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Curbing obesity from one generation to another: the effects of bariatric surgery on the *in utero* environment and beyond

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Abstract

Approximately 250,000 individuals seek bariatric surgery each year in the U.S. for the long-term resolution of obesity-related comorbidities. Greater than 80% of these individuals are women and approximately half are of child-bearing age. Although there are many positive metabolic benefits that are realized through surgical weight loss for both men and women, the various long-term hormonal, molecular, nutrient and epigenetic changes following bariatric surgery have not been evaluated for the surgical recipient or in the context of pregnancy and the offspring. Pregnancy may be a vulnerable period of time for the bariatric surgery recipient and thoughtful consideration of pregnancy management should be taken by health care providers and recipients alike. The purpose of this review is to explore potential etiologies of some of the gestation-specific outcomes for the mother and offspring.

Keywords

pregnancy; body weight regulation; bariatric surgery; vertical sleeve gastrectomy; obesity; gestation

Introduction

Obesity is a major health concern that is becoming more prevalent worldwide. The percentage of individuals who are obese, as defined as having a BMI ≥ 30 , has more than doubled from 1980 to 2015 [1]. Women, however, are even more likely to be obese than men, reaching an incidence of nearly 15% compared to 10% respectively [1]. In the United States, 33% of women childbearing age are obese [2, 3] and, 20% are obese at the beginning

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Ethical Consents

As this is a review, ethical consents for this work has been previously obtained by authors of published materials. No new ethical consents are necessary.

of pregnancy [4, 5]. Obesity is associated with several negative outcomes for the mother and child. For the mother, excess body weight leads to reproductive hormone dysfunction [6], altered menstrual cyclicity [7], and overall reduced fertility [3]. During gestation, there is increased risk for gestational diabetes [8], gestational hypertension [9], preeclampsia [10], prolonged pregnancies [11], and need for cesarean deliveries [12]. Maternal obesity during pregnancy also parlays long-term metabolic health risks to the fetus. Metabolic dysfunction prior to pregnancy carries a significant risk for both the mother and fetus.

Bariatric surgery is an effective and durable treatment for obesity and is used increasingly around the world. Compared to lifestyle changes and pharmacological interventions, bariatric surgeries result in a significant amount of weight loss and drastic improvement in insulin sensitivity [13, 14]. In 2016, over 600,000 procedures were performed worldwide, with over 200,000 taking place in the U.S. [15]. Bariatric surgeries include restrictive surgeries such as gastric band and vertical sleeve gastrectomy (VSG) and malabsorptive surgeries such as Roux-en-Y gastric bypass (RYGB), or they may be a combination of the two such as with biliopancreatic diversion with duodenal switch (BPD-DS) [14, 15]. Of these surgeries, VSG has now become the most common surgery performed, making up 53.6% of operations [15].

Women of childbearing age are increasingly turning to bariatric surgery for improved health. In a 10-year study, 80% of those that received bariatric surgery were women [16], and half of all bariatric surgeries in the U.S. are on women of childbearing age [17]. To qualify for bariatric surgery, these women must have a BMI ≥ 40 or have a BMI ≥ 35 with comorbidities such as type 2 diabetes mellitus (T2DM) or cardiovascular disease (CVD) [18, 19].

As women with clinically-severe obesity are increasingly turning to bariatric surgery to improve their health, it remains unknown how the benefits derived from surgical weight loss may alter the health of the next generation. Further, it is unknown whether the various hormonal and inflammatory changes produced by bariatric surgery may extend to the next generation. Here, we review the literature to understand the potential mechanisms underlying the benefits and risks to the mother and/or offspring following surgical weight loss. The points raised become pivotal for the development of interventions to ultimately overcome the transgenerational effects of the obesity epidemic.

Bariatric surgery classifications.

