Metabolism Clinical and Experimental 97 (2019) 25–31

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Maternal, neonatal insulin resistance and neonatal anthropometrics in pregnancies following bariatric surgery

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ARTICLE INFO

Article history:
Received 22 October 2018
Accepted 3 April 2019

Keywords:
Bariatric surgery
Pregnancy
Maternal insulin resistance
Neonatal insulin resistance

ABSTRACT

Objective: An increasing number of women present pregnant having undergone bariatric surgery, a popular treatment for sustainable weight loss. The aim of the study was to investigate the effect, if any, of bariatric surgery on maternal and neonatal insulin resistance (IR) and neonatal body fat composition.
Methods: Maternal IR, at 28 weeks of gestation during 2-hour 75 g oral glucose tolerance test (OGTT), neonatal IR, from umbilical cord venous blood, and neonatal birthweight and body fat composition (calculated by measuring skin folds) at birth were evaluated in 41 post-bariatric and 82 pregnant women with similar early pregnancy body mass index but no history of such surgery. Insulin resistance was assessed using the homeostasis model assessment of IR (HOMA-IR).
Results: In the post-bariatric surgery group, compared to the no surgery group, maternal HOMA-IR (1.15 [1.04–2.07] vs 2.20 [1.53–3.38]; $p < 0.01$), neonatal birthweight ($p < 0.01$) and body fat ($p < 0.01$) were significantly lower whereas neonatal cord HOMA-IR was similar (1.29 [0.65–2.39] vs 1.19 [0.46–1.93]; $p = 0.49$). In the no surgery group, there was a positive correlation between maternal and neonatal HOMA-IR ($p = 0.03$) and between neonatal HOMA-IR and body fat ($p < 0.01$). However, no such significant correlations were detected in the post-bariatric surgery group.
Conclusion: Pregnancy following bariatric surgery is associated with a reduction in maternal IR and altered neonatal body composition with significantly lower birthweight and adiposity but no improvement in cord IR.

1. Introduction

Rates of obesity have reached an epidemic level worldwide. In 2016, almost 40% of adults were overweight or obese and there is compelling evidence that these conditions are associated with increased morbidity and mortality [1]. Compared with pharmacological and lifestyle interventions, bariatric surgery is currently considered the most effective treatment for sustainable weight loss (up to 70% of excess weight loss) [2,3] and has been associated with a significant reduction in the incidence of type 2 diabetes [3,4], linked to reduction in insulin resistance (IR) [3–5], and improvement in the cardiovascular risk profile with a lowering effect on both systolic and diastolic blood pressure (BP), lipid levels [3] and overall mortality [4,6]. There are two main types of bariatric surgery: restrictive procedures such as gastric banding and vertical sleeve gastrectomy, which are associated with a smaller volume stomach that reduces the amount of food consumed, and malabsorptive/mixed procedures, such as Roux-en-Y gastric bypass and biliopancreatic diversion, which aim to decrease calorie absorption.

Obesity in women of reproductive age is of particular concern because it is associated with an increased risk of infertility, miscarriage and, in the case of pregnancy, with a higher risk of gestational diabetes mellitus (GDM), hypertension, large for gestational age (LGA) neonates, Caesarean delivery, anaesthetic complications and perioperative morbidity [7–9]. Due to the favourable effects of bariatric surgery on weight loss and cardiometabolic health [2–4,6], the number of pregnant women, who have previously undergone such surgery, is steadily increasing. Several epidemiological studies have demonstrated that pregnancy following bariatric surgery is associated with a reduced risk of GDM, hypertensive disorders and LGA neonates, but on the other hand, a significantly increased risk of small for gestational age babies and late preterm delivery, compared to pregnancies with similar maternal body mass index (BMI) [10,11]. However, the mechanisms

Abbreviations: BMI, body mass index; BP, blood pressure; BW, birth weight; GDM, gestational diabetes mellitus; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; LGA, large for gestational age; OGTT, oral glucose tolerance test.

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https://doi.org/10.1016/j.metabol.2019.04.005
0026-0495/

underlying these changes in pregnancy outcomes remain elusive and it is uncertain whether they are related to weight loss alone or other maternal metabolic changes. Furthermore, as bariatric surgery was first introduced in 1960s, it is not surprising that studies investigating its effect on the metabolic health of the offspring are limited and their findings, so far, inconsistent [12–14].

The aim of the current study was to investigate maternal and neonatal IR, as assessed by the homeostatic model assessment of IR, and neonatal body composition of pregnancies following bariatric surgery compared to pregnancies with similar maternal BMI but no history of weight loss surgery.

2. Materials and methods

2.1. Ethics statement

The study was approved by the West London REC (14/LO/0592) and all women provided written, informed consent.

