Obesity Surgery (2018) 28:3611–3620
https://doi.org/10.1007/s11695-018-3407-5

ORIGINAL CONTRIBUTIONS

Association of Maternal Roux-en-Y Gastric Bypass with Obstetric Outcomes and Fluid Intelligence in Offspring

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Abstract

Purpose The purpose of the study is to assess whether Roux-en-Y gastric bypass (RYGB) prior to pregnancy is associated with fluid intelligence in offspring. Additionally, perinatal and obstetric outcomes, and children nutritional status were evaluated.

Material and Methods Singleton births of women who underwent RYGB between 2000 and 2010 (BS) were matched to two control births by maternal age, delivery year, and gender. Control group 1 (CG1) and control group 2 (CG2) included women with a pre-pregnancy body mass index (BMI) < 35 kg/m^2 and ≥ 35 kg/m^2, respectively, who had never undergone bariatric surgery.

Results Thirty-two children from each group ($n = 96$) were analyzed, mostly female (59%) and Caucasian (82%), with a mean age of 7 ± 2 years. Their general intelligence scores were similar after adjusting for sociodemographic confounders; family economic class was the strongest predictor (low: $\beta = -20.57$; $p < 0.001$; middle: $\beta = -9.34$; $p = 0.019$). 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 than CG2. Post-RYGB pregnancies were associated with lower birth weight ($P = 0.021$) than controls. Child overweight and obesity was higher (OR 4.59; 95% CI 1.55; 13.61; $p = 0.006$) in CG2 (78%) than CG1 (44%) and similar to BS (65%).

Conclusions RYGB prior to pregnancy was not associated with fluid intelligence in offspring. Prior RYGB was associated with a lower frequency of gestational diabetes mellitus and hypertensive disorders than in women with a pre-pregnancy BMI ≥ 35 kg/m^2, as well as with lower birth weight than both control groups.

Keywords Bariatric surgery · Roux-en-Y gastric bypass · Obesity · Pregnancy · Raven Progressive Matrices · Intelligence

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Abbreviations

BMI	Body mass index
BW	Birth weight
GA	Gestational age
GDM	Gestational diabetes mellitus
GEE	Generalized estimating equation
GWG	Gestational weight gain
HPD	Hypertensive pregnancy disorders
IOM	Institute of Medicine
LGA	Large for gestational age
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

Introduction

Maternal obesity is adversely associated with obstetric and perinatal outcomes by increasing the risk of gestational diabetes mellitus (GDM), stillbirth, prematurity, congenital malformation, and fetal and infant death [1–5]. Experimental models and clinical studies on mothers with obesity have shown that maternal programming may have a role in offspring metabolism [6, 7]. A pro-inflammatory *milieu* is associated with obesity in early pregnancy, which can lead to greater insulin resistance than in lean mothers [8, 9]. Fetal growth could be influenced by inflammation caused by this obese intrauterine environment [10]. In addition, studies have reported a long-term association between maternal obesity and child cognitive and neurological development [11–13], which could be related to brain structure and function damage due to the adverse intrauterine *milieu* [14, 15]. A study assessed 28 full-term infants 2 weeks after birth, finding that maternal fat mass percentage was negatively associated with white matter development in offspring [15].

Roux-en-Y gastric bypass (RYGB) is used worldwide to surgically induce weight loss, and nearly 50% of women undergoing this procedure are of reproductive age [16, 17]. Although most women fail to achieve an ideal body weight and are still classified with obesity at conception, pregnancies after maternal RYGB are associated with a lower incidence of GDM, preeclampsia and large for gestational age infants than pregnancies in peers with obesity or when pre-pregnancy body mass index (BMI) was matched with controls [18–20]. These findings suggest a better intrauterine environment resulting from changes induced by surgery and/or weight loss. Increased levels of postprandial glucagon-like peptide 1 (GLP-1), an incretin hormone involved in insulin secretion, have been observed after bariatric surgery, contributing to the glucose-lowering effect of weight reduction, especially in RYGB [21, 22].

