=0.022) were negatively correlated.

Considering BS group, time from surgery to conception (either in months or stratified by lower or higher than 12 months), adherence to multivitamins supplement and maternal nutritional deficiencies assessed at any time during pregnancy (iron, ferritin, folic acid and vitamin B12) did not associate with RCPM percentile in offspring (data not shown).

From the univariate regression analyses of potential variables influencing the global cognitive score in the offspring (**Table 3**), multiple regression provided two settings, regardless the group stratification. Setting one included pre-pregnancy BMI (β= -0.727; P=0.014), family economic class (low: β= -16.097; P=0.006; middle: β= -5.467; P=0.235) and maternal age (β= 1.452; P=0.002). We found similar results replacing pre-pregnancy BMI by obesity in the model 1 (β= -11.14; P=0.012), but not for overweight category (β= -2.71; P=0.564). The same model was repeated stratified by groups and there was no group effect (P=0.207). Maternal age was not included since it was a conditioned matching factor. Setting two included economic class (low: β= -21.579; P<0.001; middle: β= -8.739; P=0.040),

breastfeeding length in months (β= 0.364; P=0.024) and maternal age (β=1.338; P=0.005) and groups were similar when adjusting for these predictors.

Gestational weight gain, GA, smoking and alcohol consumption during pregnancy, gestational diabetes mellitus, hypertensive disorders, offspring gender and marital status did not associate with offspring cognition.

Children from CG1 scored better compared to BS and similar to CG2 adjusting for economic class (model 1). By entering maternal education (model 2) or mother cognition (β= 0.090; P=0.249), there was no group effect. Maternal RSPM was removed since is strongly correlated to education (r=0.612; P<0.001).

Breastfeeding length, BW higher than 4000 g, current offspring nutritional status and children education did not modify group effect from the unadjusted analysis. Controlling for early pregnancy BMI (P=0.664) or obesity (P=0.519) groups did not differ, adjusted or not for social class.

Models 3 and 4 included economic class plus early pregnancy BMI and breastfeeding. Results were similar by replacing for early pregnancy obesity in model 3 (β= -9.826; P=0.077) and by breastfeeding less than 6 months (β= -6.769; P=0.114) in model 4. Children education and macrosomia were not included in the models since our sample was composed for 63% children at school age per group and only one newborn above 4,000 g in the BS. In all analyses, BS and CG2 did no differ. Full model is presented in **Table 4**.

Discussion

In the present study, we showed that bariatric surgery prior to pregnancy was not associated with long-term cognition in the offspring. Crude analyses disclosed a higher global cognitive score in the offspring from women with a mean pre-pregnancy BMI of 25 ± 4 kg/² compared to offspring from women with a mean pre-pregnancy BMI of 37 ± 2 kg/m², both

without a history of bariatric surgery. However, adjusting for sociodemographic confounders, family social class and maternal education, group effect disappeared. Household income was the strongest predictor of offspring global cognitive score and the only covariate remaining statistically significant in all analyses.

Economic inequalities adversely affects child health through many pathways. Poorer cognition stimulation, stressful environment, genetics and nutrition appear to contribute to this complex interplay. Additionally, children from lower household income families commonly show higher prevalence of depression, attention and conduct disorders (35, 36). Mechanisms linking early exposure to poverty and brain structure have been raised suggesting an association between a low-income background to changes in prefrontal function, smaller white and cortical gray matter, where the latter seem to be mediated by caregiving support and stressful life events (37, 38).

To our knowledge, this is the first study to evaluate the association between bariatric surgery prior to pregnancy and long-term global cognition in the offspring compared with two different pre-pregnancy BMI category groups not submitted to bariatric surgical procedures. Dell'Agnolo et al (39) found speech delays in three male children when assessing the neuropsychomotor development of 23 children from women who underwent bariatric surgery aged from birth to 6y and a possible association with the time from surgery to conception was addressed. In our sample, non-verbal global cognition was not associated with interval from RYGB to conception.

