

Reproductive Outcomes Differ Following Roux-en-Y Gastric Bypass and Adjustable Gastric Band Compared with Those of an Obese Non-Surgical Group

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Abstract

Background Little is known about how bariatric surgery type may impact reproductive health outcomes. Our objective was to determine differences in infertility and birth outcomes among women who underwent Roux-en-Y gastric bypass (RYGB), adjustable gastric band (AGB), and an obese non-surgical group.

Methods Women aged 18–45 who were evaluated for bariatric surgery were invited to complete a survey. Pre- and postsurgery outcomes were compared among women who underwent RYGB vs. AGB and to those of obese women who decided against surgery. Outcomes included infertility, time to conception from first attempt, use of infertility services, pregnancy, live birth, and birth weights. Logistic and linear regression, controlling for age, BMI, weight, and pregnancy history, were used to calculate odds ratios (ORs) and beta-coefficients with 95 % confidence intervals (CIs).

Results Two-hundred nineteen surveys were completed. RYGB resulted in a reduction in menstrual cycle irregularity

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Elizabeth S. Ginsburg EGinsburg@partners.org after surgery compared to before (OR = 0.21, CI = 0.07– 0.61). For first-pregnancy outcomes, there were lower odds of term birth after RYGB than before (OR = 0.21, CI = 0.05–0.90) and increased odds of miscarriage after RYGB compared to the no-surgery group (OR = 9.81, CI = 1.12–85.71). We found lower odds of live birth after AGB than before (OR = 0.19, CI = 0.05–0.73). Birth weight was significantly lower after RYGB but not AGB (p < 0.01).

Conclusions This small study suggests that the impact of bariatric surgery may vary by procedure type and impact menstrual regularity, live birth, and offspring birth weight. These results should be considered pilot data and support performance of a prospective study to fully investigate these preliminary findings.

Keywords Bariatric surgery \cdot Infertility \cdot Pregnancy \cdot Time to conception \cdot Obesity

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Introduction/Purpose

Obesity has become increasingly prevalent among women of reproductive age [1–5]. In addition to having greater risks of cardiovascular disease and diabetes, obese women are more likely to experience sequelae of polycystic ovary syndrome (PCOS), with menstrual cycle irregularity and infertility [6–10]. Obesity is also associated with lower pregnancy and live birth rates among women who undergo in vitro fertilization (IVF) [11]. Weight loss is often recommended for overweight and obese women who have difficulty conceiving, as data suggest that it may improve menstrual cyclicity, reduce hyperinsulinemia, and decrease leptin levels [9, 12–14].

Despite the availability of exercise and medication management, the only intervention proven to result in long-term, sustained weight loss is bariatric surgery [6, 7, 15]. The majority of people undergoing bariatric surgery are women, most of whom are of reproductive age (18 to 45 years) [5, 16]. Women are generally advised to wait 12-18 months after bariatric surgery to conceive, although data supporting this recommendation are limited [8, 17, 18]. It is believed that delaying conception until after the rapid weight loss phase is complete minimizes the impact on the fetus, improves nutritional deficiencies, and helps patients achieve their weight loss goals. Women who conceive following bariatric surgery are less likely to develop gestational diabetes or have macrosomic infants compared with their morbidly obese counterparts [5, 19, 20]. Several studies have shown a link between bariatric surgery and an increased incidence of small for gestational age infants as well as pre-term birth [19-21]. There are also several reports of maternal and fetal deaths following complications of bariatric surgery procedures during pregnancy [22, 23].

The mechanisms by which bariatric surgery causes weight loss and ameliorates weight-related co-morbidities such as diabetes have been heavily researched and are likely multi-factorial [24–26]. A growing body of evidence suggests that there are a number of neuroendocrine effects independent of weight loss that decrease hunger, improve satiation, and favorably affect metabolic processes such as glucose metabolism. These effects are more pronounced with Roux-en-Y gastric bypass (RYGB) and sleeve compared to adjustable gastric band (AGB); however, RYGB may also be associated with increased risk of nutritional deficiencies [27]. These physiologic changes that follow different bariatric surgery techniques may influence conception and pregnancy.

It is imperative to counsel reproductive-aged women about the risks and benefits different bariatric surgery procedures pose to their fertility. Few studies have examined how the type of bariatric surgery and the time to conception following the surgery might affect reproductive outcomes [28–31]. To our knowledge, no study has examined how the different types of bariatric surgery affect the time to achieve pregnancy from first conception attempt. There is also little data on the use of assisted reproductive technology (ART) after bariatric surgery [9, 31]. The current study seeks to compare reproductive and pregnancy outcomes among (1) women who have undergone RYGB; (2) women who have undergone AGB; and (3) an obese, non-surgical group.

Materials and Methods

This retrospective cross-sectional study was conducted among women aged 18–45 at study start who had seen a bariatric surgeon in consultation between 2002 and 2012 at Brigham and Women's Hospital. Patients who had undergone RYGB, AGB, and sleeve gastrectomy, as well as those who consulted with a bariatric surgeon but who elected not to undergo surgery, were identified using the Brigham and Women's Hospital bariatric surgery database. Patients were mailed a letter containing a link to our survey, and participants who did not respond to the first mailing were sent a second reminder letter 4 to 6 weeks later. Each woman received a \$5 Amazon Gift code as a token of appreciation for completing the survey. This study was approved by the Partners HealthCare institutional review board.