However, bariatric surgery prior to pregnancy has also been linked with a higher risk of maternal anemia, small for gestational age infants, preterm birth, and admissions to neonatal intensive care [18–20]. Nutritional deficiencies during pregnancy may adversely affect neonatal outcomes, such as neural tube defects, neurological development and intracranial bleeding due to folate, vitamin B12 and vitamin K deficiencies, respectively [23], although limited data have described adverse neonatal outcomes due to nutritional deficiencies in pregnancies following surgically induced weight loss [23, 24].

Considering that the mother is the only source of nutrition for fetal growth, which includes brain development, maternal nutritional status prior to and during pregnancy is a potential predictor of child cognitive function. However, the results of observational studies about this relationship have been inconclusive [25].

The purpose of this study was to assess whether RYGB prior to pregnancy is associated with fluid intelligence in offspring (≥ 5 years old) in comparison with two different pre-pregnancy BMI categories of women who had never undergone bariatric surgery. Additionally, perinatal and obstetric outcomes and nutritional status in these children were also evaluated.

Given the importance of early-life exposure factors, the hypotheses of the authors are that offspring of mothers who underwent RYGB prior to pregnancy would have lower intelligence scores compared to mothers not previously submitted to bariatric surgeries and with a lower pre-pregnancy BMI. The authors also hypothesized that higher pre-pregnancy BMI would have negative associations with obstetric and neonatal outcomes and offspring nutritional status.

Methods

Setting and Study Subject Characteristics

This case-control study nested within a prospective cohort invited all women who underwent RYGB between January 2000 and December 2010 at the Center for Obesity and Metabolic Syndrome of the *Hospital São Lucas* of the *Pontifícia Universidade Católica do Rio Grande do Sul*, Brazil (HSL-PUCRS) and subsequently became pregnant.

For each birth to a mother who had undergone RYGB prior to pregnancy (BS group), two control births selected from HSL-PUCRS and the *Hospital de Clínicas de Porto Alegre* (HCPA), Rio Grande do Sul, Brazil, were matched by maternal age, month, and year of delivery and gender. Control group 1 (CG1) and control group 2 (CG2) included women with pre-pregnancy BMI < 35 kg/m^2 and ≥ 35 kg/m^2, respectively, who had never undergone bariatric surgery. The participants from all three groups (both mother and child) were evaluated for cognitive, anthropometric and clinical parameters at the HCPA Clinical Research Center between January 2015 and June 2016. Figure 1 is a flowchart of participant identification and selection.

Exclusion criteria included (1) multiple-birth pregnancies; (2) pregnancies occurring after 2011; (3) children previously diagnosed with diseases known to alter cognitive development; (4) refusal; and (5) absence at the clinical evaluation. The HCPA and HSL-PUCRS Ethics Committees approved the study protocol; informed consent was obtained from all participants prior to inclusion.

Sociodemographic, Clinical, and Anthropometric Measurements

Pregnancy, obstetric, and neonatal outcomes were retrieved from hospital records. Standard questionnaires were used during the interview to collect data on sociodemographic status and health history [26]. Household income in Brazilian reais was converted to U.S. dollars (at the time of writing, the minimum monthly wage was approximately US$267.00).

Measured or self-reported maternal weight and height in early and late pregnancy were used to estimate BMI and gestational weight gain (GWG), which was classified according to Institute of Medicine recommendations [27].

Gestational age (GA) at delivery (estimated by ultrasound before week 20th or the date of the last menstrual period) was classified as preterm (newborn with less than 37 weeks of gestational age), term (between 37 and 41 weeks) or postterm (≥ 42 weeks). Small for gestational age was defined as weight below the 10th percentile, while infants above the 90th percentile were considered large for gestational age [28].