2.2. Study population

This was a prospective, observational, study investigating the effect of bariatric surgery on maternal and fetal/neonatal outcomes. The primary study group comprised women who had undergone previous bariatric surgery (restrictive or malabsorptive/mixed) and received pregnancy care at the Chelsea & Westminster Hospital, London between May 2015 and February 2017. Women were referred by midwives, dieticians or recruited via local posters/social media platforms. The study group was divided into booking BMI categories; <25, 25–29.9, 30–34.9, 35–39.9 and ≥40 and for each recruit two women with no weight loss surgery, a BMI in the same category and, where possible, of the same racial group, were recruited over the same time period. This resulted in a final comparison, no surgery, group with a very similar BMI and racial composition as the study group. There was no systematic matching for other variables such as parity and age as there was no sufficient number of participants, especially in the higher BMI categories, who agreed to participate to make this feasible.

Only women with singleton pregnancies who booked for antenatal care prior to 14 weeks of gestation were recruited. None of the women had pre-existing diabetes, a termination of pregnancy or stillbirth and all delivered a phenotypically normal infant.

Maternal characteristics such as age, parity, racial group, method of conception and smoking, were recorded at the initial visit. Maternal weight was measured using calibrated weighing scales with the women in light clothing and without shoes (Marsden Scales). Height was measured to the nearest cm without shoes and BMI was calculated in kg/m^2. Waist to hip ratio was assessed with waist circumference taken at the top of the iliac crest and hip circumference taken at the level of the symphysis pubis and around the greatest gluteal protuberance.

Arterial BP was measured with the subject seated using an automated device validated for use in pregnancy (Microlife WatchBP, Taipei, Taiwan) [15], which was calibrated before and at regular intervals during the study. A normal (22-32 cm) or large (33-42 cm) adult cuff was used, depending on the mid-arm circumference, and after resting for 5 min two recordings of BP were obtained on the left arm. The mean of these measurements was recorded.

Women who were recruited before 30 weeks underwent a 75 g oral glucose tolerance test (OGTT) at 28–30 weeks of gestation and GDM was defined according to NICE guidelines of fasting plasma glucose level ≥5.6 mmol/L and/or a 2-hour plasma glucose level ≥7.8 mmol/L [16]. At that time, fasting venous blood samples were taken, centrifuged and stored immediately at −80 °C for future measurement of plasma glucose, serum insulin and plasma glycated haemoglobin (HbA1c). Insulin resistance was calculated by the homeostasis model assessment of IR (HOMA-IR = fasting insulin (μIU/L) x fasting glucose (mmol/L)/22.5), which has been shown to correlate well with the euglycemic clamp [17]. Insulin sensitivity, the reverse of IR, was also calculated using the Quantitative Insulin Sensitivity Check Index (QUICKI) (QUICKI = 1/(log fasting insulin+ log fasting glucose) [18]. Low HOMA-IR values indicate high insulin sensitivity whereas high HOMA-IR values are suggestive of low insulin sensitivity (insulin resistance).

2.3. Outcome measures

Data on pregnancy outcome were obtained from the Hospital records. At delivery, cord venous blood (plasma and serum) was obtained, when possible, centrifuged and stored at −80 °C for future measurement of glucose and insulin which were used for calculation of neonatal cord IR, as assessed by HOMA-IR. Birth weight (BW), within an hour of delivery, was measured without diaper, using a calibrated electronic scale. BW for gestational age percentiles were calculated [19]. Neonatal anthropometric measurements of length (crown to heel), head (occipito-frontal) and abdominal (just above the umbilicus) circumferences, in cm, and skin fold thickness (triceps, subscapular and flank), in mm, using a calibrated Harpenden skin caliper, were obtained within 72 h of delivery by two experienced operators (TM, CK) [20]. Neonatal body fat (11.3 ± 3.7%, in an unselected population) was calculated using the formula described by Catalano et al., which has been shown to correlate well with values obtained using total body electrical conductivity [21,22]. Neonatal BP was measured electronically with a Dräger Infinity Gamma XL Monitor (Telford, PA, USA) using an appropriate size cuff, placed at the midpoint of the forearm, whilst the baby was settled and not crying, and measured in duplicate. The mean value was recorded. Serum and plasma samples were analysed using glucose (Architect cSystem assay, Abbott Laboratories; Intra-assay variability: 1.3%, Inter-assay variability: 0.89%), insulin (Architect cSystem assay, Abbott Laboratories; Intra-assay variability: 3.1%, Inter-assay variability: 2.5%) and HbA1c (G8 Glycohemoglobin Analyzer, Tosoh Corporation; Intra-assay variability 0.6%, Inter-assay variability: 0.56%) assays.

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to assess normality of the data distribution. Normally distributed continuous variables are expressed as mean ± standard deviation (SD) and non-normally as median (interquartile range, IQR). Categorical data are summarized using count and percentages. Unpaired *t*-test/Mann-Whitney *U* test and chi-square tests were used for numerical and categorical data respectively, to examine the differences in the demographic, biochemical and biophysical characteristics between the study groups.

The measured values of HOMA-IR and QUICKI were $\log_{10}$ transformed to make their distribution approximately Gaussian. Univariate analyses were performed to examine correlations between variables. Regarding maternal HOMA-IR and QUICKI, variables found to be significant predictors on univariate analyses were entered into a multiple regression and those that remained significant were then used to calculate the maternal HOMA-IR and QUICKI, adjusted for these confounders. Sensitivity analyses were also carried out in the group of participants who had complete dataset.