All women received identical surveys with questions regarding weight, health, and reproductive history, including detailed information on PCOS, diabetes, and menstrual cycle regularity (regular cycles were defined as having a variance of <7 days between menses). For this analysis, the main outcomes of interest included menstrual cycle regularity, desire for pregnancy, use of infertility services, pregnancy outcomes, time to achieve pregnancy, and birth weight. For each identified pregnancy, participants were asked the time from attempting pregnancy to conception (months), method of attaining pregnancy (e.g., spontaneous, use of clomifene citrate, gonadotropins, or IVF), duration of pregnancy (months), and pregnancy outcome (e.g., full-term birth, pre-term birth, miscarriage, and termination). Birth weight was also measured for each live birth. See Supplementary material for the complete survey. Due to the small number of women who reported undergoing sleeve gastrectomy, such women were excluded from the final analyses. Women who had an unidentified bariatric surgery procedure were also excluded.

Women who underwent RYGB and AGB were compared (i) to obese women who had not undergone surgery, (ii) to themselves pre-surgery, and (iii) to women who received the other type of surgery. In sensitivity analyses, women presurgery were compared to women who did not undergo surgery.

Analyses were controlled for a priori confounding factors, age, BMI, weight, and history of prior pregnancy. For dichotomous and multi-categorical outcomes, odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated using logistic regression and polytomous logistic regression, respectively. For continuous outcomes, mean differences (β) and 95 % confidence intervals were calculated using linear regression. Generalized estimating equations were used to take into account correlation pre-post surgery. For comparison of term birth, pre-term birth, and miscarriage, only the first pregnancies conceived before and after surgery were analyzed. Pregnancies that were ongoing at the time of survey completion (three in RYGB and two in AGB groups) were electively terminated (five in pre-RYGB and one in post-RYGB group) or were missing data on duration (one in post-AGB group) were not included in the analysis.

Results

A total of 3018 surveys were mailed out; 1644 were sent to women who underwent bariatric surgery and 1374 to women who did not undergo bariatric surgery. There were 156 surveys sent to women who underwent surgery for whom addresses were incorrect and these letters were returned unopened to sender. Surveys sent to women who did not undergo surgery were sent via a separate hospital mailing system, and undeliverable letters could not be returned to the original sender. We therefore cannot know how many incorrect addresses there were for the non-surgical group. Surveys were completed by 219 women; 111 underwent RYGB, 66 underwent AGB, 16 underwent sleeve gastrectomy or an unidentified procedure, and 26 did not have surgery.

The mean age and background characteristics of the groups were similar. At the time of survey completion (post-surgery), more women in the AGB group reported being severely obese (BMI \geq 35) than in the RYGB group (65.1 and 28.8 %, respectively; Table 1). The average BMI decrease was 14.71±6.35 in the RYGB group and 9.17±6.16 in the AGB group. Approximately 25 % of the women who underwent surgery reported a history of PCOS, while 16 % of women who did not undergo surgery reported a history of PCOS. Among women who underwent bariatric surgery, 34.2 % in the RYGB group and 19.7 % of women in the AGB group underwent surgery \geq 18 months prior to survey completion.

There were no differences in any main outcome measures between the pre-surgery and no-surgery groups. Prior to bariatric surgery, 38.7 % of women who underwent RYGB and 27.4 % of women who underwent AGB reported menstrual cycle irregularity (Table 2). This fraction is similar to that of women reporting cycle irregularity (34.6 %) who did not undergo surgery. Fewer women reported menstrual cycle irregularity after RYGB than before (OR = 0.21, CI = 0.07–0.61), while women who underwent AGB did not have statistically significant improvements in menstrual cycle regularity postsurgery. There were no differences in hormonal contraceptive use between the groups. Women post-AGB were less likely to use infertility services compared to women pre-AGB (OR=0.06, CI=0.02–0.37) and compared to women who did not undergo surgery (OR=0.08, CI=0.01–0.84). Statistically significant differences in the use of ART were not seen following RYGB.

Approximately 50 and 60 % of women desired pregnancy pre-surgery in the RYGB and AGB groups, respectively (Tables 3 and 4). Fewer women desired pregnancy after surgery in both groups (27.9 and 36.4 % in the RYGB and AGB groups, respectively). Similarly, fewer women desired pregnancy after both types of surgery compared with the nosurgery group. Among women who desired pregnancy, there were no significant differences in conception between groups. Pregnancy rates and mean number of live births among groups can be found in Tables 3 and 4.