Evaluation of the children's growth was based on height-for-age and BMI-for-age *Z*-scores according to World Health Organization (WHO) growth charts [29]. Waist circumference (WC) was classified as percentile according to sex and age [29]. A 200-kg capacity digital scale (Toledo®) and a 210-cm capacity Harpenden stadiometer (Holtain Limited®, Crymych, Dyfed, U.K.) were used to assess body weight (kg) and height (meters), respectively, with the subjects barefoot and wearing light clothes.

Fluid Intelligence

The children's general intelligence was assessed using the non-verbal Raven's Colored Progressive Matrices (RCPM) test [30], which is designed for use among children from 5 to 12 years of age and consists of 36 items grouped into three sets (A, Ab and B). Each item is a large colored figure with a missing piece, which is completed by selecting the correct piece from six alternatives presented beneath the figure. Maternal cognition was evaluated using the Raven's Standard Progressive Matrices (RSPM) test [31] which is for use with individuals 12 years or older. The RSPM consists of 60 items (figures) grouped into five sets (A to E), each with a missing part, similar to the RCPM. A trained researcher administered the tests. The purpose of Raven's test is to assess non-verbal reasoning using a visual approach. It is a worldwide-validated measure of basic cognitive functioning and has been widely applied to measure problem-solving abilities, i.e., fluid intelligence [32, 33]. Each set involves the principle of matrix transformation and increases in difficulty. Both the RCPM and RSPM raw scores were converted to percentiles according to age range.

Statistical Analysis

The distribution of the variables was assessed using the Kolmogorov-Smirnov test. Quantitative data are shown as mean and standard deviation (SD) or median and interquartile range. General intelligence scores converted to percentiles are shown as mean and standard error (SE). Group characteristics were compared using analysis of variance (ANOVA) with a Tukey post hoc test or using Kruskal-Wallis with Dunn's post hoc test. Categorical data were analyzed using χ^2 or Fisher's exact test. Odds ratios (OR) were estimated using logistic regression to form groups of conditioned factors. Correlations between continuous variables were calculated using Pearson's or Spearman's correlation coefficients. A generalized estimating equation (GEE) was used to perform regression analyses, with the offspring cognition percentile as a dependent variable. Potential confounders and mediating variables with a p value $<$ 0.2 and no multicollinearity detected in univariate analysis were also included in the multivariate analysis. Data analysis was performed using SPSS version 18.0 (IBM SPSS Statistics), with p values of < 0.05 considered significant.

Results

Sociodemographic and Clinical Characteristics

A total of 32 children born after maternal RYGB and 64 matched controls were analyzed. Most were female (59%) and Caucasian (82%), with a mean age of 7 ± 2 years, which ranged from 5 to 12 years. Maternal preoperative BMI was 47 ± 10 kg/m^2: 25% were between 35 and 39.9 kg/m^2, 44% were between 40.0 and 49.9 kg/m^2 and 31% were ≥ 50 kg/m^2. The median time between surgery and conception was 24 (13–43) months, whereas 22% of the women conceived within the first 12 months after surgery. In the BS group, compliance with vitamin and mineral supplementation during pregnancy was