Formal power calculation was not performed as there were no previous studies /data available on changes in maternal or neonatal IR. Benjamini-Hochberg procedure was performed to correct for multiple comparisons. A corrected p-value <0.05 was considered statistically significant. The statistical software package SPSS Statistics 23.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

3. Results

The study overall included 123 pregnancies; 41 with previous bariatric surgery and 82 with similar early-pregnancy maternal BMI but no history of bariatric surgery (comparison, no surgery, group). The bariatric surgery group included 19 women with a previous restrictive (9

with gastric band and 10 with vertical sleeve gastrectomy) and 22 with a malabsorptive (gastric bypass) procedure. Maternal HOMA-IR was measured in 38 (93%) women with and 82 (100%) women without bariatric surgery. Cord HOMA-IR at birth was measured in 36 (88%) and 71 (87%) neonates of the post-bariatric and comparison, no surgery, group respectively. There were 33 (80%) and 71 (87%) paired maternal neonatal samples from post-bariatric and no surgery pregnancies respectively (Fig. 1).

3.1. Maternal parameters

The characteristics of all the study participants are presented in Table 1. In general, the maternal characteristics were similar between the groups although women with previous bariatric surgery were older than women in the comparison, no surgery, group. Women with previous malabsorptive procedures had a higher BMI prior to surgery and conceived later compared to those that had undergone a restrictive procedure.

Maternal IR, as assessed by HOMA-IR, was significantly lower in the post-bariatric surgery group (Fig. 2) and this was mainly driven by the post-malabsorptive group, which had significantly lower fasting glucose and insulin levels (Table 1). This was the case even when women who were classified as having GDM were excluded (HOMA-IR: 1.12 (1.03–1.56) vs 1.99 (1.51–3.20); $p < 0.001$). As far as the post-restrictive group was concerned, maternal HOMA-IR was not significantly different between women with gastric banding and those with a vertical sleeve gastrectomy (1.85 (1.30–3.96) vs 1.49 (1.08–3.13); $p = 0.49$) or between these subgroups and the comparison, no surgery, group ($p = 0.99$ and $p = 0.30$ respectively). In univariate analyses, maternal age ($p = 0.03$), BMI at booking ($p < 0.001$) and development of GDM ($p = 0.003$) were found to be significant predictors of maternal HOMA-IR whereas maternal racial group ($p = 0.61$), parity ($p = 0.63$) and smoking ($p = 0.58$) were not. Using only the significant predictors, a multiple regression was performed and BMI at booking ($p < 0.001$) and development of GDM ($p = 0.01$) remained significant predictors of maternal HOMA-IR. These variables were then used to calculate the adjusted maternal HOMA-IR, which was still found to be statistically significantly lower in the post-bariatric, and mainly post-malabsorptive, compared to the comparison, no surgery, group (Table 1). Conversely, QUICKI, even adjusted for maternal characteristics, was found to be significantly higher in the post-bariatric, mainly malabsorptive, women compared to their no surgery counterparts, suggesting improved maternal insulin sensitivity in this group (Table 1). Furthermore, there was a strong positive correlation between the adjusted maternal HOMA-IR and systolic and diastolic BP ($p < 0.001$ and $p = 0.005$ respectively) but no correlation with surgery-to-conception interval. Maternal post-prandial glucose levels (2-h OGTT) were significantly lower in the post-bariatric group. In particular, 70% (n = 14) and 22% (n = 4) of women with a previous malabsorptive and restrictive procedure, respectively, had relative post-prandial hypoglycaemia with glucose levels <3.34 mmol/l [23].

3.2. Neonatal parameters

Compared to neonates of the comparison, no surgery group, offspring of post-bariatric women, and mainly of those with previous malabsorptive procedure, were born significantly lighter, with significantly smaller head, abdominal circumference and less body fat (%) (Table 2), even after adjusting for gestational age at delivery and sex of the neonate ($p = 0.03$ for head circumference, $p = 0.007$ for abdominal circumference and $p = 0.008$ for body fat). In the post-bariatric surgery group, there was no correlation between surgery-to-conception interval and BW percentile. There was no significant difference in cord levels of glucose, insulin or IR (HOMA-IR) between the groups/subgroups (Table 2, Fig. 2).

3.3. Relationship between maternal and neonatal parameters

In the post-bariatric surgery group, there was a borderline correlation between maternal fasting glucose levels and BW percentile ($p = 0.07$) but a strong positive correlation between maternal post-prandial (2 h OGTT) glucose levels and BW percentile ($p = 0.007$). Similarly, in the comparison, no surgery, group, there was a weak correlation between maternal fasting glucose levels and BW percentile ($p =$