The three most common surgeries within the U.S. in order of increasing complexity are the adjustable gastric band (AGB), VSG, and RYGB [20]. Greater than 90% of the surgical weight loss procedures performed in the U.S. include these methods [21]. AGB is performed by placing a cuff on the upper portion of the stomach, creating a small pouch that restricts individual meal sizes to reduce overall caloric intake. No tissue is resected, and no manipulation of the hindgut is performed. AGB is adjustable and reversible. In comparison to the other two surgeries, AGB generally results in less robust outcomes in terms of weight loss [22]. Next in complexity is VSG, a surgical procedure in which approximately 80% of the stomach is resected along the greater curvature creating a tubular sleeve linking the esophagus to the duodenum with no intestinal rearrangement. The procedure produces

profound and durable weight loss, has overall reduced post-surgical complications, and ameliorates the various comorbidities of obesity similar to RYGB [22]. Finally, RYGB is considered the “gold standard” surgical procedure for the resolution of obesity- and diabetes-related diseases. A small gastric pouch is created from the upper portion of the stomach, while a blind pouch is fashioned from the rest of the stomach to allow for gastric and pancreatic secretions to flow into the jejunum at a site of anastomosis. The primary flow of nutrients then routes from the esophagus to the gastric pouch and onward to an anastomosis directly to the jejunum.

Another important bariatric surgery prominently discussed in some regions around the globe, but far less common in the U.S. is the biliopancreatic diversion with duodenal switch (BPD/DS). BPD/DS first removes 80% of the stomach like a VSG and then also bypasses the majority of the intestine by connecting the end portion of the intestine to the duodenum near the stomach [23]. A BPD/DS both limits how much one can eat and reduces the absorption of nutrients, particularly proteins and fats. BPD/DS is most successfully performed in individuals who have a BMI of >50 with other metabolic comorbidities [23].

Major outcomes of bariatric surgery.

Excess body weight loss of ~60–65% is the key feature sought after in obtaining surgical weight loss procedures [14, 24]. Body weight outcomes following VSG are similar to RYGB [25] and significantly greater than gastric banding [24]. Further, remission of comorbidities, such as T2DM and hyperlipidemia, is similar for VSG as RYGB [24]. Some reports question the degree of the similarity in remission rates of T2DM and hyperlipidemia between RYGB and VSG when full remission is defined as having normal HbA1c levels one year after the surgical procedure [26]. A recent 5-year study of the two surgeries vs. pharmacologic therapy, however, demonstrated that there was a 13% reduction in the number of participants who required the use of insulin for blood glucose management following medical-therapy, while 35% and 34% achieved normal blood glucose control with RYGB and VSG, respectively [13]. Both surgeries cause similar improvements in plasma cholesterol and triglycerides [13]. These clinical studies demonstrate that even with the most conservative estimates of the remission rate of T2DM after VSG, it still remarkably better than gastric banding or pharmacologic therapy alone.

Effect of bariatric surgery on metabolic indices in rodent models.

In female rodents, VSG is effective for improving many of the comorbidities of the metabolic syndrome [27–29], as has been reported in males [30–32]. Excess body weight is lost during the early postoperative phase and then maintained even though the animals are consuming a high saturated fat diet. The body weight loss is almost exclusively body fat. The reduction in body fat is largely the result of reduced food intake in the initial weeks following surgery, after which food intake returns to pre-surgical levels. However, animals with this procedure do not compensate (overeate) in subsequent weeks following the surgery, as is observed with other weight loss methods, i.e. calorie restriction or weight loss therapeutics [30–32]. Similar to males [30, 32], females receiving VSG have improved glucose homeostasis and reduced hyperlipidemia and hypercholesterolemia [29].

Obesity effects on reproductive function: the impact of bariatric surgery.