Among women desiring pregnancy, those who underwent AGB were found to have lower odds of having a live birth after surgery than before (OR = 0.19, CI = 0.05-0.73). This difference in live birth was not seen in the RYGB group. For the first pregnancy achieved before or after surgery, the odds of having a term (>37-week gestational age) birth were significantly lower after RYGB compared with pre-surgery pregnancies (OR = 0.21, CI = 0.05-0.90) and compared with women who did not undergo surgery (OR = 0.16, CI = 0.03-0.94). There were no differences in term birth before or after AGB. Women who underwent AGB were more likely to have a term birth than women who underwent RYGB for post-surgery pregnancies (OR = 12.72, CI = 1.61-100.6). The odds of miscarriage were significantly higher for women after RYGB compared with women who did not undergo surgery (OR = 9.81, CI = 1.12 - 85.71). There were fewer miscarriages seen after AGB than after RYGB (OR = 0.10, CI = 0.01-0.80). There were no differences in pre-term birth, ectopic pregnancy, or terminations among groups, although numbers were small.

There were no significant differences in self-reported history of infertility among the groups. Among all women, 7.2 % of women pre-RYGB and 4.6 % of women pre-AGB reported that it took >12 months for them to conceive, compared with 1.8 and 4.6 % post-RYGB and post-AGB, respectively. Among infertile women who underwent RYGB or AGB, pregnancy rates were similar before and after surgery. However, among this same group, while 47 % of pregnancies before surgery resulted in live birth (n = 17/36), only 19 % of pregnancies after surgery resulted in live birth (n = 4/21).

Among live births, the average neonatal birth weight for women who did not undergo surgery was 3583 ± 519 g. Following RYGB, the average birth weight (2983 ± 510 g) was lower compared with women who did not undergo surgery, [β mean difference (95 % CI)]=[-727 (-1159, -295)], p=0.002. Birth weight was also significantly lower after RYGB than before (p=0.008). In contrast, there were no

Table 1 Demographics

Variable (current—at time of survey)	No surgery $n = 26$	RYGB <i>n</i> = 111	AGB $n = 66$
Age (mean ± SD)	39.7 ± 9.8	39.4 ± 7.7	40.4 ± 6.3
Median Decrease in BMI (mean ± SD)	37.9	40.6 14.71 ± 6.35	41.1 9.17 ± 6.14
DMI (automati)		(-2.42-37.46)	(-4.42-26.93)
BMI (current) 18.5–24.9	- 3 (11.5 %)	- 9 (8.1 %)	- 3 (4.6 %)
25.0–29.9	4 (15.4 %)	40 (36.0 %)	3 (4.6 %)
30.0–34.9	5 (19.2 %)	30 (27.0 %)	17 (25.8 %)
35.0–39.9	5 (19.2 %)	18 (16.2 %)	20 (30.3 %)
40.0-44.9	7 (26.9 %)	6 (5.4 %)	16 (24.2 %)
45.0–49.9	1 (3.9 %)	6 (5.4 %)	5 (7.6 %)
50.0-54.9	0	1 (0.9 %)	2 (3.0 %)
≥55	1 (3.8 %)	1 (0.9 %)	0
Time since surgery ≥ 18 months		38 (34.2 %)	13 (19.7 %)
Partner's history of infertility	2(10.0%)	7 (8.9 %) 28 (25 5 %)	3 (5.8 %)
History of PCOS Received treatment for PCOS	4 (16.0 %) 4 (15.4 %)	28 (25.5 %) 16 (14.7 %)	16 (24.6 %) 9 (14.5 %)
History of DM	-	-	-
Diet controlled	1 (3.9 %)	2 (1.8 %)	2 (3.1 %)
Oral medication	2 (7.7 %)	3 (2.7 %)	1 (1.5 %)
Insulin	0	1 (0.9 %)	0
Oral medication + insulin	0	1 (0.9 %)	1 (1.5 %)
Resolved	0	8 (7.2 %)	0
Exercise	-	-	-
>5 days/week	2 (8.0 %)	10 (9.1 %)	4 (6.2 %)
3–5 days/week	3 (12.0 %)	30 (27.3 %) 25 (21.8 %)	16 (24.6 %)
1–2 days/week Rarely/never	14 (56.0 %) 6 (24.0 %)	35 (31.8 %) 35 (31.8 %)	26 (40.0 %) 19 (29.2 %)
Smoking	0 (24.0 %)	-	19 (29.2 %) -
Current	0	5 (4.6 %)	1 (1.6 %)
Past	4 (15.4 %)	21 (19.1 %)	16 (25.0 %)
Never	22 (84.6 %)	84 (76.4 %)	47 (73.4 %)
Alcohol use	-	_	_
Never/rarely	17 (68 %)	69 (62.7 %)	32 (49.2 %)
One to two drinks/week	8 (32 %)	32 (29.1 %)	31 (47.7 %)
One to two drinks/day	0	9 (8.2 %)	2 (3.1 %)
More than two drinks/day Education level	0	0	0
Did not graduate high school	- 1 (3.9 %)	_ 1 (0.9 %)	- 0
High school/GED	4 (15.4 %)	10 (9.0 %)	6 (9.1 %)
Some college	4 (15.4 %)	29 (26.1 %)	7 (10.6 %)
Associate's degree	1 (3.9 %)	11 (9.9 %)	14 (21.2 %)
Bachelor's degree	4 (15.4 %)	34 (30.6 %)	23 (34.9 %)
Graduate or professional	12 (46.2 %)	26 (23.4 %)	16 (24.2 %)
Household income	-	-	-
<\$20,000	2 (8.3 %)	9 (8.5 %)	2 (3.1 %)
\$20,000-\$40,000	2 (8.3 %)	19 (17.9 %)	7 (10.8 %)
\$40,000-\$60,000	2 (8.3 %)	19 (17.9 %)	13 (20.0 %)
\$60,000-\$80,000 \$80,000 \$150,000	2(8.3%)	16 (15.1 %) 27 (25.5 %)	10 (15.4 %)
\$80,000-\$150,000 >\$150,000	8 (33.3 %) 8 (33.3 %)	16 (15.1 %)	23 (35.4 %) 10 (15.4 %)
Race	-	-	-
American Indian/Alaska Native	0	1 (0.9 %)	1 (1.5 %)
Asian	1 (4.0 %)	1 (0.9 %)	0
Black or African American	1 (4.0 %)	18 (16.5 %)	6 (9.1 %)
White	22 (88.0 %)	78 (71.6 %)	53 (80.3 %)
More than one race	0	5 (4.6 %)	2 (3.0 %)
Unknown/not reported	1 (4.0 %)	6 (5.5 %)	4 (6.1 %)
Ethnicity	-	-	-
Hispanic or Latino	5 (19.2 %)	20 (18.2 %)	2 (3.1 %)
Not Hispanic or Latino	19 (73.1 %)	86 (78.2 %) 5 (2.6 %)	60 (93.8 %) 2 (2 1 %)
Unknown/not reported Health insurance	2 (7.7 %)	5 (3.6 %)	2 (3.1 %)
	- 21 (80.8 %)	- 90 (82.6 %)	- 60 (90.9 %)
Private			
Private Medicare	3 (11.5 %)	9 (8.3 %)	0