Observational studies have described a negative association between pregnancy obesity and offspring cognition (14). A recent study assessed 28 full term infants two weeks after birth and maternal fat mass percentage was negatively associated with white matter development in the offspring (16). In our sample, pre-pregnancy BMI in kg/m^2 and obesity category were negatively associated to offspring cognition and suppressed group effect

controlling or not for sociodemographic covariates. However, it remains unclear, especially in observational studies, if maternal obesity does adversely affect long-term offspring cognition in a causal way linking to the fetal programming hypotheses or whether a mediator factor, accounting for well stablished obesity-related diseases, such as insulin resistance, hyperinsulinemia, hypertensive disorders, social and psychological factors is present (40).

Breastfeeding is also postulated to be positively associated to cognition and this advantage appears to remain throughout lifespan (41, 42). However, accounting only for high quality observational studies from a systematic review, a slightly improvement of 1.76 QI points (95% CI: 0.25; 3.26) was attributed to breastfeeding (42). In a randomized controlled trial, Kramer et al (43) followed 13,889 infants assigned for breastfeeding promotion from birth to 6.5y and, controlling for a number of confounders at the baseline, intervention group in which exclusive breastfeeding was 7-fold higher than control group at 3 months, performed better in several long-term tests measuring intelligence.

Pregnancy following surgically-induced weight loss is commonly associated with a higher prevalence of nutritional deficiencies (22), which may adversely affect neonatal outcomes, such as visual complications, neural tube defects, neurological development and intracranial bleeding due to vitamin A, folate, B12 and vitamin K deficiencies, respectively (23). However, in accordance with our results, bariatric surgery does not appear to be an independent risk factor for fetal adverse outcomes among adherent to vitamin and mineral supplements women during pregnancy and results (44). Moreover, data available addressing micronutrient deficiencies and adverse neonatal outcomes among post bariatric surgery pregnancies are limited (23).

In a systematic review, surgically-induced weight loss prior to pregnancy was associated with lower incidence of GDM (OR 0.47, 95% CI 0.40-0.56; P<0.001) and preeclampsia (OR 0.45, 95% CI 0.25-0.80; P=0.007) compared to obese or pre-pregnancy

BMI-matched controls (20). We found reduced risk for GDM and hypertensive disorders from both post-RYGB pregnancies and controls with lower pre-pregnancy BMI compared to controls from women with higher pre-pregnancy BMI, although 47% of women with prior RYGB were obese at conception. Increased levels of postprandial glucagon-like peptide 1 (GLP-1), an incretin hormone involved with insulin secretion, has been observed after bariatric surgery, contributing to the glucose-lowering effect of weight reduction, especially in RYGB compared to sleeve gastrectomy (45, 46).

Data from large observational studies have shown increased risk for SGA and a lower risk for LGA after bariatric surgery (19, 21). Although post-surgery pregnancies were associated with lower BW compared to both controls and Lower frequency of LGA *vs*. CG2, the risk for SGA did not differ in our sample. Offspring from mothers with pre-pregnancy greater than 35 kg/m² were more likely to LGA infants compared to pregnancies post-RYGB. We found early pregnancy BMI and GWG strong positive predictors for higher BW. Both restricted and excessive intrauterine growth are associated to adverse outcomes (47, 48). Restricted intrauterine growth is mostly compensated by rapid catch-up growth in the first years of life, which is associated to increased long-term metabolic risk, considering the following components: waist circumference, blood pressure, fasting triglycerides, high-density lipoprotein cholesterol, glucose, and insulin levels (49). In a systematic review, macrosomia was associated with higher risk of obesity through early adulthood, while low BW did not (47). In our study, pregnancy after RYGB was not associated with lower GA, Apgar score, birth length, head circumference and neonatal and intensive care unit admission.

Kral et al (50) compared 34 children aged from 2y to 18y born before and 172 born after maternal surgically-induced weight loss and found a reduction of obesity of 53% in the offspring after surgery, underlying an association with environment changes and epigenetic factors. Our results showed that long-term prevalence of overweight and obesity from

children born to mothers submitted to RYGB did not differ from controls, however, children from mothers with greater pre-pregnancy BMI (CG2) were remarkable more likely to be overweight and obese compared to those born from leaner mothers (CG1). Willmer et al (51) assessed weight development from 164 children born before and 176 born after maternal bariatric surgery at 4y, 6y and 10y and also showed no difference in prevalence rates of overweight and obesity.