Given the many overlapping metabolic improvements to obesity in males and females of various species, the effects of obesity and, subsequently, surgical weight loss on reproduction are unique to males and females due to their specific reproductive functions. Obesity in women causes reproductive health problems, which include abnormal cyclicity and hormones and resultant infertility. Obese and overweight women have shorter luteal phases and have lower levels of follicle-stimulating hormone, luteinizing hormone, and progesterone [6]. Dietel *et al.* found in one study that 40% of women had menstrual irregularities before bariatric surgery, but this number dropped to 4% afterward [33]. Marceau *et al.* also report that 47% of women who were unable to conceive before BPD-DS achieved pregnancy after their surgically-induced weight loss [34]. Obese women are also more likely to develop polycystic ovarian syndrome (PCOS), a common endocrine condition that is characterized by high androgens, irregular or no menstrual period, and infertility [35, 36]. This may be due to higher levels of androgens that are associated with increased adiposity as well as higher insulin levels that can directly stimulate testosterone secretion from thecal cells of the ovarian follicle [36–39]. Weight loss is an effective intervention for PCOS, [40], and in a meta-analysis of women who had bariatric surgery, the incidence of PCOS dropped from 45.6% beforehand to 6.8% afterward along with a reduction in androgens, insulin resistance, and irregular menstrual cycles [41–43]. Interestingly, women with PCOS also lose more weight after VSG than non-PCOS controls and are more likely to become pregnant [44]. In studies of assisted pregnancies, obese women were less likely to achieve pregnancy [45], especially when their own oocyte was used, but not when a donor oocyte was used [46] suggesting that the quality of the embryo contributes to successful conception more than the *in utero* environment. In studies of obese women with a history of infertility, RYGB and AGB procedures led to a greater rate of pregnancy with *in vitro* fertilization (IVF) [47, 48]. In another study of obese women with a history of unsuccessful assisted pregnancies, women who had received a VSG were more likely to become pregnant with IVF after surgery, increasing to 37% pregnancy success rate from 0% [49]. These studies demonstrate that weight loss following bariatric surgery is an effective intervention for fertility issues, including PCOS.

While bariatric surgery certainly seems to improve a woman's ability to become pregnant, are there potential risks to this decision to become pregnant. These include the effects of the surgery on gestation, the birthing process and the health of the neonate. Taken together, a balanced view of the impact of surgery on pregnancy can be obtained.

Obesity effects on gestation: the impact of surgical weight loss.

Obesity comes with a number of comorbidities specific to pregnancy that put the mother and child at risk for harm (i.e., gestational diabetes, gestational hypertension, and preeclampsia). Gestational diabetes mellitus (GDM) is the development of carbohydrate intolerance during pregnancy leading to chronic hyperglycemia, and it is recommended that it be diagnosed after a two-step testing process between the 24–28 week of gestation [50, 51]. This testing consists of a 50g, 1-hour oral glucose tolerance test (OGTT), which if abnormal, is then followed by a 100g, 3-hour OGTT [50]. Preexisting maternal diabetes (either type 1 or type

2) and gestational diabetes mellitus (GDM) is known to lead to fetal macrosomia independent of maternal obesity [8]. This is also true in rat models of maternal diabetes induced by streptozotocin injection (which destroys pancreatic β cells), with offspring having higher body weights as well as long term consequences such as higher insulin levels and liver triglycerides [52, 53]. In a study by Bennett *et al.* of 585 women who underwent bariatric surgery (81% were RYGB) either before or after pregnancy, those that had surgery before pregnancy were less likely to suffer from gestational diabetes [54]. In a study by Rottensteich *et al.* of 119 women who had VSG matched to non-surgery women by pre-surgery BMI, the rate of gestational diabetes was lower in the VSG group [55]. In a study of women who had bariatric surgery (either VSG, RYGB, or AGB) between their first and second pregnancy, there was a 24% decrease in gestational diabetes during the second pregnancy [56]. Women who had RYGB or AGB prior to pregnancy had a decreased rate of gestational diabetes when matched with women for their pre-surgery and pre-pregnancy BMI [57]. Obese women who had RYGB matched to obese controls, gestational diabetes was found in no women who had surgery compared to 19% of obese women [58]. In two large meta-analysis that mainly included women who had RYGB or AGB, those that had bariatric surgery were found to have lower instances of gestational diabetes [5, 59]. Taken together, bariatric surgery reduces drastically the rate of glucose intolerance and various forms of diabetes during gestation.

