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The effects of bariatric surgery on fetal development and neonatal outcomes

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THE EFFECTS OF BARIATRIC SURGERY ON FETAL DEVELOPMENT AND NEONATAL OUTCOMES

by

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THE EFFECTS OF BARIATRIC SURGERY ON FETAL DEVELOPMENT AND NEONATAL OUTCOMES

ELIZABETH FLYNN

ABSTRACT

Background: Over two-thirds of the United States population is considered overweight or obese. Bariatric surgery is often used when conservative weight loss measures fail. The majority of bariatric surgeries are performed on women of childbearing age. Women who become pregnant following bariatric surgery have a decreased occurrence of gestational diabetes, hypertensive disorders and macrosomia, but they also have an increased risk of small for gestational age infants (SGA), with the greatest risk of SGA infants following malabsorptive and mixed bariatric surgery procedures.

Study: A gap in the literature exists regarding the risks of SGA and intrauterine growth restriction (IUGR) following Roux-en-Y gastric bypass (RYGB) compared to sleeve gastrectomy (SG), the two most common procedures in the United States in 2014. This study will be a multi-center retrospective cohort study that will identify the risk of IUGR following RYGB and SG.

Conclusion: This study will improve our understanding of the effects on pregnancy following RYGB and SG. The most innovative, and hardest, part of this study will be the collection of data on as many SG women as possible. This will be the biggest hurdle because SG is a relatively new procedure, so the prevalence of pregnancy following SG is low.

Public health significance: A better understanding of the effects of the most common bariatric procedural types on pregnancy is important given the prevalence of bariatric surgery among women of childbearing age. It will allow bariatric surgeons to better council their patients on a surgery type for those that may be considering pregnancy afterwards, and enable obstetricians to have a better understanding of the risks associated with their patient's pregnancy.

TABLE OF CONTENTS

TITLE…………………………………………………………………………...i

COPYRIGHT PAGE………………………………………………………….....ii

READER APPROVAL PAGE……………………………………………….....iii

ACKNOWLEDGMENTS iv

ABSTRACT v

TABLE OF CONTENTS vii

LIST OF TABLES ix

LIST OF FIGURES x

LIST OF ABBREVIATIONS xi

INTRODUCTION 1

- Background..1
- Statement of the Problem 2
- Hypothesis 3
- Objectives and specific aims 3

REVIEW OF THE LITERATURE 4

- Overview 4
- Existing research 10
  - Nutritional Deficiencies...10

Pregnancy planning 12

Small for gestational Age 17

METHODS 27

Study design 27

Study population and sampling 27

Study Variables and Collection 28

Recruitment 28

Data Analysis 29

Timeline and Resources 29

Institutional Review Board 30

CONCLUSION 31

Discussion 31

Summary 31

Public health significance 32

LIST OF JOURNAL ABBREVIATIONS 33

REFERENCES 34

CURRICULUM VITAE 38

LIST OF TABLES

Table	Title	Page
1	Classification of BMI Parameters	4
2	Birth Defects and Pregnancy Complications Associated with Micronutrient	12
3	Data variable and corresponding collection time	28

LIST OF FIGURES

Figure	Title	Page
1	Drawing of RYGB	7
2	Drawing of SG	9
3	SGA versus IUGR	18

LIST OF ABBREVIATIONS

BIDMC	Beth Israel Deaconess Medical Center
BMC	Boston Medical Center
BMI	Body mass index
BPD	Biliary pancreatic diversion
BS	Bariatric surgery
BWMC	Brigham and Women’s Medical Center
DS	Duodenal switch
EMR	Electronic medical record
IUGR	Intrauterine growth restriction
LAGB	Laparoscopic gastric band
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
SGA	Small for gestational age

INTRODUCTION

Background

Obesity is an epidemic in the United States with over two-thirds of the population overweight or obese.[1] Not only does obesity lead to chronic health diseases like diabetes, heart disease, and arthritis, but it also has an economic impact through increased health care costs.[2] Obesity during pregnancy has its own set of problems including increased risk of gestational diabetes, hypertensive disorders, prolonged labor, cesarean section, and fetal macrosomia.[3] With over 40% of pregnant women being overweight or obese, this is not a small problem in the United States.[3] Obese individuals that are unable to lose weight with diet and exercise can turn to bariatric surgery (BS) to shed excess weight and improve their overall health.

It is estimated that between 50%[4] and 83%[5] of all BS occur in women of childbearing age, ages 18 to 45, which has created a unique, high risk obstetric population. Women that become pregnant following BS have a decreased risk of gestational diabetes, macrosomia and hypertensive disorders. However, they have increased fertility and an increased risk of SGA infants and micronutrient deficiencies as compared to obese women without BS.[6,7] SGA infants have higher morbidity and mortality due to premature delivery, polycythemia, hypoglycemia, impaired immune function, and perinatal asphyxia. Long-term consequences include decreased adult growth potential and poor neurologic development with developmental delay. Additionally, infants are at an increased risk of micronutrient deficiencies that can lead to fetal abnormalities, including neural tube defects and long-term neurologic deficits. The severity of SGA heightens the urgency to accurately assess the effects of different BS procedures to discover the probability of neonatal risks, and if those risks can be correlated to dietary factors during pregnancy such as malabsorption and nutrient deficiency. This information is essential to better inform healthcare providers and patients which BS procedure is best for the patient and whether positive aspects related to BS outweigh the negative impacts of BS on neonatal outcomes.

Statement of the Problem

The increased risk of SGA neonates following BS compared to the general population has been found in several studies, but it is unclear why this is occurring. It is possible that is it due to micronutrient deficiencies as a result of malabsorption of nutrients, rapid weight loss following surgery leading to alteration of maternal metabolic environment, or dietary intolerances following BS. Because most of the literature published has multiple procedural types in the BS groups, it is important that we study specific bariatric procedures' effect on pregnancies. Additionally, SGA is an unspecific marker for the measurement of fetal outcomes. A more specific measurement of fetal malnutrition is IUGR. SGA is an easier outcome to measure because it is based on the infant's gestational age and weight at birth whereas IUGR is measured by ultrasound prior to birth and may not be readily available in large database. Because IUGR is a more specific measurement, this study proposal will focus on this outcome.