This study has some limitations. Sample size may be insufficient to find significant differences in secondary outcomes and this accounted for the wide confidential interval in some results. Moreover, a number of potential predictors of cognitive function were not assessed due to the observational study design, as well as survival bias by excluding fetal mortality. Additionally, the main difficulty was to contact women previously submitted to RYGB to invite to participate. Indeed, adherence to multidisciplinary follow-up care is often low (52, 53) and it is likely that women included in the final analysis represent those who maintain follow-up evaluation at the referral bariatric surgery center and, likewise, with greater health self-care as we found high compliance rate to vitamins and minerals supplementation during pregnancy. Therefore, the results cannot be generalized to other populations with different adherence rates. Strengths of this study includes, for the first time, in loco evaluation of 32 children from 5y to 12y born after women who conceived post-RYGB. Moreover, we were able to compare obstetric outcomes and general cognition with two different pre-pregnancy BMI category groups matched for mother-child age and offspring gender. By using GEE analysis with matched groups for delivery month and year, we eliminated possible changes that may have occurred overtime in the medical and hospital protocols regarding obstetric procedures.

Conclusions

Pregnancy in women with previous bariatric surgery was associated with less frequency of gestational diabetes mellitus and hypertensive disorders when compared to pregnancy in obese women (pre-pregnancy BMI ≥35 kg/m²) and with lower birth weight compared to both women with pre-pregnancy BMI higher and lower than 35 kg/m². Roux-en-Y gastric bypass prior to pregnancy was not associated with poorer long-term offspring global cognition, whereas lower family economic class was the strongest negative predictor. Larger prospective studies comparing post bariatric surgery women with different adherence rates for vitamin and mineral supplementation are required.

Disclosures: The authors declare that they have no conflict of interest.

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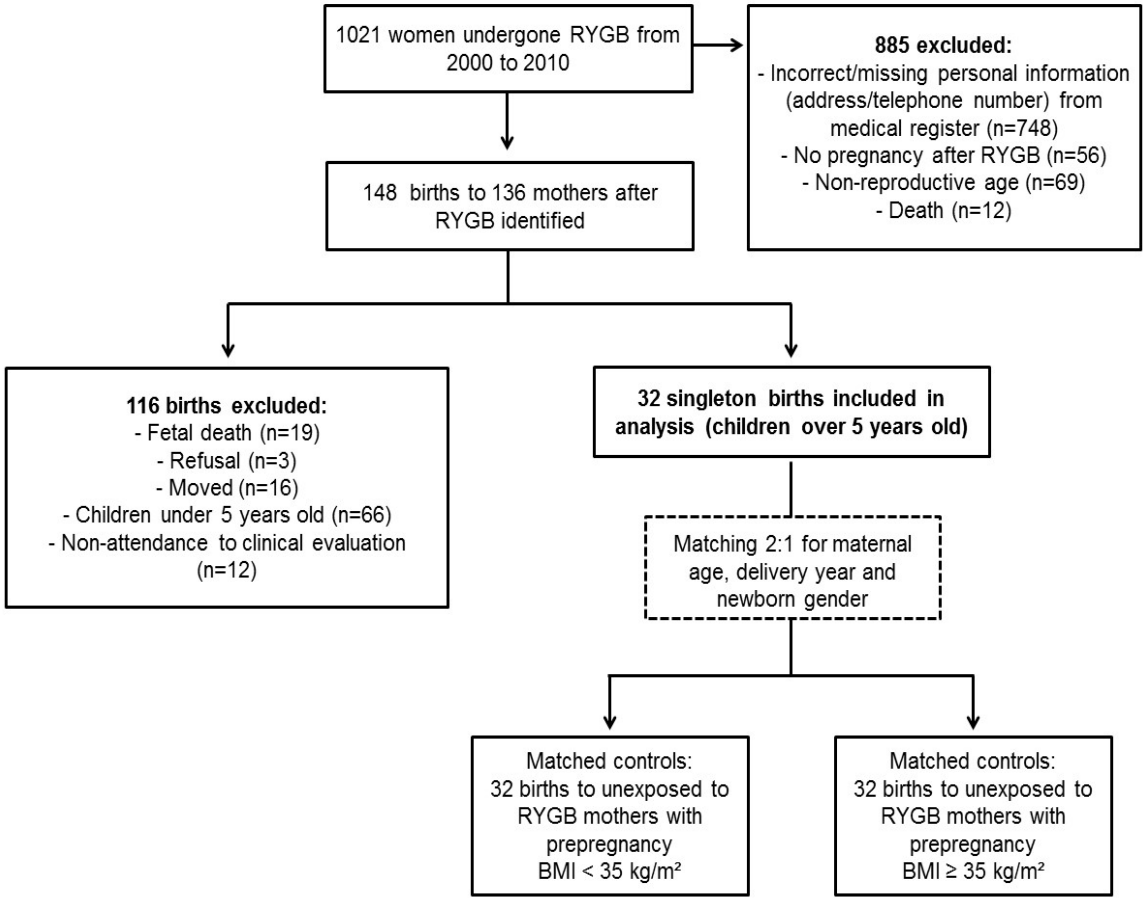