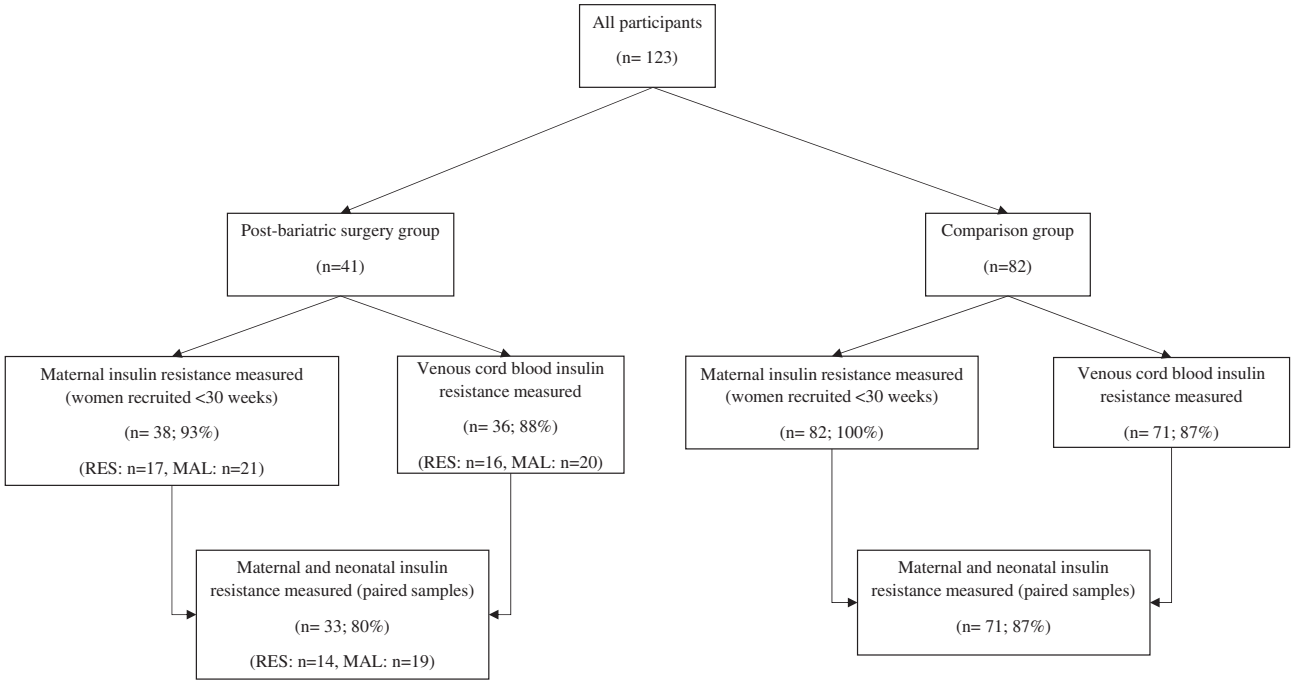

Fig. 1. Flow diagram of the study participants. RES: participants who had undergone a restrictive procedure; MAL: participants who had undergone a malabsorptive procedure.

Table 1
Maternal biophysical, biochemical characteristics and pregnancy outcomes of the study participants.