Obesity is also a risk factor for hypertensive disorders during pregnancy, including gestational hypertension and preeclampsia. Gestational hypertension is the onset of hypertension (having a systolic pressure (BP) ≥ 140 mm Hg or diastolic BP ≥ 90) following pregnancy, which is diagnosed after 20 weeks of gestation [60, 61]. Preeclampsia is the occurrence of gestational hypertension with the addition of proteinuria, or other severe criteria such as having a low platelet count or impaired liver function indicated by high transaminases in circulation [60, 61]. Gestational hypertension and preeclampsia carry with them increased risk of death, cesarean section, growth restriction, and preterm birth [60, 61]. In a study of 585 women of who underwent bariatric surgery (81% were RYGB) either before or after pregnancy, those that had surgery before pregnancy were less likely to suffer from preeclampsia or gestational hypertension [54]. In Ibebele *et al.*'s study of bariatric surgery before a second pregnancy, there was a 67% decrease in all hypertension during the second pregnancy [56]. De Alencar Costa, *al.*, also found no preeclampsia in their study that focused on pregnancies with prior RYGB [58]. In Rottenstreich *et al.*'s study that focused on maternal VSG surgery, however, there was significant difference found in the rate of hypertensive disorders but sample size may have been underpowered to compare this parameter [55]. Additionally, two meta-analyses of bariatric surgery before pregnancy found less risk of all hypertensive disorders [5, 59].

Obesity effects on the neonate: impact of bariatric surgery.

Elevated maternal body weight during gestation negatively impact the offspring. Infants born to obese women are more likely to be born macrosomic or large-for-gestational-age (LGA). Macrosomia is defined as having a birth weight of 4000g or greater regardless of gestational age [62]. LGA is a birth weight greater than the 90th percentile of a cohort for a given gestational age, which for full term in 2011 was 4,057g [62]. Several studies support the

ability of bariatric surgery to reduce the risk of macrosomic or LGA births [56, 57, 63–65]. Results from a study 507 deliveries after the mother had any bariatric surgery compared to 301 deliveries preceding a bariatric surgery, indicated a decrease in macrosomia to 3.2% from 7.6% [65]. Additionally, lower rates of LGA were found in births following VSG [55] or when the focus was on RYGB [58]. One study found an increase in macrosomia in women who had bariatric surgery, however, this was in comparison to all other births and not to obese controls [66].

These studies illustrate the positive benefits of bariatric surgery in women who want become pregnant and may have had difficulties with fertility in the past. Bariatric surgery is proven to increase fertility in obese women with or without symptoms of PCOS and can even increase the chances of conceiving with the use of *in vitro* fertilization. Furthermore, once a pregnancy is achieved, women who have lost weight and alleviated their insulin insensitivity with surgery, provide a safer pregnancy for the infant by decreasing the chances of gestational hypertension and hyperglycemia. These changes can greatly benefit the outcome of the pregnancy and the long-term health of the child.

Unintended consequences of bariatric surgery on pregnancy.

While surgical weight loss and concurrent treatment of diabetes and hypertension are associated with many benefits to women who become pregnant, there is also cause for concern as many studies show adverse consequences. Obesity sets women up for difficulties during the time of parturition, increasing the morbidity and mortality of both the mother and neonate, but bariatric surgery exacerbates or makes no improvement in these outcomes. Of women with reoccurring miscarriages studied, obese women have a greater frequency of miscarriage than nonobese women [67]. Miscarriage is more common in obese individuals, even when pregnant with donor oocytes [68]. Obesity is also associated with a reduced chance of live births after *in vitro* fertilization [69]. Findings in pregnancies following bariatric surgery have somewhat mixed reports in outcomes. In a study comparing pregnancies post RYGB with non-surgical obese, an increased odds of miscarriage was identified after RYGB [70]; however, little data has been reported on this topic to date [71].