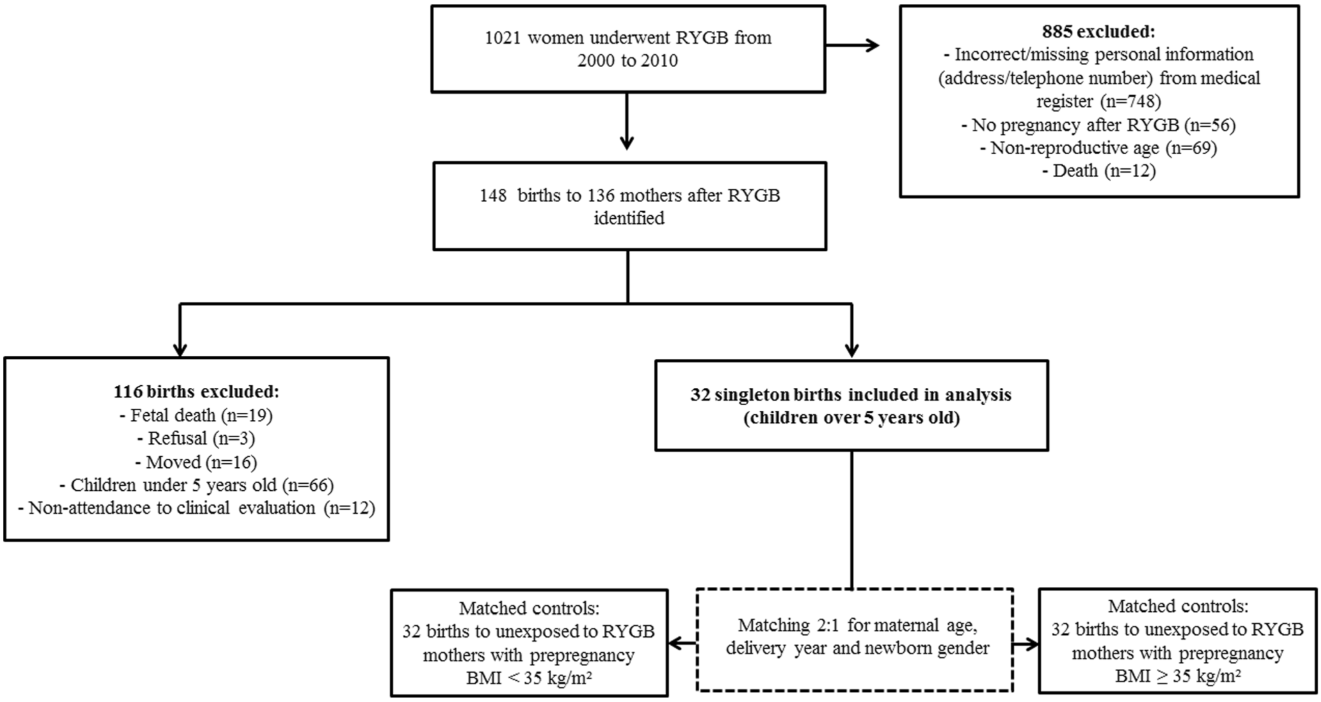

Fig. 1 Flow chart of study population identification and selection. The pre-pregnancy Roux-en-Y gastric bypass (RYGB) group was selected from the Center for Obesity and Metabolic Syndrome (COM, Hospital São Lucas-PUCRS, Porto Alegre, Brazil). The matched control population (no RYGB) was selected from COM, Hospital São Lucas-PUCRS and the Hospital de Clínicas de Porto Alegre. Abbreviation: BMI, body mass index

nearly 87%, and 69% of the women attended at least two prenatal nutrition evaluations at the bariatric surgery referral center. Folic acid, vitamin B12 and iron supplements were taken by 94%, 97 and 100% of the subjects, respectively, in addition to the routinely prescribed multivitamin. The prevalence of nutritional deficiencies for folic acid, vitamin B12, and iron any time during pregnancy were 12, 22, and 16%, respectively.

Maternal age in early pregnancy ranged from 19 to 41 years, and preexisting conditions included hypertension (in 6%, 9 and 28% of BS, CG1 and CG2, respectively; $p = 0.050$) and diabetes mellitus (in 6% of CG2; $p = 0.320$). Maternal sociodemographic and clinical characteristics are summarized in Table 1.

Gestational weight gain was lower in BS than CG2 ($p = 0.004$) and similar to CG1 ($p = 0.428$) after adjusting for early pregnancy BMI ($\beta = -0.739$; $p = 0.002$). In the BS group, besides pre-pregnancy BMI ($\beta = -0.754$; $p < 0.001$), time from surgery to conception (in months) was associated with GWG ($\beta = 0.252$; $p < 0.001$). For each additional year between surgery and conception, there was an increase of 3.16 kg in GWG.