Characteristics	Comparison No surgery group (n = 82)	Post-bariatric surgery group (n = 41)	P	Post-Restrictive surgery group (n = 19)	Post-Malabsorptive surgery group (n = 22)
Maternal age (years)	30.29 ± 4.94	33.70 ± 4.72	<0.01*	33.31 ± 4.33	34.04 ± 5.12 *
Parity, n (%)			0.12		
Nulliparous	52 (63.4)	20 (48.8)		10 (52.6)	10 (45.5)
Parous	30 (36.6)	21 (51.2)		9 (47.4)	12 (54.5)
Racial group, n (%)			0.75		
White	64 (78)	33 (80.5)		16 (84.2)	17 (77.3)
Other	18 (22)	8 (19.5)		3 (15.8)	4 (22.7)
Conception, n (%)			0.17		
Spontaneous	79 (96.3)	37 (90.2)		17 (89.5)	18 (81.8)
Assisted reproductive techniques	3 (3.7)	4 (9.8)		2 (10.5)	4 (18.2)
Smoking, n (%)			0.06		
No	78 (95.1)	35 (85.4)		17 (94.7)	19 (86.4)
Yes	4 (4.9)	6 (14.6)		1 (5.3)	3 (13.6)
Family history of diabetes, n (%)			0.02		
No	63 (76.8)	22 (53.7)		11 (47.9)	11 (50)
Yes	19 (23.2)	19 (46.3)		8 (42.1)	11 (50)
Surgery-to-conception interval (months)	–	56.97 (31.80)	–	45.63 (29.83)	66.77 (30.77) **
Body mass index prior to surgery (kg/m^2)	–	46.85 (8.20)	–	42.48 (7.07)	50.62 (7.28) **
Booking body mass index	33.90 ± 6.90	33.00 ± 5.21	0.47	33.30 ± 6.49	32.74 ± 3.94
Booking waist to hip ratio	0.88 ± 0.09	0.85 ± 0.08	0.16	0.87 ± 0.08	0.84 ± 0.08
Gestational age at OGTT (wks)	28.46 ± 0.73 (n = 82)	28.32 ± 0.88 (n = 38)	0.37	28.33 ± 1.01 (n = 17)	28.32 ± 0.78 (n = 21)
Body mass index at OGTT (kg/m^2)	36.25 ± 6.42 (n = 82)	35.52 ± 5.10 (n = 38)	0.54	35.88 ± 6.67 (n = 17)	35.23 ± 3.52 (n = 21)
Systolic blood pressure at OGTT (mmHg)	113.78 ± 12.23 (n = 82)	108.63 ± 10.09 (n = 38)	0.03	109.23 ± 12.02 (n = 17)	108.14 ± 8.51 (n = 21)
Diastolic blood pressure at OGTT (mmHg)	71.33 ± 9.54 (n = 82)	67.97 ± 8.33 (n = 38)	0.06	69.17 ± 9.32 (n = 17)	67.00 ± 7.52 (n = 21)
Maternal fasting glucose at OGTT (mmol/L)	4.58 (4.22–4.92) (n = 82)	4.25 (4.12–4.61) (n = 38)	0.30	4.55 (4.23–5.25) (n = 17)	4.14 (4.02–4.30) * (n = 21)
Maternal fasting insulin at OGTT (mIU/L)	11.10 (8.34–15.92) (n = 82)	6.30 (5.57–9.24) (n = 38)	<0.01*	8.40 (6.10–16.25) (n = 17)	5.90 (5.35–6.30) * (n = 21)
Maternal HOMA-IR at OGTT	2.20 (1.53–3.38) (n = 82)	1.15 (1.04–2.07) (n = 38)	<0.01*	1.65 (1.11–3.42) (n = 17)	1.08 (0.99–1.23) * (n = 21)
Adjusted maternal HOMA-IR at OGTT†	2.10 (1.71–2.83) (n = 82)	1.40 (1.14–1.93) (n = 38)	<0.01*	1.83 (1.43–2.08) (n = 17)	1.29 (0.89–1.43) * (n = 21)
Maternal QUICKI at OGTT	0.34 (0.32–0.36) (n = 82)	0.37 (0.34–0.38) (n = 38)	<0.01*	0.35 (0.32–0.37) (n = 17)	0.38 (0.37–0.38) * (n = 21)
Adjusted maternal QUICKI at OGTT†	0.62 (0.61–0.64) (n = 82)	0.64 (0.63–0.65) (n = 38)	<0.01*	0.63 (0.62–0.64) (n = 17)	0.65 (0.64–0.66) * (n = 21)
Maternal glucose at 2 h OGTT (mmol/l)	5.50 (4.59–6.30) (n = 82)	3.45 (2.90–4.61) (n = 38)	<0.01*	4.49 (3.35–7.20) (n = 18)	3.10 (2.70–3.50) * (n = 20)
Maternal HbA1c (mmol/mol)	31.54 ± 4.08 (n = 82)	32.44 ± 3.90 (n = 38)	0.26	33.17 ± 5.04 (n = 17)	31.85 ± 2.65 (n = 21)
Gestational diabetes mellitus, n (%)			1		
No	74 (90.2)	37 (90.2)		15 (78.9)	22 (100.0)
Yes	8 (9.8)	4 (9.8)		4 (21.1)	0 (0)
Mode of delivery			0.76		
Vaginal, n (%)		13 (31.7)		7 (36.8)	6 (27.3)
Emergency caesarean section, n (%)		21 (51.2)		7 (36.8)	14 (63.6)
Elective caesarean section, n (%)		7 (17.1)		5 (26.3)	2 (9.1)

Data are mean ± SD or median (interquartile range), unless otherwise indicated. All comparisons were done with the comparison, no surgery, group. The *p* value refers to Unpaired *t*-test, Mann-Whitney *U* and chi-square tests between the comparison, no surgery, and post bariatric groups. *$p < 0.05$ following Benjamini-Hochberg corrections for multiple testing. **$p < 0.05$ for comparison between the post-restrictive and post-malabsorptive groups. †Values are adjusted for maternal booking body mass index and development of gestational diabetes mellitus (significant determinants of maternal HOMA-IR and QUICKI).
OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment of insulin resistance; HBA1c, glycated haemoglobin: QUICKI, Quantitative Insulin Sensitivity Check Index.

0.08) but a significant positive correlation between maternal postprandial glucose levels and BW percentile ($p = 0.03$).

With regard to HOMA-IR measurements, in the post-bariatric group we found no significant correlation between maternal and neonatal HOMA-IR or between neonatal HOMA-IR and body fat (%). However, in the comparison, no surgery group, there was a positive correlation between maternal and neonatal HOMA-IR ($p = 0.03$) and between neonatal HOMA-IR and body fat (%) ($p < 0.001$) (Fig. 3), even after adjusting for gestational age at delivery, maternal racial group, development of GDM and sex of the neonate ($p = 0.03$ and $p < 0.001$ respectively).

When all the above analyses were carried out only in participants with paired maternal neonatal samples, the results were unchanged (data not provided but available on request). In addition, the maternal characteristics of those with missing values were not significantly different from those with available paired values (data not provided but available on request).