Additionally, obesity puts women at increased risk for preterm births [72, 73] and bariatric surgery prior to pregnancy only further increases this risk [71]. Preterm birth is defined as giving birth before 37 weeks of gestation and increases the risk of infant mortality and long term disabilities [74]. In a study of 1,857,822 women in Sweden who gave birth between 1992 and 2010, obese women were twice as likely to have an extremely preterm birth, defined as giving birth 22–27 weeks into gestation, compared to normal weight mothers [72]. Many studies of pregnancy following bariatric surgery find increased rates of preterm births. Roos et al., for instance, found that post-bariatric surgery mothers were twice as likely to have a preterm birth than non-bariatric surgery mothers [75]. While a few studies show a decreased rate of preterm birth in mothers who had bariatric surgery when compared to obese controls [55, 76, 77], the more consistent finding is an increased risk for preterm birth [57, 59, 64, 76, 78]. A few studies of bariatric surgery before pregnancy also record neonatal intensive care (NICU) admissions, finding an increased rate in mothers who have had weight loss surgery. Chevrot *et. al*, found that mothers who had bariatric surgery were

twice as likely to have their infant received by the NICU when compared to obese controls [76]. Other studies also support this finding of an increased rate of NICU admissions in women who have had weight loss surgery [19, 57, 79]. Data on cesarean section deliveries, however, is conflicting, with some studies finding a reduced use of Cesarean section during labor [55, 56, 80], while other studies that did not use weight-matched controls found an increase [63, 78].

Even though bariatric procedures decrease the number of LGA births, there is increasing evidence that the number of small-for gestational-age (SGA) are increased. In the U.S., SGA is typically defined as having a birth weight that is less than the 10th percentile for gestational age whereas fetal growth restriction is an estimated fetal weight that is less than the 10th percentile for gestation age [81]. Many studies have found a striking increase in the number of low birth weight and SGA infants following bariatric surgery. The risk of SGA births doubles in VSG pregnancies [55, 76] when compared to obese controls, and in malabsorptive surgeries, whether matched with obese controls or not [34, 56, 57, 63, 64, 66, 78, 82, 83]. A meta-analysis also concluded that bariatric surgery before pregnancy comes with increased risk for complications such as SGA [71].

Using the rat model of VSG in females coupled with pregnancy, we have characterized the impact of VSG on rat pregnancy [27, 84]. Prior to VSG surgery, the females were made obese on a high-fat diet and have glucose intolerance and hyperlipidemia. Following VSG, the rats experience significant weight loss, improved glucose tolerance and an altered (mostly improved) repertoire of metabolic hormones [27, 84]. Pups born to females following VSG had reduced weight and length in comparison to pups from either lean or obese control dams [27].

The VSG dams showed increased numbers of resorptions and reduced numbers of live pups at gestational day 19 in post-surgery pregnancies [84]. However, the placenta-to-fetus weight ratio remained normal at gestational day 19 and there was no significant difference in the individual weights of each fetus or placenta by group [84]. However, the offspring was significantly smaller than controls when measured at birth [27]. If during the pregnancy the VSG dam consumed a high-fat diet, the litter size was either greatly reduced or there were no live births, and the size of the offspring was substantially smaller than controls at birth [27]. Because the reduced birth weight occurred in both low-fat and high fat-fed VSG dams, it points to an important impact of surgery on the maternal environment that appears independent of the level of dietary fat consumed by the dam. During the postnatal period, whether VSG dams were maintained on chow or HFD, offspring of VSG dams failed to catch up in body weight [27], and they had less lean body mass at weaning [27]. Maternal diet adversely affects the adiposity of the weanlings, as pups whose dams feed on HFD have the greatest level of adiposity [27] irrespective of the surgery. Most importantly, despite being smaller, the offspring of H-VSG were glucose intolerant [27] relative to the other groups. When offspring were weaned to chow, there were few effects of either maternal diet or maternal surgery. The smaller chow- and high-fat diet-fed VSG offspring experienced “catch-up” growth, and there appeared to be no lingering effect on glucose homeostasis during young adulthood. To determine what happens when these offspring are further challenged by a high-fat diet after puberty, they were switched to high-fat diet at postnatal