Figure 1. Flow chart showing identification and selection of the study population
Exposed to Roux-em-Y Gastric Bypass (RYGB) prior to pregnancy group were selected from Surgery Center of Obesity and Metabolic Syndrome (COM, Hospital São Lucas PUCRS, Porto Alegre - Brazil). Matched control population unexposed to RYGB were selected from both COM, Hospital São Lucas PUCRS and Hospital de Clínicas de Porto Alegre – Brazil.

Table 1. Maternal characteristics according to group

Characteristic	Bariatric Surgery (n = 32)	CG1 BMI < 35kg/m² (n = 32)	CG2 BMI ≥ 35kg/m² (n = 32)	P-value
Sociodemographic characteristics				
Early pregnancy age, years	30 ± 5	29 ± 5	30 ± 6	0.686
Early pregnancy age, categories				
19-24 yr	5 (15.6)	7 (21.9)	6 (18.8)	0.966
25-29 yr	7 (21.9)	5 (15.6)	7 (21.9)	
30-34 yr	12 (37.5)	13 (40.6)	10 (31.2)	
35-41 yr	8 (25)	7 (21.9)	9 (28.1)	
Ethnicity				
White	31 (97)[a]	21 (65.6)[b]	27 (84.4)[ab]	0.004
Brown/black	1 (3)[a]	11 (34.4)[b]	5 (15.6)[ab]	
Educational level, years	14 ± 3[a]	11 ± 4[b]	9 ± 4[b]	<0.001
Educational level, categories				
≤ 8 yr	2 (6.2)[a]	7 (21.9)[ab]	10 (31.2)[b]	<0.001
9-11 yr	8 (25)[a]	15 (46.9)[ab]	18 (56.3)[b]	
≥ 12 yr	22 (68.8)[a]	10 (31.2)[b]	4 (12.5)[b]	
Marital status				
Married/cohabiting	23 (71.9)	26 (81.2)	25 (78.1)	0.662
Single/divorced/widowed	9 (28.1)	6 (18.8)	7 (21.9)	
Household income, U$	939 (523-2121)[a]	758 (470-1325)[a]	515 (364-758)[b]	0.001
Economic class				
A (high)	14 (43.7)[a]	9 (28.1)[ab]	4 (12.5)[b]	0.040
B	6 (18.8)	9 (28.1)	6 (18.8)	
C	7 (21.9)	6 (18.8)	6 (18.8)	
D-E (low)	5 (15.6)[a]	8 (25)[ab]	16 (50)[b]	
Clinical characteristics				
Pre-pregnancy BMI, kg/m²	30 ± 6[a]	25 ± 4[b]	37 ± 2[c]	<0.001
Pre-pregnancy BMI, categories				
18.5-24.9	6 (18.8)[a]	15 (46.9)[b]	NA	<0.001
25-29.9	11 (34.4)	12 (37.5)	NA	
30-34.9	9 (28.1)	5 (15.6)	NA	
35.0-39.9	5 (15.6)[a]	NA	26 (81.2)[b]	
≥ 40	1 (3)	NA	6 (18.8)	