4. Discussion

The study has demonstrated that pregnancy following bariatric surgery is associated with reduced maternal IR, as assessed by HOMA-IR, compared to pregnancies with similar maternal BMI but no previous history of such surgery, suggesting a broader positive impact of the operation beyond what would be expected by the resulting weight loss alone. However, this effect does not appear to extend to the neonates. Offspring of post-bariatric surgery women, despite being lighter and

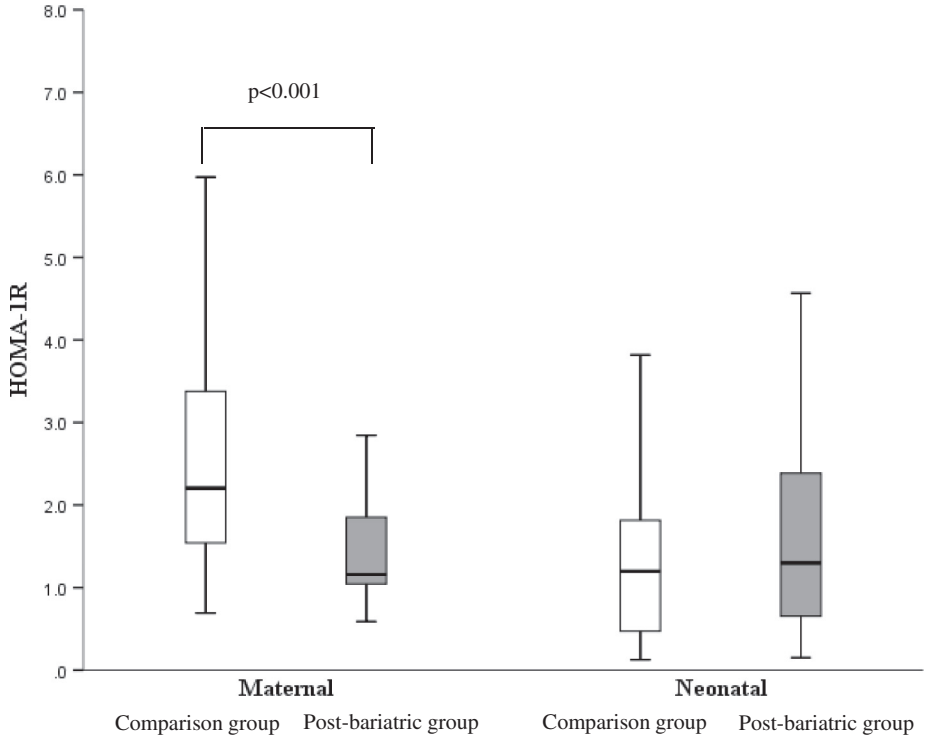

Fig. 2. Box and whisker plot demonstrating the distribution of insulin resistance, as assessed by HOMA-IR (homeostasis model assessment of insulin resistance), in pregnant women at 28–30 weeks of gestation and in neonates at birth. Boxes represent interquartile range, where the line represents the median. Whiskers at top and bottom of the box represent the highest and lowest values. White boxes = comparison, no surgery, group; grey boxes = post-bariatric surgery group.

thinner, had similar cord IR compared to offspring of women without surgery.

The reduction in maternal IR seen in the group of women following a malabsorptive procedure is in agreement with the only previous study in pregnancy demonstrating altered maternal glucose regulation during OGTT but not during parenteral glucose administration [24]. Although pregnant women in our two study groups had a similar BMI, those with a history of bariatric surgery demonstrated reduced IR indicating a lasting, multifactorial process, regardless of surgery-to-conception interval, which could also be linked to the reported reduced prevalence of GDM in those pregnancies [10]. Our findings are also consistent with findings outside the setting of pregnancy, where reduction in IR, following bariatric surgery, is reported to be due not only to weight loss but to other humoral mediators such as adipokines, incretins, inflammatory markers and gastrointestinal hormones i.e. gastric inhibitory polypeptide, glucagon-like peptide-1 (GLP-1) and ghrelin [6,25,26]. In our population, maternal IR appeared to be positively associated with BP, which was relatively lower in the post-bariatric population and this may provide an insight into the mechanisms underlying the lower prevalence of hypertensive disorders reported in this group of pregnant obese women [10].

There is a wealth of literature supporting the association between low BW and increased risk of hypertension, cardiovascular disease and mortality, impaired glucose tolerance, metabolic syndrome and type 2 diabetes, as a result of fetal programming mediated through alterations of metabolic pathways and cardiovascular remodelling aiming to facilitate the fetal adaptation to changes of the intra-uterine environment [27–29]. Although pregnancy following bariatric surgery is known to be associated with higher risk of small for gestational age neonates [10], studies on metabolic profile of these offspring are scarce [12–14]. Our study characterised the anthropometrics of the post-bariatric offspring at birth, who were smaller, lighter and with less body fat compared to neonates of women without surgery. The BW of post-bariatric offspring was independent of operation-to-conception interval, contrary to previous reports, probably due to the fact that only five women in our population conceived soon, <24 months, after the operation [30]. The mechanisms underlying suboptimal fetal growth in post-bariatric pregnancies remain uncertain, although maternal nutritional deficiencies of proteins, B and fat-soluble vitamins, essential fatty acids and minerals [31] have been implicated. However, it is conceivable that fetal growth restriction in these pregnancies may be related to altered maternal carbohydrate metabolism. In support of this notion, we found a positive correlation between maternal, mainly post-prandial (2-hour OGTT), glucose levels and BW. The maternal post-prandial glucose levels were markedly lower in the post-bariatric, mainly malabsorptive, compared to the no surgery group, probably due to the effect of GLP-1, which has been shown to play a role in the postprandial hyperinsulinaemic hypoglycaemia seen in these individuals [32]. The above, taking together, suggest that periods of relative maternal post-prandial hypoglycaemia in the post-bariatric, malabsorptive group, can have a negative impact on offspring's growth. Low maternal glucose may impair the maternal-fetal concentration gradient and diffusion/transfer of glucose, the main energy source for the fetus as its own gluconeogenesis is minimal [33,34], which in turn could lead to initiation of epigenetic changes that alter fetal metabolism allowing for preferential glucose use by the brain and other vital organs [35] at the expense of deposition of neonatal fat mass and eventually cause poor growth.