day 60 (PD60). The offspring of VSG dams developed the greatest levels of adiposity [27] and the poorest glucose control [27], implying that maternal VSG prior to pregnancy increases the risk of their offspring being more susceptible to the deleterious effects of a high-fat diet.

These studies in humans and in rats demonstrate that even though bariatric surgery is attractive for women wanting to become pregnant, there are many troubling risks that must be considered. Preterm, SGA, and NICU admitted infants all face an increased risk of health challenges throughout life. The implications of maternal bariatric surgery on developmental programming remain undetermined.

Adverse outcomes for bariatric pregnancies: potential etiologies.

Though adverse outcomes after bariatric pregnancy continue to be steadily and consistently reported, no specific mechanism has been methodically tested to delineate the causal factor(s) for the adverse outcomes. Untested hypotheses that have been proposed in the literature include pregnancy-timing, calorie malnutrition, reduced levels of key vitamins and minerals, and altered metabolic hormones (Figure 1).

Timing pregnancy after surgery.

During the weight loss phase following bariatric surgery, dynamic changes are occurring to many metabolic and hormonal parameters. Weight loss stabilization takes a variable amount of time. A variety of task force recommendations suggest women desiring pregnancy after bariatric surgery to wait anywhere from 12 –18 months after surgery [85, 86]. The reasoning behind this wait is that catabolic physiologic events in the months after surgery require time to plateau. In this mode of thinking, the female should be afforded time to achieve weight loss goals without subjecting the fetus to the rapid weight loss of the mother.

In a retrospective cohort study comparing females who became pregnant before 12 months after surgery versus women who waited 12 months or more, gestational weight gain was reduced, and a higher frequency of weight loss during pregnancy was observed when women did not wait at least 12 months [87]. However, there was no difference in birth weights in either of the categories of pregnancies [87].

Another study compared women who had VSG and had become pregnant 18 months after surgery to those who became pregnant within 18 months of VSG; no differences in risk for gestational complications and maternal or fetal health were reported between the groups [88]. In a study of 158 women who had RYGB and then conceived in the first year and 128 women who conceived more than a year after surgery, there was no reported difference in birth weight or birth age, or risk for preeclampsia, GDM, and C-section [82]. In general, though the recommendation to wait may appear clinically sound, direct evidence that waiting for any specific amount of time after surgery is advantageous appears lacking.

Waiting too long after surgery, however, may be problematic as well. If an extended length of time to follow-up and poor compliance with the micronutrient supplementation has occurred after bariatric surgery, the pregnancy could be fraught with complications due to

years of less-than-optimal levels of vitamins and minerals [85]. Therefore, pregnancy counseling and risk assessment are important for women who have had surgical weight loss procedures.

Macronutrient partitioning problems?