Gestational weight gain, kg	9 (6-17)[a]	14 (11-20)[b]	12 (8-16)[ab]	0.019
Gestational weight gain adequacy				
Below the ideal	7 (21.9)	6 (18.8)	4 (12.5)	0.514
Ideal	8 (25)	9 (28.1)	5 (15.6)	
Above the ideal	17 (53.1)	17 (53.1)	23 (71.9)	
Prenatal care				
Median, no. of visits	8 (3-11)	8 (6-11)	8 (7-11)	0.683
Cigarette smoking				
Smoking during pregnancy	7 (21.9)	3 (9.4)	2 (6.3)	0.223
≥ 10 cigarettes per day	5 (71.4)	1 (33.3)	2 (100)	0.392
Alcohol consumption				
Drinking during pregnancy	6 (18.8)[a]	0 (0)[b]	3 (9.4)[ab]	0.035
≥ 500ml per week	1 (16.7)	0 (0)	2 (66.7)	0.770

Bariatric surgery group: singleton births of women submitted to Roux-en-Y Gastric Bypass prior to pregnancy.
Control group 1 (CG1): singleton control births of women without a history of bariatric surgery and pre-pregnancy BMI lower than 35 kg/m², using maternal age, delivery year and newborn gender as matching factors.
Control group 2 (CG2): singleton control births of women without a history of bariatric surgery and pre-pregnancy BMI grater or equal to 35 kg/m², using maternal age, delivery year and newborn gender as matching factors.
Data are presented as mean ± SD, median (interquartile range) or proportions (n, %).
Mean, median or proportion values followed by different letters significantly differ by analysis of variance (ANOVA) complemented with Tukey post hoc, Kruskall-Wallis with Dunn post hoc, Chi square or Fishers exact test at the significance level of 5%.
Economic class was determined according to minimum salaries in *reais* (a minimum salary was equivalent to nearly U$267.00 in September 2016).
Gestational weight gain adequacy was determined according to the recommendations of the Institute of Medicine (IOM, 2009).
Abbreviations: BMI, body mass index; RYGB, Roux-en-Y gastric bypass; NA, not applicable.

Table 2. Pregnancy, obstetric and neonatal outcomes according to group

Characteristic	Bariatric Surgery (n = 32)	CG1 BMI < 35kg/m² (n = 32)	CG2 BMI ≥ 35kg/m² (n = 32)	P-value	Odds Ratio (95% CI) RYGB *vs.* CG1	Odds Ratio (95% CI) RYGB *vs.* CG2
Gestational diabetes	1 (3.0)[a]	4 (12.5)[a]	11 (34.4)[b]	0.003	0.23 (0.01; 1.64)	0.06 (0.03; 0.35)
Gestational hypertensive disorders	2 (6.3)[a]	4 (12.5)[a]	13 (40.6)[b]	0.001	0.46 (0.06; 2.58)	0.09 (0.01; 0.40)
Cesarean delivery	22 (68.8)[a]	9 (28.0)[b]	18 (56.3)[a]	0.004	4.87 (1.73; 14.71)	1.48 (0.62; 4.86)
Preterm birth (< 37 weeks)	4 (12.5)	2 (6.3)	7 (21.9)	0.221	2.14 (0.38; 16.33)	0.51 (0.12; 1.89)
Apgar score (5min) <7	1 (3.0)	2 (6.3)	6 (18.8)	0.137	0.48 (0.02; 5.31)	0.14 (0.007; 0.89)
Small for gestational age	2 (6.3)	1(3.0)	1 (3.0)	>0.999	2.06 (0.19; 26.02)	2.06 (0.19; 26.02)
Large for gestational age	2 (6.3)[a]	7 (21.9)[ab]	11 (34.4)[b]	0.021	0.24 (0.03; 1.09)	0.13 (0.02; 0.54)
Birth weight >4000 g	1 (3.0)	3 (9.4)	6 (18.8)	0.150	0.31 (0.015; 2.59)	0.14 (0.07; 0.89)
Birth weight <2500 g	3 (9.4)	1 (3.0)	2 (6.3)	0.872	3.21 (0.38; 66.85)	1.55 (0.24; 12.43)
Neonatal intensive care unit	4 (12.5)	3 (9.4)	5 (15.6)	0.926	1.38 (0.28; 7.54)	0.77 (0.17; 3.21)