Despite being smaller, neonates of post-bariatric pregnant women had similar cord glucose, insulin and IR as the neonates of women without surgery suggesting that both groups have comparable carbohydrate kinetics at birth. Previous studies have documented a positive correlation between maternal and neonatal IR in obese pregnant women [36] and a linkage between umbilical cord insulin/C peptide levels and neonatal adiposity [22]. In our study, we found similar positive associations in the no surgery group but these correlations were not detected in the post-bariatric group highlighting a disruption in the feto-maternal metabolic signalling, possibly due to altered placental transporter gene expression and fetal programming, in the latter group.

Our findings generally suggest an altered maternal neonatal metabolic interrelationship in post-bariatric pregnancies which may have

Table 2
Infant characteristics of the study participants.

Characteristics	Comparison no surgery group (n = 82)	Post-bariatric surgery group (n = 41)	P	Post-restrictive surgery group (n = 19)	Post-malabsorptive surgery group (n = 22)
Birth weight (g)	3479.84 ± 557.82 (n = 82)	3094.02 ± 599.03 (n = 41)	<0.01*	3165.84 ± 527.51 (n = 19)	3032.0 ± 660.53 * (n = 22)
Gestational age at delivery (weeks)	39.41 ± 1.47 (n = 82)	38.63 ± 2.25 (n = 41)	0.02*	38.75 ± 2.14 (n = 19)	38.53 ± 2.38 (n = 22)
Birth weight (percentile)	57.88 ± 32.38 (n = 82)	41.41 ± 30.62 (n = 41)	<0.01*	45.50 ± 32.85 (n = 19)	37.88 ± 28.86 * (n = 22)
Birth weight percentile <10th, n (%)	9 (11) (n = 82)	7 (17.1) (n = 41)	0.34	3 (15.8) (n = 19)	4 (18.2) (n = 22)
Length (cm)	51.27 ± 3.00 (n = 81)	49.78 ± 3.89 (n = 41)	0.02*	50.47 ± 2.84 (n = 19)	49.22 ± 4.57 * (n = 22)
Head circumference (cm)	34.92 ± 1.74 (n = 75)	33.97 ± 1.59 (n = 38)	<0.01*	34.08 ± 1.52 (n = 18)	33.87 ± 1.69 * (n = 20)
Abdominal circumference (cm)	33.54 ± 2.15 (n = 75)	32.08 ± 2.69 (n = 38)	<0.01*	32.32 ± 2.67 (n = 18)	31.86 ± 2.75 * (n = 20)
Head/abdominal circumference (ratio)	1.04 ± 0.05 (n = 75)	1.06 ± 0.09 (n = 38)	0.08	1.06 ± 0.08 (n = 18)	1.06 ± 0.09 (n = 20)
Systolic blood pressure (mmHg)	77.56 ± 15.50 (n = 75)	78.13 ± 12.62 (n = 38)	0.84	77.63 ± 11.67 (n = 18)	78.63 ± 13.81 (n = 20)
Diastolic blood pressure (mmHg)	39.02 ± 9.53 (n = 75)	37.57 ± 11.57 (n = 38)	0.48	38.0 ± 10.37 (n = 18)	37.15 ± 12.92 (n = 20)
Skin folds (mm)					
Triceps	5.87 ± 1.37	5.20 ± 1.44	0.02*	5.36 ± 1.37	5.04 ± 1.52 *
Subscapular	5.20 ± 1.27	4.71 ± 1.35	0.06	5.15 ± 1.51	4.30 ± 1.06 *
Flank	4.08 ± 1.03 (n = 75)	3.76 ± 1.20 (n = 38)	0.14	3.98 ± 1.42 (n = 18)	3.55 ± 0.94 (n = 20)
Neonatal fat mass (gr)	437.8 ± 176.9 (n = 75)	336.4 ± 174.59 (n = 38)	<0.01*	352.2 ± 188.48 (n = 18)	320.6 ± 163.40 * (n = 20)
Neonatal body fat (%)	12.14 ± 3.67 (n = 75)	10.06 ± 3.95 (n = 38)	<0.01*	10.45 ± 4.55 (n = 18)	9.67 ± 3.34 * (n = 20)
Neonatal cord glucose (mmol/L)	4.17 (3.66–5.02) (n = 71)	4.59 (3.73–5.20) (n = 36)	0.56	4.28 (3.49–5.12) (n = 16)	4.79 (3.73–5.31) (n = 20)
Neonatal cord insulin (mIU/L)	6.00 (2.70–9.60) (n = 71)	6.10 (3.67–11.60) (n = 36)	0.57	6.45 (3.22–11.57) (n = 16)	6.10 (3.75–11.90) (n = 20)
Neonatal cord HOMA-IR	1.19 (0.46–1.93) (n = 71)	1.29 (0.65–2.39) (n = 36)	0.49	1.21 (0.51–2.45) (n = 16)	1.36 (0.65–2.39) (n = 20)