Pregnancy, Obstetric, and Neonatal Outcomes

Each group's pregnancy, obstetric, and neonatal outcomes are shown in Table 2. The mean GA was 38 ± 2 weeks, with no significant difference among groups ($p = 0.217$). Birth weight (BW) in the BS (3044 ± 405 g) was lower than both CG1 (3331 ± 450 g; $p = 0.016$) and CG2 (3344 ± 561 g; $p = 0.045$). However, after adjusting for pre-pregnancy BMI ($\beta = 36$; $p = 0.002$) and GWG in kg ($\beta = 22$; $p < 0.001$), the only group lower than CG1 was BS (mean difference = − 348.09 g; 95% CI − 602.47; 93.70; $p = 0.003$). No congenital malformations were diagnosed.

Birth length (48 ± 2 cm) and head circumference (34 ± 2 cm) were similar among groups ($p = 0.599$ and $p = 0.257$, respectively). The median breastfeeding time was 3 (1–11) months in BS, 15 (5–29) [34] months in CG1 and 6 (1–22) months in CG2, i.e., BS was lower than CG1 ($p < 0.001$). Breastfeeding for less than 6 months was higher in BS (72%) than both CG1 (28%) and CG2 (47%) ($p = 0.002$).

Concurrent Mother-Child Anthropometric Evaluation

The mothers' mean BMI was 35 ± 8 kg/m^2 in BS, 29 ± 5 kg/m^2 in CG1 and 38 ± 6 kg/m^2 in CG2 ($p < 0.001$). The children's height-for-age *Z*-score was similar among the groups ($p = 0.170$). The BMI-for-age *Z*-score was lower in CG1 than BS ($p = 0.024$) and CG2 ($p = 0.003$), while BS was similar to CG2 ($p = 0.846$). Forty-seven percent of children in BS, 34% in CG1 and 59% in CG2 were classified above the 90th percentile in WC ($p = 0.134$). Overweight was 31%, 22 and 25%, in BS, CG1 and CG2, respectively, while obesity was 34%, 22 and 53% in BS, CG1 and CG2, respectively, i.e., these

Table 1 Maternal characteristics according to group

Characteristic	Bariatric surgery ($n = 32$)	CG1 BMI < 35 kg/m^2 ($n = 32$)	CG2 BMI ≥ 35 kg/m^2 ($n = 32$)	p value
Sociodemographic characteristics				
Age in early pregnancy, years	30 ± 5	29 ± 5	30 ± 6	0.686
Ethnicity				
White	31 (97)^{a}	21 (65.6)^{b}	27 (84.4)^{ab}	0.004
Mixed/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 years	2 (6.2)^{a}	7 (21.9)^{ab}	10 (31.2)^{b}	< 0.001
9–11 years	8 (25)^{a}	15 (46.9)^{ab}	18 (56.3)^{b}	
≥ 12 years	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, US$	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/m^2	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
Adequacy of gestational weight gain				
Below ideal	7 (21.9)	6 (18.8)	4 (12.5)	0.514
Ideal	8 (25)	9 (28.1)	5 (15.6)	
Above 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
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
≥ 500 ml per week	1 (16.7)	0 (0)	2 (66.7)	0.770

Bariatric surgery group: singleton births of women who had undergone Roux-en-Y gastric bypass prior to pregnancy

Control group 1 (CG1): singleton births of women who had never undergone bariatric surgery and had a pre-pregnancy BMI < 35 kg/m^2 , using maternal age, delivery year, and gender as matching factors

Control group 2 (CG2): singleton births of women who had never undergone bariatric surgery and had a pre-pregnancy BMI ≥ 35 kg/m^2 , using maternal age, delivery year, and 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 according to analysis of variance with Tukey post hoc, Kruskal-Wallis with Dunn post hoc, chi-square, or Fisher's exact test at a significance level of 5%

Economic class was determined according to multiples of the minimum monthly wage in Brazilian Reais, which was approximately US$267.00 in September, 2016