SG was the most commonly performed BS in the United States in 2014 followed by RYGB. These surgeries have different mechanisms that promote weight loss, but they have comparable weight loss outcomes. Because SG and RYGB are the most common and result in comparably good weight loss the majority of patients will elect to have one of these operations. Thus, it is important to study the neonatal effects following both procedures, which will allow bariatric surgeons to better counsel patients, especially those that wish to have children after surgery. If a significant difference in neonatal outcomes between BS procedures is found, it could potentially decrease the avoidable cases of IUGR neonates and the potentially devastating complications associated with it.

Hypothesis

Women of child-bearing age that have undergone RYGB will be more likely to give birth to IUGR neonates than women that had SG.

Objectives and specific aims

More than half of BS are performed on women of childbearing age resulting in a high risk obstetric population. These women generally have improved maternal and neonatal outcomes as compared to their obese counterparts, but women receiving BS have a unique set of adverse outcomes, including an increased risk of SGA infants. Many studies have exhibited a correlation between maternal BS and SGA infants; however, there are few studies specifically addressing this topic or addressing the impact on maternal and fetal outcomes based on procedural type.

The specific aims of this project proposal are to:

- Determine which BS procedure results in highest risk of IUGR infants.
- Determine if weight gain during pregnancy is affected by different BS procedures.
- Determine if there is a greater risk of iron, B12 and vitamin D deficiencies based on BS procedure type.

REVIEW OF THE LITERATURE

Overview

Obesity is an epidemic in the United States and in many developed nations. It is arguably one of the biggest current public health crises in our nation. Obesity is most commonly defined by an individual's body mass index (BMI), which is calculated by dividing a person's weight in kilograms by their height in meters squared (BMI=kg/m^2). Overweight is defined as a BMI of greater than 25 and obesity is a BMI of greater than 30. The full range of weight classifications is described in Table 1 below. The rate of obesity in the United States has increased from 13.4% in 1962 to 34.3% in 2008 with the rate of extreme obesity increasing from 0.9% to 6% in the same time interval.[8] Today, more than two-thirds of adults in the United States are overweight or obese.[2] Changes in our environment including increased access to transportation, which has reduced daily physical activity, and increased access to high-calorie foods are among the greatest contributors to obesity.[9]

Table 1. Classification of BMI parameters.

BMI	**Weight Classification**
Below 18.5	Underweight
18.5-24.9	Normal
25-29.9	Overweight
30 or higher	Obese
40 or higher	Extreme obesity

Obesity is associated with numerous chronic illnesses, including diabetes, heart disease, stroke, arthritis, sleep apnea, and is associated with a shorter lifespan.[10] Obesity and its comorbidities not only decrease the quality of life, but they are an economic burden as well. A study by Thompson et al[11] found that obese adults had 36% higher healthcare costs per year with 105% higher pharmacy costs and 39% higher primary-care cost visits compared to healthy-weight adults. Overweight adults had 10% higher total annual health-care costs, with a 37% increased pharmacy cost and 13% higher primary-care cost. Additionally, obesity is associated with higher indirect costs like absenteeism, disability, and premature mortality that are estimated at $66 billion per year.[11] Hammond et al[2] review of economic impacts of obesity suggests direct and indirect costs of obesity total an excess of $215 billion annually in the United States.

There is a clear public health push within our society to combat obesity. New York City is notable for their efforts to require restaurants to post calorie counts on food items.[12] Prevention campaigns have been worked into both schools and workplaces to promote health-eating and physical activity.[9] The CDC has established guidelines for physical activity and dietary intake to give clear recommendations to the public for a healthy lifestyle.[13] While a healthy lifestyle is the optimal route to both prevention of obesity and weight loss, BS can be a solution when conservative measures fail. In order to be considered a candidate for BS, a patient must have a BMI greater than 40 or a BMI greater than 35 along with weight-related comorbidities of hypertension, type 2 diabetes, sleep apnea, or heart disease. They also must have been unable to attain healthy weight with other weight lose strategies and be psychologically stable.[14]

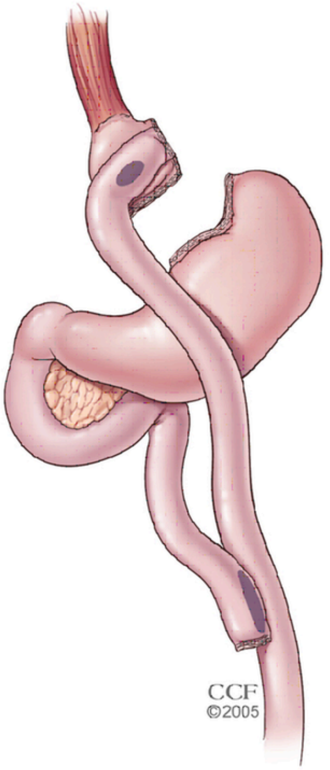
The three types of BS are restrictive, malabsorptive and mixed which has elements of both procedures. Restrictive procedures limit intake by creating a smaller stomach and malabsorptive procedures bypass part of the small intestine resulting in micro- and macronutrient malabsorption. Purely malabsorptive procedures result in dangerous nutrient deficiencies and are rarely performed. Mixed and restrictive procedures are the most common BS performed today.