Data are mean ± SD or median (interquartile range), unless otherwise indicated. All comparisons were done with the comparison, no surgery, group. The *p* value refers to Unpaired *t*-test, Mann-Whitney *U* and chi-square tests between the comparison, no surgery, and post bariatric groups. *$p < 0.05$ following Benjamini-Hochberg corrections for multiple testing.
HOMA-IR, homeostatic model assessment of insulin resistance.

implications for the perinatal metabolic health of the offspring so that the initial indication for bariatric surgery, such as treatment of metabolic syndrome, may be perpetuated in future generations. However, it should be noted that our results related to cord glucose/insulin levels should be interpreted with caution as there are factors that could have influenced the cord glucose and insulin levels such as mode of delivery [37], the presence of fetal distress, infection or maternal glucose intake. Larger studies stratified according to the mode of delivery and

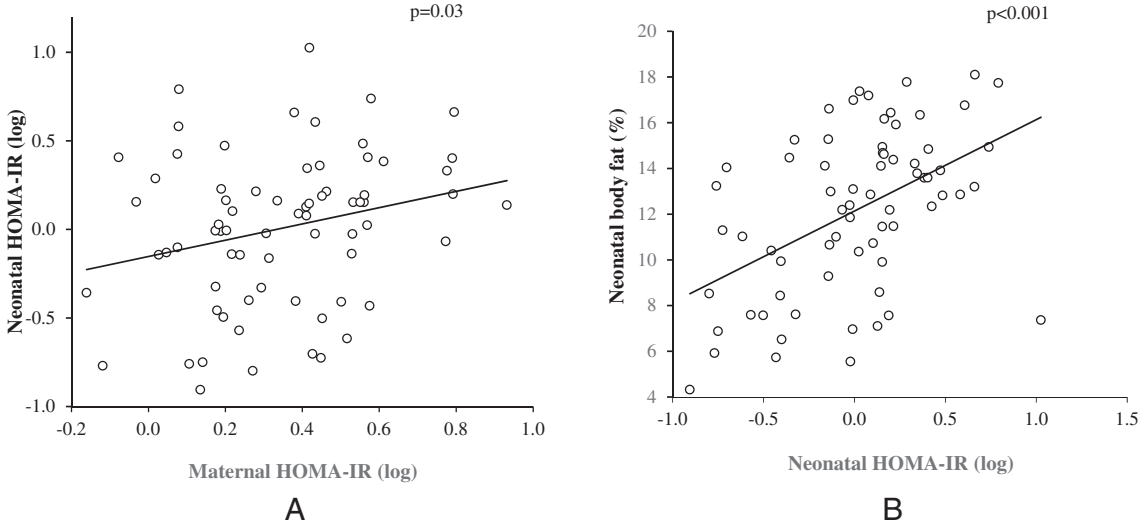

Fig. 3. Regression analyses showing a positive correlation between: (A) maternal and neonatal cord insulin resistance, as assessed by HOMA-IR, (Log Neonatal HOMA-IR = −0.153+ (0.459*Log Maternal HOMA-IR)) and (B) neonatal cord insulin resistance, as assessed by HOMA-IR, and neonatal body fat (% Neonatal body fat = 12.139 + (3.997*Log Neonatal HOMA-IR) in the comparison, no surgery, group. HOMA-IR: homeostasis model assessment of insulin resistance.

controlling for the above factors may help clarify these issues. Additionally, there is limited information on the relevance of cord IR at birth, as assessed by HOMA-IR, and future metabolic health. The relatively small number of cases in our study also precludes robust analyses by the type of operation performed.

We conclude that pregnancy following bariatric surgery is associated with a reduction in maternal IR but altered neonatal body composition with significantly lower BW and adiposity, which may be associated with an impaired maternal neonatal metabolic linkage. Therefore, if prevention and treatment of metabolic effects of obesity in future mothers is to be achieved by bariatric surgery, the potential transgenerational consequences of it warrant further consideration.

Acknowledgements

The authors would like to thank Professor Phil Steer and Khadija Randell for their help with statistical analyses and interpretation of the data.

Authors contributions

Tanya Maric researched data and wrote the manuscript. Chidimma Kanu researched data. Mark Johnson conceived the study and reviewed/edited the manuscript. Makrina Savvidou conceived, designed the study, researched data and wrote the manuscript. All authors contributed to the critical revision of the manuscript and refined and expanded the understanding of the results.

Funding

The work was supported by BORNE (UK Registered Charity number: 1167073).

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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