The adequacy of gestational weight gain was determined according to Institute of Medicine recommendations (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 < 35 kg/m^2 ($n = 32$)	CG2 BMI ≥ 35 kg/m^2 ($n = 32$)	*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 (5 min) < 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 who had undergone Roux-en-Y gastric bypass prior to pregnancy

Control group 1 (CG1): singleton births of women who had never undergone bariatric surgery and had a pre-pregnancy BMI < 35 kg/m^2 , using maternal age, delivery year, and gender as matching factors

Control group 2 (CG2): singleton births of women who had never undergone bariatric surgery and had a pre-pregnancy BMI ≥ 35 kg/m^2 , using maternal age, delivery year, and gender as matching factors

Gestational hypertensive disorders include gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension

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

conditions were more frequent in CG2 than CG1 (OR 4.59; 95% CI 1.55; 13.61; $p = 0.006$).

Fluid Intelligence

The mean RCPM percentile 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 ($p = 0.032$). In this unadjusted analysis, children from CG1 presented higher mean percentiles than CG2 (mean difference = 12.31; 95% CI 0.20; 24.22; $p = 0.045$). Seventy-two percent of the children in BS, 69% in CG1 and 62% in CG2 scored above the 75th percentile ($p = 0.716$), indicating above-average intelligence. Maternal fluid intelligence assessed by RSPM was higher in BS vs. CG2 ($p = 0.007$); however, groups were similar when adjusted for maternal educational level ($p = 0.704$).

Household income ($r = 0.537$; $p < 0.001$), maternal age ($r = 0.348$; $p < 0.001$), maternal education ($r = 0.223$; $p = 0.029$) and maternal RSPM scores ($r = 0.201$; $p = 0.040$) were positively correlated with the children's general intelligence, while pre-pregnancy BMI ($r = -0.272$; $p = 0.007$) and child WC in cm ($r = -0.255$; $p = 0.022$) were negatively correlated with it.

In BS, the time from surgery to conception, adherence to multivitamin supplements and maternal nutritional deficiencies (iron, folic acid and vitamin B12) assessed at any time during pregnancy were not associated with RCPM percentile in offspring (data not shown).

In the univariate regression analyses of variables that could influence the children's global cognitive scores (Table 3), multiple regression provided two statistically significant models, regardless of group stratification. The first included pre-pregnancy BMI ($\beta = -0.727$; $p = 0.014$), family economic class (low: $\beta = -16.097$; $p = 0.006$; middle: $\beta = -5.467$; $p = 0.235$), and maternal age ($\beta = 1.452$; $p = 0.002$). This model was repeated and stratified by groups, but there was no group effect ($p = 0.207$). The second included economic class (low: $\beta = -21.579$; $p < 0.001$; middle: $\beta = -8.739$; $p = 0.040$), breastfeeding time in months ($\beta = 0.364$; $p = 0.024$) and maternal age ($\beta = 1.338$; $p = 0.005$); when adjusted for these predictors, the groups were similar.

Control group 1 scored better than BS and similar to CG2 when adjusted for economic class (model 1). When adjusting either for maternal education (model 2) or maternal general intelligence ($\beta = 0.090$; $p = 0.249$), there was no group effect. Post-RYGB group and CG2 did not differ in any analysis. The full model is presented in Table 4.

Table 3 Univariate regression analysis of potential variables influencing the general intelligence score in the offspring ($n = 96$)

Independent variable	*B*	Standard error	95% CI	*p* value
Maternal variables				
Age in early pregnancy, years	1.498	0.5001	0.517; 2.479	0.003
Ethnicity, mixed/black	−7.783	6.177	−19.890; 4.324	0.072
Education, years	0.917	0.506	−0.074; 1.908	0.070
Education, ≤ 12 years	−11.741	5.960	−23.424; −0.059	0.049
Education, 9–11 years	−7.344	6.391	−19.872; 5.184	0.142
Household income, US$	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/m^2	−0.936	0.294	−1.513; −0.358	0.001
Pre-pregnancy obesity, BMI ≥ 30 kg/m^2	−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 time, 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 intelligence score converted to percentile according to age, derived from Raven's Colored Progressive Matrices and adjusted for the following conditional matching factors: maternal age, delivery year, and gender. Household income, US$: determined at each increase of US$100.00

Abbreviations: BMI, body mass index; CI, confidence interval; RSPM, Raven's Standard Progressive Matrices

Discussion

The results of present study demonstrate that bariatric surgery prior to pregnancy was not associated with the fluid intelligence of offspring after adjusting for sociodemographic confounders. Household income was the strongest predictor and the only covariate that remained statistically significant in all analyses.