The University of Minnesota performed the first BS specifically for weight loss in the 1950s. The jejunoileal bypass induced malabsorption by bypassing most of the small intestines, but it was associated with severe malnutrition and many other medical conditions including cirrhosis, resulting in its discontinuance. This operation showed the dangers of long-term malabsorption and importance of long-term follow-up in BS patients.[15]

Gastric bypass was developed in the 1960s after weight loss was seen in patients with a partial gastrectomy due to gastric ulcers. Gastric bypass has evolved from an initial loop bypass with a large stomach to the RYGB.[15] RYGB is a mixed-type procedure that involves the creation of a small 30 milliliter pouch from the proximal stomach to which a divided jejunum is connected to the small stomach pouch. The other half of the divided jejunum is reattached the distal jejunum to allow for pancreatic and biliary products to enter the digestive tract. Food will then enter a smaller stomach, restricting intake, and bypass the duodenum and proximal jejunum resulting in malabsorption of calories as well as micronutrients. It also impacts hormones of satiety allowing for longer satiety and decreased hunger.[16]

The most common long-term consequences of RYGB procedures are anemia and osteoporosis due to chronic malabsorption of iron and calcium. Thiamin and B12 deficiencies are also associated with RYGB so long-term follow-up and vitamin supplementation in this population are important. RYGB has been the most commonly performed weight loss surgery until it moved to the second most commonly performed surgery in the United States after SG.[17]

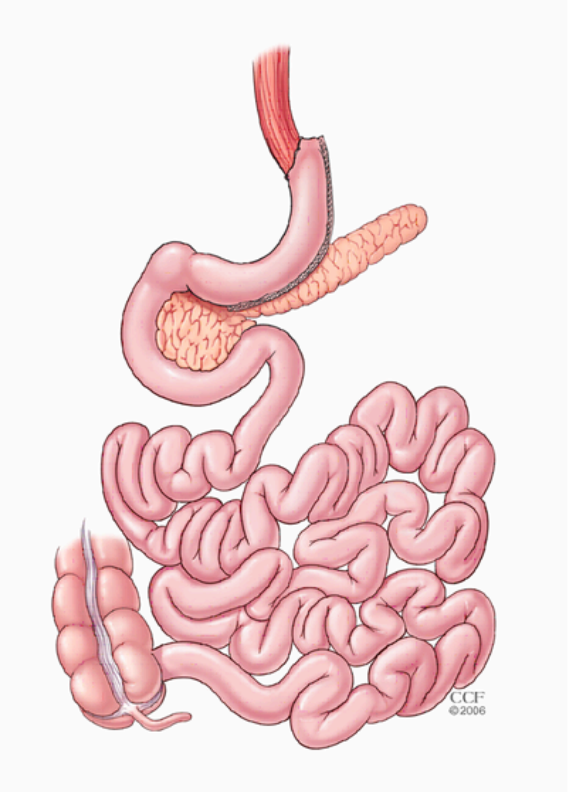
Figure 1: Drawing of RYGB[16]



Gastric banding, a purely restrictive BS, was started in 1978.[15] Although materials used for the procedure have changed over time, the mechanism of weight loss has stayed the same. A band is placed around the proximal stomach to create a smaller pouch in order to restrict food intake, preventing complications associated with malabsorption because the gastrointestinal tract remains intact. However, gastric banding has unique complications like band slippage and erosion of the band into the stomach. Gastric banding accounted for 35.4% of BS performed in 2011, however, this rate dropped to 9.5% in 2014 due to poorer weight loss outcomes compared to RYGB and SG.

SG is a restrictive procedure that removes 75 to 80% of the stomach with removal of the greater curvature resulting in a tubular structure that is composed of the lesser curvature of the stomach and the antrum.[18] SG also results in hormonal changes that allow patients to feel less hungry and fuller for a longer period of time. The laparoscopic SG procedure was initially performed as the first step in a two-part biliary pancreatic diversion (BPD) duodenal switch (DS) BS procedure. In the early 2000s, it was identified that weight loss after the first of two procedures was adequate and, with some modifications, the standalone SG were performed for weight loss. In 2014, it was the most commonly performed procedure with a rate of 51.7%.[17] Because SG is a relatively new BS procedure, there are few studies regarding its long-term effects.

Figure 2: Drawing of SG[16]



Since the 1950s, BS has evolved significantly and long-term consequences of these surgeries have become more apparent. As of 2014, SG is the most commonly performed procedure followed by RYGB.[17] RYGB has a greater risk of nutrient deficiencies compared to SG because the proximal small intestine is bypassed. However, RYGB has better weight loss outcomes compared to SG. Carlin et al[19] showed good weight loss outcomes from both RYGB and SG, but with overall greater weight loss from RYGB. Three year excess body weight loss for RYGB was 67% compared to SG weight loss of 56%. These two procedures have the most similar weight loss outcomes, are the most common procedures in the US, and should be considered comparable procedures for a potential study.

More than 60% of women are overweight and obese[20] and more than 40% of pregnant women are obese or overweight. Obesity during pregnancy is associated with gestational and obstetric complications including gestational diabetes, hypertensive disorders, fetal macrosomia, shoulder dystocia, prolonged labor, cesarean section and postpartum complications including hemorrhage and infection.[3] It is estimated that between 50%[4] and 83%[5] of all BS occurs in women of childbearing age, ages 18 to 45, which has created a unique, high risk obstetric population. Women that undergo BS during childbearing years can reduce obstetric risks including, but not limited to, gestational diabetes, hypertensive disorders, macrosomia, and shoulder dystocia, but they increase their risk of SGA infants and micronutrient deficiencies.

While existing research into pregnancy following BS shows many good outcomes, the problem of SGA infants needs to be more closely studied. Because RYGB and SG are both the most common procedures, and they result in similar weight loss outcomes, these procedures should be compared with respect to pregnancy outcomes. This will allow bariatric surgeons to better counsel female patients of childbearing age which procedure is likely to have safer obstetric and neonatal outcomes.

Existing research

Nutritional Deficiencies

Although there are no formal guidelines for pregnancy following BS, close follow up with a multidisciplinary team including bariatric surgeons and nutritionists is recommended. Appropriate nutrition to support maternal nutrition and prevent fetal malformations is one of the most important factors before and during pregnancy. Monitoring and treating deficiencies is important for both normal pregnancy as well as post-BS pregnancies and special consideration should be given to nutrients that are at risk for deficiency after BS. Patients with SG may develop deficiencies due to limited intake, low-nutrient dense foods, and food intolerance.[21] Anemia is a common occurrence in this population. Like SG, RYGB has a restrictive component leading to similar complications as SG. Additionally, RYGB has a malabsorptive component due to bypass of the proximal small intestine leading to poor absorption of specific nutrients. Iron, calcium, vitamin D, folate, and thiamin were found to be deficient following RYGB in Jans et al[21] study.