Table 1 (continued)

Variable (current—at time of survey)	No surgery $n = 26$ RYGB $n = 111$		AGB $n = 66$	
None	0	1 (0.9 %)	0	
Marital status	-	-	_	
Never married	7 (26.9 %)	26 (23.9 %)	16 (24.2 %)	
Married	17 (65.4 %)	57 (52.3 %)	39 (59.1 %)	
Long-term partner	1 (3.9 %)	10 (9.2 %)	6 (9.1 %)	
Divorced	1 (3.9 %)	13 (11.9 %)	3 (4.6 %)	
Separated	0	3 (2.8 %)	2 (3.0 %)	

significant differences in neonatal birth weight post-AGB $(3385 \pm 723 \text{ g})$ compared to the no-surgery and pre-AGB groups. There were no statistically significant differences in time to conception between the groups (see Tables 3 and 4).

Conclusion

The benefits of bariatric surgery are numerous and include decreased incidence of diabetes, PCOS, and cardiovascular disease, as well as improvements in menstrual regularity and ovulation [4, 5, 24, 32]. Different types of bariatric surgery appear to have differing impacts on reproductive outcomes, while the mechanisms causing changes in reproductive outcomes are largely unknown. It has been well described that the physiologic changes occurring after AGB. Gut hormone biology and changes in insulin resistance are more strongly affected by procedures like RYGB than with AGB [24–26, 33–36]. A growing body of evidence suggests that

Table 2 Menstrual characteristics and use of infertility services

gut hormone biology impacts reproduction, and the role bariatric surgery plays is an exciting avenue of research [37].

Our study supports previous findings that menstrual cycle regularity increases following both RYGB and AGB [5]. In the current study, women in the RYGB group reported menstrual cycle irregularity less frequently after surgery than before. There was a trend toward decreased menstrual cycle irregularity in the AGB group as well, although this did not reach the threshold of statistical significance, which may be a result of limited power in this group. However, women who undergo RYGB tend to lose more weight and sustain the weight loss longer than women who undergo AGB [4]. At the time of the survey, we found that fewer women in the RYGB group were severely obese (BMI < 35) compared with women in the AGB group (28.8 and 65.1 %, respectively). The higher degree of weight loss in the RYGB group may be associated with improved cycle normality.

The rapid weight loss associated with bariatric surgery may be detrimental to follicle development, and women who have had bariatric surgery and are undergoing ART may have fewer