Bariatric surgery group: singleton births of women submitted to Roux-en-Y Gastric Bypass prior to pregnancy.

Control group 1 (CG1): singleton control births of women without a history of bariatric surgery and pre-pregnancy BMI lower than 35 kg/m², using maternal age, delivery year and newborn gender as matching factors.

Control group 2 (CG2): singleton control births of women without a history of bariatric surgery and pre-pregnancy BMI grater or equal to 35 kg/m², using maternal age, delivery year and newborn gender as matching factors.

Gestational hypertensive disorders includes gestational hypertension, preeclampsia and superimposed preeclampsia on chronic hypertension.

Data are presented as proportions n (%). Proportion values followed by different letters significantly differ. Odds ratios were estimated by logistic regression conditioned on matching factors: maternal age, year of delivery and newborn gender. Abbreviations: CI, confidence interval; NA, not applicable.

Table 3. Univariate regression analysis of potential variables influencing the global cognitive score in the offspring (n=96)

Independent variable	B	Standard error	95% CI	P-value
Maternal variables				
Early pregnancy age, years	1.498	0.5001	0.517; 2.479	0.003
Ethnicity, brown/black	- 7.783	6.177	- 19.890; 4.324	0.072
Education, years	0.917	0.506	- 0.074; 1.908	0.070
Education, ≤ 12y	- 11.741	5.960	- 23.424; - 0.059	0.049
Education, 9-11y	- 7.344	6.391	- 19.872; 5.184	0.142
Household income, U$	0.191	0.046	0.100; 0.281	<0.001
Family social class, low	- 21.834	5.843	- 33.387; - 10.480	<0.001
Family social class, middle	- 9.462	4.305	- 18.901; - 2.023	0.015
Pre-pregnancy BMI, kg/m²	- 0.936	0.294	- 1.513; - 0.358	0.001
Pre-pregnancy obesity, BMI ≥ 30 kg/m²	- 14.947	4.441	- 23.650; - 6.244	0.002
RSPM, percentile	0.162	0.097	0.028; 0.352	0.095
RSPM adjusted for education, percentile	0.183	0.108	0.028; 0.395	0.090
Offspring variables				
Birth weight, > 4000 g	- 2.951	8.633	- 9.876; -3.972	0.060
Breastfeeding length, months	0.293	0.181	0.062; 0.646	0.063
Breastfeeding, < 6 months	- 6.769	4.288	-15.175; 1.637	0.072
Education, years	2.004	1.045	- 4.05; 0.045	0.056
BMI-for-age, z-score	- 1.688	1.699	- 5.019; 1.643	0.188
Obesity, BMI-for-age ≥ 2 z-score	- 5.694	4.901	- 15.299; 3.910	0.127
Waist circumference, cm	- 0.245	0.136	- 0.512; 0.021	0.071
Waist circumference, >90th	- 6.289	4.272	- 14.662; 2.084	0.141

Dependent variable: General cognition score converted to percentile by age derived from Raven's Coloured Progressive Matrices adjusted for conditional matching factors: maternal age, year of delivery and newborn gender. Household income, U$: determined at each increase in income of U$100.00.
Abbreviations: BMI, body mass index; CI, confidence interval; RSPM, Raven's Standard Progressive Matrices.