To our knowledge, this is the first study that have assessed the association between bariatric surgery prior to pregnancy and fluid intelligence in offspring compared to two control groups with different pre-pregnancy BMIs. Dell'Agnolo et al. [35] found speech delays in three male children aged from birth to 6 years while assessing the neuro- and psychomotor development of 23 children of women who had undergone bariatric surgery, as well as a possible association between the time from surgery to conception. In this sample, non-verbal global cognition was not associated with the time from RYGB to conception.

Economic inequalities adversely affect child health through many pathways. Poorer cognition stimulation, a stressful environment, genetics and nutrition all appear to contribute to this complex interplay. Additionally, children from families with lower household incomes commonly show a higher prevalence of depression, attention and conduct disorders [36, 37]. Mechanisms linking early exposure to poverty and brain structure have been proposed, suggesting an association between a low-income and changes in prefrontal function, as well as reduced white and cortical gray matter, since they seem to be mediated by caregiving support and stressful life events [38, 39].

In this sample, pre-pregnancy BMI in kg/m^2 and obesity category were negatively associated with the general intelligence of offspring. However, it remains unclear, especially in observational studies, whether maternal obesity adversely affects offspring cognition, causally linking to the fetal programming hypotheses, or whether some mediating factor accounts for well-established obesity-related diseases, such as insulin resistance, hyperinsulinemia, hypertensive disorders, and social and psychological factors [40].

Breastfeeding has also been postulated as positively associated with cognition, and would appear to be a lifelong effect [41, 42]. However, in high-quality observational studies used in a systematic review, only a slight IQ improvement, 1.76 points (95% CI 0.25; 3.26), could be attributed to breastfeeding [42].

Table 4 Multiple regression analysis of variables potentially influencing offspring general intelligence scores ($n = 96$)

Independent variable	*B*	Standard error	95% CI	*p* value
Model 1—economic class				
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—economic class, 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—economic class, pre-pregnancy BMI, kg/m^2				
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—economic class, breastfeeding time in 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 according to age, derived from Raven's Colored Progressive Matrices and adjusted for the following conditional matching factors: maternal age, delivery year, and gender. Abbreviations: BMI, body mass index; CI, confidence interval

Models 1: Economic class (low: $\beta = -20.576$; $p < 0.001$; middle: $\beta = -9.348$; $p = 0.019$),

Model 2: Economic class (low: $\beta = -23.740$; $p < 0.001$; middle: $\beta = -11.434$; $p = 0.026$), maternal education ($\leq$ 8y: $\beta = -3.995$; $p = 0.172$; 9–11y: $\beta = -3.878$; $p = 0.475$)

Model 3: Economic class (low: $\beta = -21.477$; $p < 0.001$; middle: $\beta = -9.812$; $p = 0.064$), pre-pregnancy BMI ($\beta = -0.532$; $p = 0.357$)

Model 4: Economic class (low: $\beta = -23.624$; $p < 0.001$; middle: $\beta = -11.410$; $p = 0.018$), breastfeeding time ($\beta = 0.279$; $p = 0.136$)

Model 5: Economic class (low: $\beta = -24.348$; $p < 0.001$; middle: $\beta = -9.550$; $p = 0.059$), maternal education ($\leq$ 8y: $\beta = -3.392$; $p = 0.521$; 9–11y: $\beta = 7.023$; $p = 0.406$), pre-pregnancy BMI ($\beta = -0.542$; $p = 0.356$), breastfeeding time ($\beta = 0.302$; $p = 0.069$)

Pregnancy following surgically induced weight loss is commonly associated with a higher prevalence of nutritional deficiencies [24]. However, in the present sample, results indicate that bariatric surgery is not an independent risk factor for adverse fetal outcomes among those who take vitamin and mineral supplements during pregnancy [43].