_	Roux-en-Y gas	stric hypass				
Outcome	No surgery, n(%)	Pre-RYGB, n (%)	Post-RYGB, <i>n</i> (%)	Post-RYGB vs. No surgery (referent) ^a OR (95 % CI)	Pre-(referent) vs. Post ^a OR	RYGB (referent) vs. AGB ^a OR (95 % CI)
Menstrual cycle regularity	<i>n</i> = 26	n = 106 (missing 5)	<i>n</i> = 111	-	_	-
Regular	15 (57.7)	47 (44.3)	56 (50.5)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Irregular	9 (34.6)	41 (38.7)	32 (28.8)	1.04 (0.31-3.56)	0.21 (0.07-0.61)	0.33 (0.12-0.87)
Using hormonal contraceptives	2 (7.7)	18 (17.0)	23 (20.7)	2.32 (0.46–11.70)	-	0.93 (0.39–2.22)
Use of infertility services	4 (15.4)	13 (12.0)	3 (2.8)	0.23 (0.04–1.40)	0.18 (0.03–1.27)	0.36 (0.03–4.77)
_	Adjustable gas	tric band				
Outcome	No surgery, n (%)	Pre-AGB, <i>n</i> (%)	Post-AGB, <i>n</i> (%)	Post-AGB vs. no surgery (referent) ^a OR (95 % CI)	Pre- (referent) vs. post-OR ^a (95 % CI)	-
Menstrual cycle regularity	<i>n</i> = 26	$n = 62 \pmod{4}$	$n = 62 \pmod{4}$	-	_	-
Regular	15 (57.7)	38 (61.3)	40 (64.5)	1.00 (ref)	1.00 (ref)	-
Irregular	9 (34.6)	17 (27.4)	8 (12.9)	0.23 (0.06-0.96)	1.84 (0.55-6.20)	-
Using hormonal contraceptives	2 (7.7)	7 (11.3)	14 (22.6)	3.28 (0.55–19.65)	_	-
Use of infertility services	4 (15.4)	10 (15.9)	1 (1.6)	0.08 (0.01–0.84)	0.06 (0.02–0.37) ^b	-

Significant differences between groups are indicated in bold, p < 0.05

^a Adjusted for age, BMI, height, and previous pregnancy

^b Iteration limit exceeded in fully adjusted mode-age-adjusted model presented

Outcome	No surgery, n (%)	Pre-RYGB, n (%)	Post-RYGB, n (%)	RYGB: Post vs. No surgery (referent) OR (95 % CI)	RYGB: Pre (referent) vs. Post-OR (95 % CI)
Among all women ^a					
Infertility	4 (16.0)	23 (21.90)	11 (10.5)	0.81 (0.21-3.08)	0.53 (0.14-1.95)
Desired pregnancy	19 (73.1)	57 (51.4)	31 (27.9)	0.16 (0.06-0.44)	0.18 (0.07-0.47)
Among women desiring pre	egnancy ^b				
Pregnancy	16 (84.2)	47 (82.85)	25 (80.6)	1.06 (0.21–5.41)	0.75 (0.14-4.15)
Live birth	15 (79.0)	44 (77.2)	15 (48.39)	0.27 (0.07-1.08)	0.58 (0.21–1.66) ^g
Among pregnant women— Term birth ^d	first-pregnancy outcome	es ^b			
No	4 (25.0)	8 (19.05)	11 (52.4)	1.00 (ref)	1.00 (ref)
Yes	12 (75.0)	34 (80.95)	10 (47.62)	0.16 (0.03-0.94)	0.21 (0.05–0.90) ^c
Pre-term birth ^e					
No	12 (85.7)	34 (94.4)	10 (83.3)	1.00 (ref)	1.00 (ref)
Yes	2 (14.3)	2 (5.6)	2 (16.7)	2.56 (0.12-46.14)	2.64 (0.14-49.64)
Miscarriage ^f					
No	14 (87.5)	36 (85.7)	12 (57.1)	1.00 (ref)	1.00 (ref)
Yes	2 (12.5)	6 (14.3)	9 (42.9)	9.81 (1.12-85.71)	2.76 (0.46–16.99) ^g
				Linear regression estimate (95	% CI)
Time to pregnancy (months)				
Mean (SD)	1.62 (2.02)	4.22 (6.60)	4.31 (6.35)	3.47 (-0.24, 7.18)	3.13 (-0.89, 7.16)
Birth weight (grams)					
Mean (SD)	3583.51 (518.93)	3405.0 (729.03)	2983.78 (510.01)	-727.18 (-1159.48, -294.87)	-601.01 (-1045.84, -156.18)

Table 3 Reproductive outcomes in Roux-en-Y gastric bypass group

Significant differences between groups are indicated in bold, p < 0.05

^a Adjusted for age, height, BMI, and pregnancy history

^b Defined as first temporal birth occurring pre- and post-surgery, adjusted for age, height, and BMI

^c Adjusted for age due to non-convergence

^dReferent is pre-term + miscarriage

e Referent is term birth

^fReferent is pre-term + term birth

g Unable to adjust for confounders

mature oocytes [38]. Interestingly, in some women, the concentration of anti-Müllerian hormone (used as a measure of ovarian reserve) decreases after bariatric surgery, possibly due to the transient stress of surgery, a permanent effect on gene expression, or depletion of the follicular pool [9, 39]. In our study, there were no differences in reported infertility between groups, although women in the pre-RYGB group were most likely to report taking >12 months to conceive (7.2 %) compared to the other groups. Women who underwent AGB were less likely to utilize ART services after surgery than before. ART use was also less after AGB compared to women who did not undergo bariatric surgery. There was a trend toward decreased use of ART after RYGB as well, although this did not reach statistical significance. These differences in ART utilization may reflect the improved cycle regularity and ovulatory profiles post-bariatric surgery, increasing fertility and thus requiring less intervention by ART specialists. There was a decreased desire for future fertility after both types of bariatric surgery, possibly due to age or fear of gaining weight with pregnancy. The majority of women had undergone surgery within 18 months of survey completion and were in their late 30s, so they may have been done with childbearing by that time; however, age was adjusted for in all models.