Table 4. Multiple regression analysis of potential variables influencing the global cognitive score in the offspring (n=96)

Independent variable	B	Standard error	95% CI	P-value
MODEL 1 – economic class (EC)				
Bariatric surgery group	- 12.637	4.491	- 21.4409; - 3.835	0.035
Control group 2	- 9.453	4.545	- 18.362; - 0.544	0.113
Control group 1	0			
MODEL 2 – EC, maternal education				
Bariatric surgery group	- 11.806	5.114	- 21.830; 1.782	0.063
Control group 2	- 7.398	4.086	- 15.407; 0.611	0.070
Control group 1	0			
MODEL 3 – EC, pre-pregnancy BMI, kg/m²				
Bariatric surgery group	- 8.552	5.606	- 19.541; 2.436	0.127
Control group 2	- 1.361	8.862	- 18.732; 16.009	0.878
Control group 1	0			
MODEL 4 – EC, breastfeeding length, months				
Bariatric surgery group	- 8.537	4.466	- 17.293; 0.218	0.056
Control group 2	- 5.813	4.632	- 14.892; 3.265	0.209
Control group 1	0			
MODEL 5 – full model				
Bariatric surgery group	- 4.161	6.539	- 17.978; 7.655	0.430
Control group 2	0.949	9.021	- 16.732; 18.631	0.916
Control group 1	0			

Dependent variable: General cognition score converted to percentile by age derived from Raven's Coloured Progressive Matrices adjusted for conditional matching factors: maternal age, year of delivery and newborn gender. Abbreviations: BMI, body mass index; CI, confidence interval.

Models 1: Economic class (low: β= -20.576; P<0.001; middle: β= -9.348; P=0.019),

Model 2: Economic class (low: β= -23.740; P<0.001; middle: β= -11.434; P=0.026), maternal education (≤8y: β= -3.995; P=0.172; 9-11y: β=-3.878; P=0.475).

Model 3: Economic class (low: β= -21.477; P<0.001; middle: β= -9.812; P=0.064), pre-pregnancy BMI (β= -0.532; P=0.357).

Model 4: Economic class (low: β= -23.624; P<0.001; middle: β= -11.410; P=0.018), breastfeeding length (β=0.279; P=0.136).

Model 5: Economic class (low: β= -24.348; P<0.001; middle: β= -9.550; P=0.059), maternal education (≤8y: β= -3.392; P=0.521; 9-11y: β=7.023; P=0.406), pre-pregnancy BMI (β= -0.542; P=0.356), breastfeeding length (β= 0.302; P=0.069).

CONSIDERAÇÕES FINAIS E PERSPECTIVAS

Os resultados deste estudo sugerem que a cirurgia bariátrica prévia à gestação não tem associação com o desenvolvimento cognitivo tardio da prole, enquanto que a classe econômica familiar mais baixa foi o preditor mais fortemente associado em todas as análises de regressão, sugerindo que a desvantagem econômica afeta negativamente a saúde infantil através de muitas vias. Portanto, medidas de saúde pública devem ser consideradas com o objetivo de atenuar o impacto da desvantagem socioeconômica.

Não foi possível avaliar o efeito das deficiências de micronutrientes sobre o desenvolvimento cognitivo, pois, nesta amostra estudada, a aderência à suplementação de vitaminas e minerais foi alta entre as gestantes que realizaram cirurgia bariátrica. Portanto, os resultados são incertos e não podem ser generalizados para outras populações.

Em relação aos desfechos perinatais e obstétricos, os resultados encontrados estão de acordo com a literatura que relaciona a derivação gastrojejunal em Roux-en-Y prévia à gestação com melhores resultados em comparação às mulheres com obesidade pré-gestacional não submetidas ao tratamento cirúrgico. Porém, esta população apresenta maior risco de recém-nascidos com restrição de crescimento intrauterino e baixo peso ao nascer. Portanto, o acompanhamento destas crianças em longo prazo e a atuação de profissionais de saúde com condutas preventivas são necessários.

A partir desta dissertação, estudos maiores prospectivos incluindo gestantes com diferentes taxas de adesão à suplementação e ao autocuidado são necessários para elucidar o entendimento da relação entre as mudanças provocados no *milieu* intrauterino após o tratamento cirúrgico da obesidade, a absorção e a biodisponibilidade de micronutrientes e o desenvolvimento cognitivo da prole em longo prazo.