In a systematic review, surgically induced weight loss prior to pregnancy was associated with a 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; $p = 0.007$) than controls with obesity or pre-pregnancy BMI-matched peers [19]. The present study shows a reduced risk of GDM and hypertensive disorders in both post-RYGB pregnancies and controls with lower pre-pregnancy BMI than in controls with higher pre-pregnancy BMI, although 47% of the RYGB mothers were classified with obesity at conception.

Data from large observational studies have shown a higher risk of SGA and a lower risk of LGA after bariatric surgery [18, 20]. Although post-RYGB pregnancies were associated with a lower BW than either controls group, as well as a lower frequency of LGA than in CG2, there was no difference in SGA risk among the groups in the present sample. Mothers with pre-pregnancy BMI ≥ 35 kg/m^2 were more likely to have LGA infants than post-RYGB mothers. Both restricted and excessive intrauterine growth are associated with adverse outcomes [44, 45].

Kral et al. [46] compared 34 children aged 2 to 18 years who were born before maternal surgically induced weight loss and 172 children of the same age range born afterwards and found that obesity was 53% less frequent in the post-surgery offspring, which demonstrates an underlying association with environmental changes and epigenetic factors. Results from the present study showed that the long-term prevalence of overweight and obesity in children born to RYGB mothers did not differ from controls, although children of higher pre-pregnancy BMI mothers (CG2) were much more likely to be classified with overweight than the children of leaner mothers (CG1). Willmer et al. [47] assessed weight development at 4, 6 and 10 years of age in 164 children born before and 176 born after maternal bariatric surgery and also found no difference in overweight and obesity rates.

This study has some limitations. The sample size may have been insufficient to detect significant differences, which accounts for the wide confidence interval in most analysis. Several potential cognitive function predictors were not assessed due to the observational study design, and there was a survival bias since fetal mortality was excluded. Additionally, this study focused on only one type of cognition (fluid intelligence) assessed by Raven's Progressive Matrices. Fluid intelligence is a wide measure of cognitive ability and this may have accounted for the above-average scores in this sample. Further studies searching for different cognitive abilities using more specific intelligence tests and including neurodevelopmental assessment are required. Moreover, since results suggest that general intelligence is highly heritable [48], parental intelligence assessment should always be considered as part of the analysis. The main difficulty was in finding participants who had undergone RYGB. Since adherence to multidisciplinary follow-up care is often low [49, 50] and the women included in the final analysis continued their follow-up evaluations at the bariatric surgery referral center, this sample should be considered to have an above-average level of self-care. Thus, the results cannot be generalized to other populations with different adherence rates.

Regarding the study's strengths, it is the first general intelligence assessment of 5- to 12-year-olds born after maternal RYGB compared with two different pre-pregnancy BMI groups matched for mother-child age and gender.

Conclusions

Roux-en-Y gastric bypass prior to pregnancy was not associated with lower fluid intelligence in offspring; low family economic class was the strongest negative predictor. Previous bariatric surgery was associated with a lower frequency of gestational diabetes mellitus and hypertensive disorders than in women with obesity (pre-pregnancy BMI $\geq$ 35 kg/m^2) and was associated with lower birth weight than all controls, regardless of pre-pregnancy BMI.

Funding Sources The study was funded by the *Fundo de Incentivo à Pesquisa e Eventos* (FIPE) of the Hospital de Clínicas de Porto Alegre and the National Council of Technological and Scientific Development (CNPq).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval The study was performed according to the principles of the Helsinki Declaration. The HCPA and HSLPUCRS Ethics Committees approved the study protocol.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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