No significant differences in the likelihood of conception were seen after bariatric surgery; however, a significant decrease in term birth was found after RYGB. Similar trends have been observed in prior studies, in which bariatric surgery is associated with shorter gestation [19, 21]. It is generally believed that nutritional deficiencies, particularly of vitamins A, B12, K, iron, folate, and calcium, may have negative maternal and fetal consequences [40-43], although the mechanisms have yet to be elucidated. These nutritional deficiencies are more severe following RYGB than AGB, which may help explain why the decrease in term birth was seen only after RYBG but not AGB. Furthermore, women who underwent RYGB were less likely to have a term birth and more likely to miscarry than women after AGB, suggesting that the type of surgery may influence pregnancy outcome and duration. Although the risk of pre-term birth was not statistically different between groups, numbers were small.

In our analysis, pregnancies in the AGB group had a lower chance of resulting in live birth after surgery than did presurgery pregnancies. This finding was not seen in the RYGB group and may suggest that women who undergo the AGB procedure have worse pregnancy outcomes, with live birth as the desired endpoint. These findings are interesting, particularly

Table 4 Reproductive outcomes in adjustable gastric band group

Outcome	No surgery, n (%)	Pre-AGB, <i>n</i> (%)	Post-AGB, <i>n</i> (%)	AGB: Post vs. No surgery (referent) OR (95 % CI)	AGB: Pre (referent) vs. Post OR (95 % CI)	RYGB (referent) vs. AGB OR (95 % CI)
Among all women ^a						
Infertility	4 (16.0)	13 (20.3)	10 (15.6)	0.99 (0.25-3.90)	1.96 (0.50-7.67)	1.20 (0.44–3.28)
Desired pregnancy ^b	19 (73.1)	40 (60.6)	24 (36.4)	0.24 (0.09-0.69)	0.25 (0.09-0.71)	1.31 (0.65–2.63)
Among women desiring	g pregnancy ^b					
Pregnancy	16 (84.2)	31 (77.5)	19 (79.2)	1.20 (0.21-6.92)	1.67 (0.35, 7.92) ^g	0.88 (0.22-3.54)
Live birth	15 (79.0)	30 (75.0)	14 (58.3)	0.59 (0.14-2.65)	0.19 (0.05-0.73)	1.40 (0.46-4.24)
Among pregnant wome	n—first-pregna	ncy outcomes ^b				
Term birth ^d						
No	4 (25.0)	5 (16.1)	3 (18.75)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	12 (75.0)	26 (83.4)	13 (81.3)	2.41 (0.29-20.47)	0.52 (0.09–3.06) ^c	12.72 (1.61-100.6)
Pre-term birthe						
No	12 (85.7)	26 (92.9)	13 (92.9)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	2 (14.3)	2 (7.1)	1 (7.1)	0.83 (0.02-40.11)	1.16 (0.03-56.43)	0.17 (0.01-3.53)
Miscarriage ^f						
No	14 (87.5)	28 (90.3)	14 (87.5)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	2 (12.5)	3 (9.7)	2 (12.5)	0.47 (0.04–5.81)	2.58 (0.59–11.35) ^c	0.10 (0.01-0.80)
				Linear regression estimate (95 % CI)		
Time to pregnancy (months)						
Mean (SD)	1.62 (2.02)	2.35 (4.07)	4.57 (7.39)	1.86 (-2.40, 6.12)	0.46 (-3.98, 4.90)	-1.11 (-5.10, 2.87)
Birth weight (grams)						
Mean (SD)	3583.51 (518.93)	3774.47 (500.44)	3385.40 (722.71)	-394.57 (-900.03, 110.89)	-355.32 (-764.57, 54.04)	372.21 (-54.15, 798.58)

Significant differences between groups are indicated in bold, p < 0.05

^a Adjusted for age, height, BMI, and pregnancy history

^b Defined as first temporal birth occurring pre- and post-surgery, adjusted for age, height, and BMI

^c Adjusted for age due to non-convergence

^d Referent is pre-term + miscarriage

e Referent is term birth

^fReferent is pre-term + term birth

^g Unable to adjust for confounders

in light of the greater nutritional derangements that more commonly follow RYGB. However, it is also known that women who undergo AGB lose less weight, on average, than women who undergo RYGB, a trend that was also seen in our study. It is possible that the greater prevalence of obesity among post-AGB patients was the driver of worse pregnancy outcomes in that group. Another explanation for the differences in pregnancy outcomes among surgery groups may lie in dietary intake variation. Recent data suggest that dietary fat content and type of fat intake may impact fertility [44]. Diets lower in low-fat dairy food and higher in certain types of high-fat dairy products may correlate with improved fertility. Patients who undergo RYGB tend to favor lower-fat diets than those who undergo AGB, but it remains unclear what effect, if any, that has on fertility after surgery. It is also important to note that obese patients who have not had surgery may also have nutritional deficiencies, as a consequence of poor food choices. The impact of nutritional depletion and dietary choices on reproductive and ART outcomes following bariatric surgery is an avenue of research that requires more attention. Further research is needed to confirm the findings in this study.