In all BS patients, periodic testing is recommended to identify subclinical vitamin and mineral deficiencies. In pregnancy following BS, a general recommendation proposed by Kominiarek et al[5] is to screen for deficiencies every trimester with further workup if a deficiency is found. Mechanick et al[7] suggests measuring maternal folic acid and vitamin B12 during pregnancy and breastfeeding. There are no official nutritional recommendations for pregnancy following BS; however, recommendations for non-pregnant BS population include long-term daily multivitamin with an emphasis on calcium, vitamin D and iron. Most prenatal vitamins contain the recommended supplements for the non-pregnant post-BS population.[5]

There are a limited number of quality studies on micronutrient deficiencies during pregnancy following BS, but a systematic review by Jans et al[21] found that, in general, pregnant post-BS women have depleted or deficient levels of vitamin A, vitamin B12, phylloquinone, folate and iron despite prenatal supplement use. In this population, it is important to monitor patients for deficiencies, and to educate patients about nutrition and clinical management of deficiencies.[21] Discussing the consequences of nutritional deficiencies in pregnancy allows for better patient understanding of their condition and will hopefully improve compliance with nutritional guidelines and supplement use. Table 2 below is a list of nutrients that may be deficient following BS and the neonatal and maternal complications associated with deficiency.

Table 2: Birth Defects and Pregnancy Complications Associated with Micronutrient Deficiencies[22]

Nutrient	**Complications Associated with Nutrient Deficiency**
Folate	Fetal neural tube defects
Iron	Infant mortality, premature birth, low birth weight, impaired cognitive and behavioral function
Calcium	Pre-eclampsia and excessive maternal bone loss
Vitamin B12	Neural tube defects and neurological deficits
Vitamin A	Anemia, slower infant growth and development, overall increased maternal and infant morbidity and mortality

Pregnancy planning

An important consideration for perioperative counseling includes contraception because fertility has been shown to increase after BS.[7] Increased fertility results in more unplanned pregnancy, which could result in high-risk pregnancy or malformation of the fetus if the mother has not adhered to her nutritional regimen including vitamin supplements. Alastishe et al[23] study population reported two-thirds of pregnancies following BS were unplanned pregnancies. Additionally, 30% of women plan to become pregnant sometime after BS.[5] This rate of both planned and unplanned pregnancies after

BS further underlines the importance of determining the long-term neonatal and maternal effects of this population.

Surgeons and clinicians working with this population should address family planning before and after surgery in order to inform patients on the likelihood of increased fertility and risks associated with pregnancy. If pregnancy is desired, it is recommended to wait 12 to 18 months following surgery to avoid pregnancy during the rapid weight loss phase to optimize maternal weight loss. Avoiding pregnancy during this timeframe is speculated to decrease the risk of malnutrition and poor maternal weight loss outcomes[5] due to theoretical risks that a catabolic state and sudden onset of vitamin deficiencies would cause impacts on fetal development.[24]

A national survey regarding perioperative and postoperative reproductive counseling from US bariatric surgeons showed inconsistencies between the reported concern for pregnancy and action taken on behalf of bariatric surgeons.[25] The survey asked questions about contraceptive screening and counseling, contraceptive methods, and provision of contraception. Within this survey, bariatric surgeons reported a majority of their patients were women and 63% of these women were of reproductive age. Most providers referred their patients to obstetrician-gynecologists or primary care provider to obtain contraception. However, 35% of respondents did not know how their patients would obtain contraception. Fifty-two percent of providers required patients to use contraception after BS. Most respondents recommended their patients delay pregnancy between 12 and 24 months after surgery, but nearly 20% did not explore their patients' future pregnancy intentions. The study concluded that while most bariatric surgeons where cognizant of their patients' fertility, all providers should optimize patient outcomes, which includes consistent discussions about fertility, contraception, and referral to appropriate resources.[25]

Wax et al[26] studied maternal and neonatal outcomes following RYGB at early pregnancy intervals, conception less than 18 months after surgery, and late pregnancy intervals, conceptions greater than 18 months after surgery. A total of 52 subjects enrolled, 20 in early pregnancy group and 32 in the late pregnancy group. There was no data to suggest that early pregnancies resulted in higher complications compared to the late pregnancy. There were no differences found between obstetric complications including gestational diabetes, IUGR, preterm or post-term labor or neonatal outcomes including birth defects and intensive care admissions. While the rate of premature deliveries was not different between the two study groups, the rate of preterm delivery within the study was 26%, which was much higher than the US national average of 11% at the time of the study.[26]

This study concluded that pregnancy within 18 months of RYGB was not associated with an increased rate of adverse outcomes compared to pregnancy 18 months after surgery; however, it is important to note the small sample size that included at total of 52 women.[26] Even though no difference was found in this study, it is still recommended to postpone pregnancy 12 to 18 months after surgery to decrease adverse outcomes.

A very similar Danish study addressed the effects of fetal growth following laparoscopic or open RYGB based on early and late surgery-to-conception intervals, but had a much larger sample size of 387 post-BS women.[24] A fetal growth index was developed to compare neonatal outcomes between an early pregnancy group, surgery-to-conception within 18 months of RYGB, and a late pregnancy group, surgery-to-conception interval greater than 18 months. Fetal growth was measured by ultrasound in the first and second trimester. The fetal growth index was calculated with a ratio between the estimated time of gestation as determined form the ultrasounds and the actual calendar time between the two ultrasounds, $(GA_{20}-GA_{12})/Days$. The fetal growth index thus expressed the observed versus the expected fetal growth within a time intervals of days. An index of one means there was no deviation in observed versus expected growth. A value of less than one indicated growth restriction and a value above one indicated accelerated growth. Fetal growth of post-BS neonates was compared to non-BS neonates. The study also reported on SGA infants which was defined as infants that were below the 10th percentile for gestational age.[24]

The study showed no difference in the fetal growth index between the surgery-to-conception interval groups, which suggests that there was no increased risk for pregnancies during the rapid weight loss phase after BS as compared to pregnancies that occur when weight loss has plateaued. This study also compared RYGB procedures, regardless of surgery-to-conception interval, to the general population and found a statistically significant decreased fetal growth index within RYGB population. Because there is no difference in fetal growth between early and late pregnancy groups, but there is a difference in fetal growth compared to the general population, this suggests a persistent factor after surgery predisposes women to have SGA infants after BS.[24]