Among infertile women, pregnancy rates before and after surgery remained largely unchanged, ranging from 46.2 to 56.5 % in the pre-surgery groups and 45.5 to 50.0 % in the post-surgery groups. Prior to surgery, 52.2 and 38.5 % of infertile women had live births in the RYGB and AGB groups, respectively. Interestingly, despite a similar pre-surgery pregnancy rate, infertile women who underwent RYGB (18.2 %) and AGB (20.0 %) had fewer live births after their surgeries. Due to the small number of women who were infertile,

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underwent surgery, and became pregnant, adjusted odds ratios could not be calculated for comparison among groups. These findings, however, do raise important questions about whether pregnancies among infertile patients post-bariatric surgery incur distinct risks and what the mechanisms might be. The current analysis of these women had limited power and lack of confounding control by age.

As seen in prior studies, birth weights appear to be lower after surgery than before surgery. This is an important finding about which patients who undergo surgery should be counseled [19-21, 45]. Among all groups, the lowest neonatal birth weights were found in the post-RYGB group. Women who underwent RYGB had smaller infants after surgery than before. They also had smaller infants after surgery compared with women who did not undergo surgery. These striking differences in birth weight were not seen in the AGB group, possibly because this surgery group did not lose as much weight. As noted earlier, dietary and nutritional changes that occur post-RYGB are distinct from post-AGB changes, and this may have differential effects on fetal growth throughout pregnancy. There were no differences in time to conception, miscarriage, ectopic pregnancy, or terminations among groups between groups, although we had limited power to detect substantial differences.

This study has multiple strengths; although recall bias is possible with any survey study, many of the answers given by patients, including BMI, weight loss and gain, surgical dates, and pregnancy data (if available), were confirmed for accuracy in the bariatric surgery database and the electronic medical record. Patients were able to act as internal controls by answering questions from before and after surgery, limiting variability among groups. Furthermore, a non-surgical group of patients who saw the same bariatric surgeons in consultation but did not undergo surgery was used as an additional comparison group. No significant differences in the outcomes of interest were seen between those women who did not undergo surgery and women pre-surgery, indicating limited confounding between groups.

Limitations of this study include limited response rate (~10 % of patients responded to the survey), which may lead to issues of selection bias and external validity. Unfortunately, we are unable to estimate how many addresses could not be confirmed. As noted previously, recall bias cannot be entirely eliminated from survey studies. Patients who underwent bariatric surgery closer to the end of the study period had less time to try to conceive post-surgery than those who underwent their procedures earlier. In fact, the majority of women in each group underwent surgery within 18 months of survey completion. Nevertheless, because there were many pregnancies and live births in both the post-RYGB and post-AGB groups, this should have little effect on the comparisons between these groups.

It is important to note that the driving factors influencing both the choice to have bariatric surgery, the type of surgery, and the decision to participate in a survey study may differ between groups and may affect interpretation of results. Given these limitations, findings should be interpreted with caution and conclusions regarding clinical management should not be made based solely on this study. Despite these limitations, however, this is the most comprehensive analysis on fertility, pregnancy outcomes, and time to conception by bariatric surgery type to date.

Women for whom bariatric surgery is a weight loss option should be counseled that different procedures could potentially affect their overall health and future childbearing in distinct ways. Findings from this study should be considered pilot data and suggest that RYGB and AGB differentially impact term birth and live birth. Questions remain regarding the impact of bariatric surgery on infertile women and the desire for fertility, as well as how post-surgery dietary intake affects pregnancy outcomes. The significant findings of this study suggest that this is an avenue worthy of further prospective research to better inform patient counseling and clinical practice.

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Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of Interest Author EG has received a research grant from Serono, as well as royalties from Up-To-Date that are outside of the submitted work. Authors RG, SM, MR, and LF declare that they have no conflicts of interest.

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References

- NIH Conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. Ann Intern Med. 1991;115:956–61.
- Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366:1567–76.
- Robinson MK. Surgical treatment of obesity—weighing the facts. N Engl J Med. 2009;361:520–1.
- Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273:219–34.
- Maggard MA, Yermilov I, Li Z, et al. Pregnancy and fertility following bariatric surgery: a systematic review. JAMA. 2008;300:2286–96.

- Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
- Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med. 2014;370:2002–13.
- Tan O, Carr BR. The impact of bariatric surgery on obesity-related infertility and in vitro fertilization outcomes. Semin Reprod Med. 2012;30:517–28.
- 9. Shah DK, Ginsburg ES. Bariatric surgery and fertility. Curr Opin Obstet Gynecol. 2010;22:248–54.
- Sharpe RM, Franks S. Environment, lifestyle and infertility—an inter-generational issue. Nat Cell Biol. 2002;4(Suppl):s33–40.
- Shah DK, Missmer SA, Berry KF, et al. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. Obstet Gynecol. 2011;118:63–70.
- Van Dam EWCM, Roelfsema F, Veldhuis JD, et al. Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS. Am J Physiol Endocrinol Metab. 2002;282:E865–72.
- Pasquali R, Casimirri F, Vicennati V. Weight control and its beneficial effect on fertility in women with obesity and polycystic ovary syndrome. Hum Reprod. 1997;12 Suppl 1:82–7.
- 14. Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. Reproduction. 2010;140:347–64.
- Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus nonsurgical treatment for obesity: a systematic review and metaanalysis of randomised controlled trials. BMJ. 2013;347:f5934.
- Shekelle PG, Newberry S, Maglione M, et al. Bariatric surgery in women of reproductive age: special concerns for pregnancy. Evid. Rep. Technol. Assess. (Full. Rep). Agency for Healthcare Research and Quality (US); 2008;1–51.
- American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet. Gynecol. 2009;113:1405–13.
- Parikh R, Lavoie M, Wilson L, et al. Timing of pregnancy after bariatric surgery. Obstet Gynecol. 2014;123(Suppl):165S.
- Roos N, Neovius M, Cnattingius S, et al. Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. BMJ. 2013;347:f6460.
- Lesko J, Peaceman A. Pregnancy outcomes in women after bariatric surgery compared with obese and morbidly obese controls. Obstet Gynecol. 2012;119:547–54.
- Kjær MM, Lauenborg J, Breum BM, et al. The risk of adverse pregnancy outcome after bariatric surgery: a nationwide registerbased matched cohort study. Am J Obstet Gynecol. 2013;208:464. e1–5.
- Moore KA, Ouyang DW, Whang EE. Maternal and fetal deaths after gastric bypass surgery for morbid obesity. N Engl J Med. 2004;351:721–2.
- Loar PV, Sanchez-Ramos L, Kaunitz AM, et al. Maternal death caused by midgut volvulus after bariatric surgery. Am J Obstet Gynecol. 2005;193:1748–9.
- Stefater MA, Wilson-Pérez HE, Chambers AP, et al. All bariatric surgeries are not created equal: insights from mechanistic comparisons. Endocr Rev. 2012;33:595–622.
- Myronovych A, Kirby M, Ryan KK, et al. Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. Obesity (Silver Spring). 2014;22:390–400.

- Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature. 2014;509:183–8.
- Puzziferri N, Nakonezny PA, Livingston EH, et al. Variations of weight loss following gastric bypass and gastric band. Ann Surg. 2008;248:233–42.
- Bilenka B, Ben-Shlomo I, Cozacov C, et al. Fertility, miscarriage and pregnancy after vertical banded gastroplasty operation for morbid obesity. Acta Obstet Gynecol Scand. 1995;74:42–4.
- 29. Marceau P, Kaufman D, Biron S, et al. Outcome of pregnancies after biliopancreatic diversion. Obes Surg. 2004;14:318–24.
- Nomura RMY, Dias MCG, Igai AMK, et al. Anemia during pregnancy after silastic ring Roux-en-Y gastric bypass: influence of time to conception. Obes Surg. 2011;21:479–84.
- Doblado MA, Lewkowksi BM, Odem RR, et al. In vitro fertilization after bariatric surgery. Fertil Steril. 2010;94:2812–4.
- Deitel M, Stone E, Kassam HA, et al. Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. J Am Coll Nutr. 1988;7:147–53.
- Wang Y, Liu J. Plasma ghrelin modulation in gastric band operation and sleeve gastrectomy. Obes Surg. 2009;19:357–62.
- Korner J, Bessler M, Cirilo LJ, et al. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab. 2005;90:359–65.
- Korner J, Inabnet W, Conwell IM, et al. Differential effects of gastric bypass and banding on circulating gut hormone and leptin levels. Obesity (Silver Spring). 2006;14:1553–61.
- Peterli R, Wölnerhanssen B, Peters T, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg. 2009;250:234–41.
- Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. Hum Reprod Update. 2014;20:153–74.
- Christofolini J, Bianco B, Santos G, et al. Bariatric surgery influences the number and quality of oocytes in patients submitted to assisted reproduction techniques. Obesity (Silver Spring). 2014;22:939–42.
- Merhi ZO, Minkoff H, Feldman J, et al. Relationship of bariatric surgery to Müllerian-inhibiting substance levels. Fertil Steril. 2008;90:221–4.
- Poitou Bernert C, Ciangura C, Coupaye M, et al. Nutritional deficiency after gastric bypass: diagnosis, prevention and treatment. Diabetes Metab. 2007;33:13–24.
- 41. Woodard CB. Pregnancy following bariatric surgery. J Perinat Neonatal Nurs. 2004;18:329–40.
- Guelinckx I, Devlieger R, Vansant G. Reproductive outcome after bariatric surgery: a critical review. Hum Reprod Update. 2009;15:189–201.
- Jans G, Matthys C, Bogaerts A, et al. Maternal micronutrient deficiencies and related adverse neonatal outcomes after bariatric surgery: a systematic review. Adv Nutr. 2015;6:420–9.
- Chavarro JE, Rich-Edwards JW, Rosner B, et al. A prospective study of dairy foods intake and anovulatory infertility. Hum Reprod. 2007;22:1340–7.
- Johansson K, Stephansson O, Neovius M. Outcomes of pregnancy after bariatric surgery. N Engl J Med. 2015;372:2267.