Overall within the study, 19% of newborns were SGA, with an inverse association between maternal BMI and rate of SGA within this study's population. Women with a BMI less than 25 had 29.6% SGA newborns, BMI of 25 to 30 resulted in 18.8% SGA newborns, and BMI above 30 had 16.8% SGA newborns; however, the differences was not statistically significant. In summary, the surgery-to-conception interval after BS does not significantly affect pregnancy outcomes; however, pregnancy after BS is at greater risk of decreased fetal growth and SGA. These pregnancies should be viewed as high risk regardless of the surgery-to-conception interval.[24]

Some limitations of this study include the inability to control for factors that can increase the risk of SGA infants independently of BS like nutrition, smoking, and exercise because these measures were not recorded in all medical records. Additionally, gestational weight gain was not reported which is a risk factor for SGA. Some strengths of this study included a large sample size of 387 pregnancies after RYGB and that RYGB was the only procedure evaluated.[24]

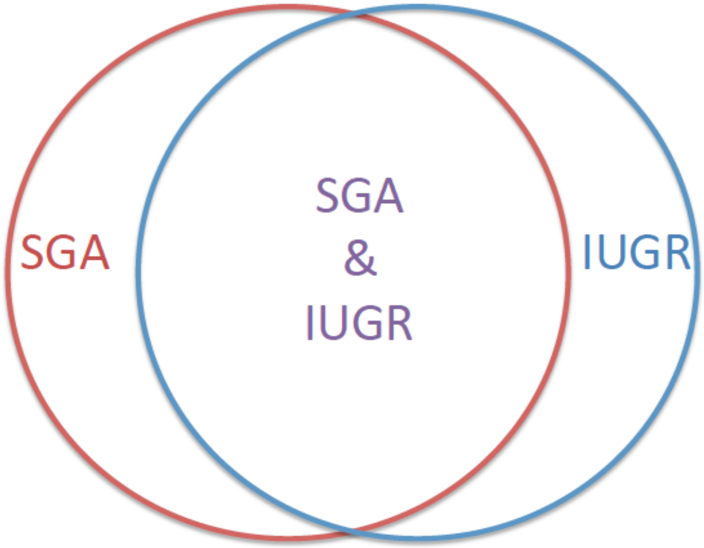
Notably, Denmark implemented its first guidelines for obstetric care of women with prior BS in 2012 which recommends close obstetric surveillance that calls for several ultrasounds throughout pregnancy to monitor weight, blood sampling for vitamin deficiencies, and glucose monitoring.[24] Because Denmark has formal recommendations for pregnant women following BS, it is plausible that the US could create and implement similar guidelines.

Small for gestational Age

Pregnancies following BS are much more likely to result in SGA infants;[6,27] however the definition of SGA versus IUGR are poorly defined in many study methods. Within the literature, SGA and IUGR are used interchangeably to denote the same outcome; however, they are not synonymous. SGA refers to infants with a birth weight below the 10th percentile for gestational age. An infant can be constitutionally small, meaning they are small compared to other infants, but appropriately small given maternal factors including height and weight. These children are healthy and often achieve a normal growth potential.

IUGR occurs in fetuses that do not meet expected growth in utero due to environmental or genetic factors and have an estimated fetal weight below the 10th percentile for gestational age. Most IUGR infants are classified as SGA at birth but some will be just above the 10th percentile for gestational age. These outliers that are "normal" at birth but developed with IUGR in utero will have all the morbidity and mortality associated with IUGR but will not be identified. Therefore, many SGA and IUGR infants overlap, but each group has outliers. Proper dating by ultrasound performed no later than 20 weeks gestation or by last menstrual period is essential in the identification and proper management of IUGR. In summary, a SGA infant can be constitutionally small but appropriately small given parental attributes whereas an IUGR fetus is inappropriately small due to a genetic problem, an infection or malnutrition. All IUGR infants have increased morbidity and mortality and most, but not all, SGA infants are also IUGR.

Figure 3: SGA versus IUGR



IUGR is divided into symmetric and asymmetric growth; symmetric IUGR means the fetus's head circumference, length, and weight are proportionally small and asymmetric IUGR refers to adequate head circumference with disproportionally decreased weight, length or abdominal circumference. Symmetric IUGR occurs with genetic malformations and in first-trimester infections whereas asymmetric IUGR is a result of malnutrition and placental inadequacies. IUGR resulting from BS is most likely asymmetric with malnutrition as the primary risk factor. The rationale for asymmetry from malnutrition is that this insult results in an overall decreased fetal size with preservation of brain growth, lung maturation, and increased red blood cell production. This results in a wasted appearance of the fetus due to decreased body fat, lean mass and bone mineralization. These infants have increased mortality and morbidity including, but not limited to, premature delivery, polycythemia, hypoglycemia, impaired immune function, perinatal asphyxia. Long-term consequences include decreased adult growth potential and poor neurologic development with developmental delay.

Meta-analysis of maternal and fetal outcomes following BS by Yi et al[6] analyzed five studies, and found a statistically significant increase in SGA after BS as compared to pregnancies in women without BS. Additionally, four of the studies analyzed noted a similar rate of SGA infants in early pregnancy, 24 months from surgery-to-conception, and late pregnancy, greater than 24 months from surgery-to-conception, suggesting pregnancy during rapid weight loss phase in non-contributory to SGA outcomes.[6] While many of these studies have a small sample size, multiple showed no link between poor outcomes and short surgery-to-conception intervals.

A meta-analysis regarding maternal and neonatal outcomes following BS by Galazis et al[27] reviewed 17 studies of which 11 addressed “small neonates”. The authors found inconsistent definitions or a lack of definitions of SGA and IUGR. Definitions varied from decreased fetal growth velocity on ultrasound to less than 10th percentile birth weight for gestational age to less than 5th percentile as well as low birth weight defined as less than 2500 grams. Due to the differing definitions and terms, the paper referred to this endpoint as “small neonates” and determined that the risk of small neonates is increased by about 80% following BS.[27] An interesting subgroup analysis showed that patients that underwent laparoscopic gastric banding (LAGB), a restrictive procedure, did not have a higher risk of SGA compared to women without BS. This suggests restrictive surgeries may be safer than malabsorptive or mixed procedures for women of childbearing age. This area deserves further research because it suggests that certain types of BS may be safer than others with regard to neonatal outcomes.[27] One caveat of this meta-analysis was that all studies were observational, leading to confounding factors and bias that are unavoidable. Another deficiency arises from the varied definitions of small neonates, which does not compare the exact same outcome across studies and should be taken into account when interpreting this study's outcome. Finally, most studies did not separate study participants by BS procedure types, preventing identification of which surgery is the safest prior to pregnancy.

A study included in Galazis meta-analysis by Kjaer et al[28] compared pregnancy following BS to non-BS pregnancies. The study had two arms, with the BS arm including 339 participants and the control group of women without BS that had 1277 participants who were matched to the BS arm for prepregnancy BMI, age, parity, and date of delivery. The exposure group was composed of 83% RYGB and 17% LAGB participants. Both groups were obese with a mean BMI near 32. The BS group had an increased risk of SGA with an adjusted odds ratio (AOR) of 2.29. The RYGB participants and their BMI-matched unexposed counterparts showed an increased risk of SGA with AOR of 2.78. The RYGB cohort had a greater risk of SGA compared to the BS group as a whole. There were otherwise no difference in outcomes between the RYGB group compared to grouped analysis.[28] This suggests the mixed type RYGB procedure affects fetal growth more than restrictive type LAGB. RYGB leads to greater weight loss and greater risk of micronutrient deficiencies for all patients, but it is unclear from this study what specific factors are related to the increased risk of SGA within the RYGB cohort.

Kjaer et al[28] study was strong because it had prepregnancy BMI-matched controls for its exposure group to limit the effect of women's weight loss on measured maternal and neonatal outcomes. It is important to note that many women are still overweight or obese after BS. Obesity is a pregnancy risk factor by itself so comparing women with similar BMIs at the beginning of pregnancy paints a clearer picture of the effects of just BS on pregnancy outcomes.[28] The study excluded twin births, which are high risk for their own reasons, and it extracted birth weight and height from patient files to determine if an infant was SGA instead of relying on ICD codes.

A retrospective study comparing singleton pregnancy outcomes after RYGB, SG, and a malabsorptive procedure, BPD, found that births after BPD and RYGB were significantly more likely to result in SGA compared to the general population. SGA occurred in 9.6% of births after BPD, 8.9% after RYGB, 0% after SG, and in 1.3% of the total hospital population. Again, we see that malabsorptive and mixed procedures result in a greater risk of SGA than restrictive procedures. However, this study was low powered with a total of 113 women with 64 BPD participants, 34 RYGB, and 15 in the SG arm. While there were no SGA infants reported in the SG group, the group was underrepresented. As mentioned previously, SG became a standalone procedure in the early 2010s, and the time frame for this study was between June 1994 and December 2011[29] so this is why the SG group was underpowered.

Because SG is relatively new, there are few studies specifically addressing pregnancy outcomes following this procedure. There are only two studies that specifically looked at pregnancy outcomes after laparoscopic SG, one at a Korean health center by Han et al[30] and another at a French health center by Ducarme et al.[31] The Korean study was the first of its kind to report exclusively on pregnancy outcomes after laparoscopic SG. This retrospective study included 12 women resulting in 13 singleton pregnancies. An important aspect of this study is that none of the 12 women told their obstetrician about their BS history because "these patients are afraid of revealing their bariatric surgical history in South Korea." These women gained an average of 15.1 kilograms during pregnancy, above the recommended 12 kilogram gestational weight gain in South Korea. Investigators attributed patient weight gain to patients adding foods and supplements during pregnancy without consulting their nutritionist or obstetrician. Despite greater than recommended gestational weight gain and undisclosed surgical history to obstetricians, there were no obstetric complications or fetal complications. SGA neonates was not an outcome reported within this study. Overall, this study reported good outcomes following laparoscopic SG, but the study was had a small sample size and some of the data was self-reported by study participants. Investigators called for larger studies with a longer follow-up given the results of this study.[30]

The French study also looked only at laparoscopic SG, but it focused on outcomes after SG based on maternal BMI at conception and the interval of surgery-to-conception. Data was collected on 63 pregnancies from 54 women that had laparoscopic SG. Except for one twin pregnancy, the rest were singleton pregnancies. Eighteen percent of pregnancies occurred in women within 12 months of surgery and the rest occurred 12 months after surgery. Average gestational weight gain was higher among women that conceived greater than 12 months after surgery, 6.1 kilograms in pregnancies less than 12 months after surgery compared to 9.0 kilograms greater than 12 months after SG. Overall, there were no statistically different maternal or neonatal outcomes between the early and late surgery-to-conception interval groups.[31]

The other outcome Ducarme et al[31] studied was the differences between conception at a BMI greater than or equal to 30, the obese group, and BMI less than 30, the non-obese group. Forty-one percent of pregnancies were conceived while the mother was obese. As compared to non-obese women, obese women had a statistically significant longer interval between SG and pregnancy, 37.5 months for obese versus 26.4 month in non-obese, and obese women gained less weight during pregnancy, 7.7 kilograms in obese women versus 10.8 kilograms in non-obese women. The obese women had significantly worse neonatal outcomes compared to non-obese women. Neonates born to obese women had an increased risk of premature delivery and a lower mean birth weight. Otherwise, there were no differences in neonatal or maternal outcomes including SGA.[31]

In summary, this study exhibited no difference in maternal or neonatal outcomes based on the interval from surgery-to-conception. The did data show that continued obesity after laparoscopic SG resulted in increased neonatal risks including preterm delivery and lower birth weight.[31] From this study and others reviewed, it can be reasonably inferred that pregnancies after BS compared to pregnancies without maternal BS result in higher risk pregnancies and women that remain obese after BS may be more likely to have higher risk pregnancies compared to non-obese women.

A large Swedish study took data from the Swedish Medical Birth Register and extracted 670 women that had singleton births and previously underwent BS.[32] Sweden's birth register is robust because there is nearly 100% participation in the prenatal care program and information for 98% of births since 1973 is included in the database. Ninety-eight percent of the BS population in this study underwent gastric bypass of an unspecified type, 2% had gastric banding of an unspecified type, and less than 1% had unnamed procedures. Each BS woman was matched to five women without BS and both groups had singleton births. Controls were matched to BS women's presurgery BMI with controls' early pregnancy BMI as well as for age, parity, smoking, education, and delivery year. The median time from surgery-to-conception was 1.1 years which should be taken into account while interpreting results as women were likely within the rapid weight loss phase at this point and at a theoretically increased risk of malnutrition. As discussed previously, documentation of gestation by ultrasound or last menstrual period is important for proper gestational age and growth. Ninety-five percent of women in this study had ultrasound for determination of gestational age and the rest reported last menstrual period. At the time of early pregnancy, the BS populations mean BMI was 30.3 and the controls mean BMI was 41.8. SGA infants were identified by ICD-10 codes. SGA was defined as birth weight less than 10th percentile for gestational age. Post BS pregnancies were associated with an increased risk of SGA with an odds ratio of 2.20. The study subgrouped women based on their decrease in BMI, which was defined as presurgery BMI minus early pregnancy BMI, and found that those with the greatest decrease in BMI had the greatest risk of SGA infants. Of note, weight gain was similar between the BS and non-BS pregnancies, 8.8 kilograms BS versus 9.0 kilograms, respectively.[32]

In summary, data from this Swedish study found an increased risk of SGA in women after BS compared to controls matched to presurgery BMI. There was also an increased risk of SGA in women that lost the most weight after their surgery.[32] It is not clear if there is a relationship between the large amount of weight loss after surgery and SGA. Perhaps the women who had a large weight loss had an altered metabolic environment compared to those who lost less weight and this affected fetal growth. We need more data to ascertain the direct effects of BS on pregnancy outcomes.

A strong aspect of this study was its large study population compared to many similar studies in this field. A notable considerations about this study is that the Swedish population is overwhelming Caucasian so this study should not be generalized to populations outside of the Swedish Caucasian group. Additionally, this study consisted mostly of gastric bypass procedures and should not be generalized to all BS. There was a short surgery-to-conception interval so this information cannot be generalized to longer intervals; however, a few other studies[24,26,30] discussed in this literature review saw no difference in outcomes between short and long surgery-to-conception intervals.

Chevrot et al[33] recently published a study looking specifically at SGA outcomes after BS as well as SGA outcomes based on BS procedural type. This was a single-center retrospective case-control study performed in France. The procedures were categorized into malabsorptive which included 58 gastric bypass patients and restrictive which included 72 gastric banding patients and 9 SG patients. First, the study looked at the effects of weight loss on pregnancy outcomes by comparing pregnancies after BS to obese controls without BS. Controls were matched to BS group based on pre-surgical BMI. Compared to controls, there were no differences in obstetric or neonatal outcomes except for outcomes of size for gestational age. The BS group had 17% SGA infants compared to controls that had 9% SGA infants.

Next, the investigators looked specifically at the incidence of SGA based on BS type, restrictive versus malabsorption, that were matched to controls based on prepregnancy BMI. The participants were matched based on prepregnancy BMI for this portion to study the outcomes of fetal growth restriction independently of weight loss. The malabsorptive group had an incidence of SGA infants more than three times greater than the restrictive group and the controls. These findings suggest a strong association between SGA infants and malabsorption.

In summary, there is a strong link between BS and SGA neonates with a greater likelihood of SGA after malabsorptive and mixed procedures. Many studies have researched the effects of RYGB because this procedure has been in use for decades, but there are few studies on the effects following SG since it is a relatively new procedure. Chevrot et al[33] called for further investigation into the pregnancy outcomes of SG given its increasing prevalence. Comparing RYGB to SG would be appropriate because SG was the most commonly performed procedure in 2014 and RYGB was the second most common.[17] Additionally, RYGB results in greater but comparable weight loss compared to SG.[19]

METHODS

Study design

The study design will be a multi-institutional retrospective cohort to evaluate the risk of IUGR neonates in a two-armed fashion. One arm will contain women that have had RYGB and the other will contain women that have had SG. Both groups will have had pregnancies following BS.

Study population and sampling

Study participants will be extracted from a list of women that have had BS between January 1, 2000 and December 31, 2014. Women that had RYGB or SG between the ages of 18 and 45 will be identified and contacted via mail for enrollment in this study. If they wish to be apart of the study they will be assigned a study number and, their charts will be reviewed for history of pregnancy. If there is no information regarding pregnancy, participants will be contacted by telephone to inquire about obstetric history. Only singleton and naturally conceived pregnancies will be included in analysis. If a participant has more than one pregnancy, it can be included. Exclusion criteria include pregnancy following fertility treatments, multiple gestation pregnancies, reversal of BS, and patients with underlying conditions that would cause malnutrition like cancer and IBD

The sample size will be calculated based on relative risk of a neonate being classified as IUGR or not IUGR. Based on an expected incidence of IUGR in 10% of restrictive BS which is close to the findings in Chevrot et al,[33] an assumed relative risk of 1.5 based on estimates of relative risk in several studies reviewed within the literature,[6,27,33] a confidence interval of 95%, and a power of 0.8 the estimated sample size is 683 births per group.[34]

Study Variables and Collection

The primary outcome this study will evaluate is the occurrence of IUGR in pregnancies following BS. IUGR is defined as estimated fetal weight less than the 10th percentile for gestational age. This study will identify IUGR through a search of diagnosis codes. Additional variables to be collected include maternal age, maternal pre-surgery BMI, weight loss and decrease in BMI since surgery, gestational weight gain, prenatal vitamin intake, and maternal serum levels of iron, vitamin B12 and vitamin D.

Table 3: Data variable and corresponding collection time

Variable	**Collection**
IUGR	Diagnosis code
Pre-surgery BMI	Measurement of height and weight on the day of BS
Weight loss since BS	Difference between pre-surgery weight and weight recorded at earliest prenatal visit. Must be prior to 12 weeks gestation
Decrease in BMI since BS	Difference between pre-surgery BMI and BMI at earliest prenatal visit. Must be prior to 12 weeks gestation.
Gestational weight gain	Weight increase from earliest prenatal visit (prior to 12 weeks gestation) to weight on day of delivery.
Prenatal vitamin intake	Self reported prenatal vitamin adherence from obstetric records
Maternal serum iron, vitamin B12 and vitamin D	Serum levels measured during the third trimester

Recruitment

Women will be identified via EMR based on past surgical history of RYGB or SG. Women with this history will be mailed a consent form to see if they are willing to participate in the study. If willing, data regarding maternal and neonatal outcomes will be primarily taken from EMR, but if it is not available participants will be contacted to provide supplemental information. Because Boston Medical Center (BMC) has a limited number of SG patients who become pregnant, we will contact regional institutions, including Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Medical Center (BWMC), in order to recruit a sufficient sample size.

Data Analysis

Demographics will be represented with mean standard deviation and proportion. Variables include age, children post BS, pre-surgery and prepregnancy BMI, gestational weight gain, and weight loss post BS. Incidence of IUGR will be presented for RYGB and SG groups. Relative risk of IUGR in RYGB will be compared to IUGR in SG. Logistic regression with covariates will be used to control for confounding factors.

Timeline and Resources

This study will be completed within two years of the start date. Because this is a retrospective cohort study, most of the data will be extracted from EMR. We will need access to the all the patients that have received RYGB and SG at BMC and regional hospitals that collaborate with our study. Patients identified that are within this study's inclusion criteria will be contacted by mail regarding willingness to participate in the study. If they do not respond within three weeks of initial contact, they will be contacted a second time. If there is still no response within three weeks of the second notification, they will be excluded.

Pregnancies following BS will also be evaluated by EMR. If the participant had care at outside these three institutions, she will be called in order to collect missing obstetric history.

A principal investigator (PI) will be needed to direct the study. A study coordinator will be required to act as an administrator between the PI and research assistance. A total of 0.4 FTE will be allocated to research assistants to collect data and patient consent. A statistician will be part of this project for data analysis.

Equipment does not need to be exclusively used for this study, but the following will be required:

- Three computers with access to EMR
- Office with two to three rooms to house computers and staff
- Printer, paper, envelopes, stamps for research consent forms
- Telephones to contact study participants

Institutional Review Board

This study protocol will be submitted to the IRB for expedited review under 45 CFR 46.110 criteria. This study will involve the minimally invasive collection of patient records along with patient identification in order to ask patient specific questions important for study outcomes. Additionally, information on minors will be collected within this study. It is low risk to the study population, but does require patient identification and therefore qualifies under the expedited IRB submission criteria. The value of the information collected during this study will benefit future BS recipients more than it endangers the study subjects under investigation.

CONCLUSION

Discussion

Due to the nature of our study design, this study must be retrospective. Data collection by EMR review and patient recollection, as proposed, has limitations because data points of interest may be missing and data collection times will not be uniform. For example, IUGR will be collected through identification of diagnosis codes. If this information was not recorded in obstetric records it will lead to under identification of IUGR. Data that is not available by EMR and is collected from patient recollection will be at risk for recall bias. Depending on the demographics of participants and the number of participants enrolled in the study, the information may or may not be generalizable to patients that undergo RYGB and SG. A major concern is the ability to collect enough pregnancies following SG since SG is a relatively new procedure.

Strengths of this study will include evaluation of specific surgery procedures that have similar weight loss outcomes and prevalence and measurement of IUGR, which is a more specific neonatal outcome than SGA. The exclusion criteria will reduce variables that put neonates at risk for IUGR and SGA independently of BS history.

Summary

We have reviewed the impact obesity has on the economy, the health of the general population, and maternal and neonatal health. More specifically, we explored the effect of BS on pregnancy, which has been found to have positive effects like decreased gestational diabetes, hypertensive disorders, macrosomia, and prolonged labor, but also negative effects like SGA infants and micronutrient deficiencies. Several studies have discussed the effects of BS as a whole, but few have looked at specific surgical types. Because the most common BS types, SG and RYGB, have different mechanisms of weight loss and different risks of malnutrition it is important that we look at these surgeries specifically. This study will address this literature gap. By studying this more deeply, clinicians will be able to understand which BS is a higher risk procedure and which surgery women of childbearing age should have if they are considering pregnancy after surgery.

Public health significance

By understanding the impact of RYGB and SG on IUGR infants, this study will help bariatric surgeons advise their patients that are women of childbearing age which procedure may be most appropriate for them, especially if they are considering conception following surgery. It will also allow obstetricians to better understand what a patient and her child are at risk for based on the patient's surgical history. Most importantly, this study will allow for counseling in order to avoid IUGR and the severe long-term complications associated with it. The impact of the safest BS for a women of childbearing age will improve medical outcomes for both the mother and the child.

LIST OF JOURNAL ABBREVIATIONS

Adv Nutr Int Rev J	Advances in NutritionL An International Review Journal
Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Ann Surg	Annals of Surgery
Best Pract Res Clin Obstet Gynaecol	Best Practice & Research Clinical Obstetrics and Gynaecology
Diabetes Metab Syndr Obes Targets Ther	Diabetes, Metabolic Syndrome and Obesity: Targets and Therapies
Eur J Obstet Gynecol Reprod	European Journal of Obstetrics & Gynecology and Reproductive Biology
Int J Gynaecol Obstet	International Journal of Gynaecology and Obstetrics
Natl Cent Health Stat	National Center for Health Statistics
N Engl J Med.	New England Journal of Medicine
Obes Rev	Obesity Reviews
Obes Surg	Obesity Surgery
QJM Int J Med	QJM: An International Journal of Medicine
Semin Perinatol	Seminars in Perinatology
Surg Obes Relat Dis	Surgery for Obesity and Related Disease
US Dep Health Hum Serv	U.S. Department of Health and Human Services

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