Bariatric surgeries differ concerning to the volumetric capacity of the stomach and consequently, the severity of reduction in caloric intake of each meal. Further, the type of surgery alters the transit path of nutrients through the gut following the surgical procedure. In a study investigating nutrient intake six months after surgery, AGB compared to RYGB individuals consumed approximately 33% more calories overall, 8% more protein, 42% more fat, and 57% more carbohydrates; both groups still had a total consumption within a healthy range [89]. In another study, VSG patient overall daily caloric intake more closely matched RYGB patient intake than AGB [90]. There are a greater number of reports of malabsorption with RYGB than either AGB or VSG, although this is not always found [91]. In normal-weight human pregnancies, calorie requirements increase in the second trimester to 200–300 extra calories/day and 300–500 calories/day in the third trimester, although obstetric recommendations for higher BMI pregnancies suggest little to no weight gain. However, to date, there have not been studies reporting the caloric intake of women in the various stages of pregnancy following surgical weight loss. AGB and RYGB are also associated with a mild [92] to severe protein-deficiency [93]. However, circulating amino acid levels are elevated 3 and 6 months post-surgery [94]. Many rodent models induce IUGR during pregnancy using protein deficient diets to reduce *in utero* growth [95]. So it is plausible that protein deficiency is responsible for the reduced growth we identified in VSG pregnancies.

Micronutrient availability following bariatric surgery?

Anemia and other vitamin deficiencies, especially vitamin D deficiency, are present after bariatric surgery despite supplement regimens. Anemia after RYGB is thought to be related to diminished consumption of red meat, diminished gastric acid secretion, and duodenal nutrient exclusion (site of iron absorption) [96]. During normal pregnancy, maternal anemia is independently associated with low birth weight, preterm birth, and neonatal death [97]. Coupling pregnancy with bariatric surgery would predict significant complex problems to iron resorption. In a study comparing BPD, VSG and RYGB pregnancies, anemia was reported in 24.2% of BPD, 15.6% of RYGB and not at all with VSG; none of the pregnancies were severely anemic [98]. Other studies found varying elevated rates of anemia also find increased instances of anemia in pregnant women who had bariatric surgery [58, 99–103]. Even with avid supplementation during pregnancy, iron deficiencies were not averted [104].

In our rodent model of VSG, we indeed found a significant reduction in ferritin levels and reduced hematocrit in VSG pregnancy [27]. We also reported reduced levels of folate both in VSG pregnancies as well as obese pregnancies; vitamin B12 levels were normal [27]. Given the relationship of anemia and birth weight, iron deficiency could be a viable contributor to reduced birth weight following bariatric surgery in both the rat and human though the

relationship of maternal anemia and birth weight in pregnancies complicated by prior bariatric surgery has not been reported to date.

Because of the increased potential risk for neural tube defects, folate levels are important to augment following surgical weight loss. Isolated case reports suggests folic acid deficiency occurs in pregnancies following bariatric surgery [105]. In another study, folic acid levels were elevated in pregnant women receiving one of three bariatric procedures [98] potentially due to attentive follow-up during prenatal visits.

Testing for vitamin deficiencies before pregnancy is not routinely done though more commonly performed in pregnancies complicated by prior bariatric surgery [106]. Vitamin A and B1 deficiencies increase significantly across pregnancy following bariatric surgery with significantly reduced levels of vitamin D deficiency as well [102]. A met-analysis of 27 articles of bariatric pregnancies reports deficiencies in maternal concentrations of vitamins A, B1, B6, B12, C, D, K, iron, calcium, selenium, and phosphorous [103]. Certain vitamin deficiencies were the most problematic because of their associated conditions i.e., anemia with vitamin B12 and iron deficiencies, night blindness with vitamin A deficiency, and urinary tract infections with vitamin A and D deficiencies [103]. They concluded that despite these deficiencies, there was no correlations with these reduced blood vitamin levels and adverse outcomes [103]. In one study, among other reduced vitamin concentrations, zinc deficiency was also reported [107]. Vitamin D deficiency is particularly prevalent after RYGB [108]. In a study comparing BPD, VSG, and RYGB, bioavailable vitamin D concentrations and vitamin B12 levels were lower in all groups with no further decrease during pregnancy [26]. Taken together, hypovitaminosis

Direct consequences of altered metabolic hormones after surgical weight loss?

Bariatric surgery results in robust changes in metabolic hormones such as ghrelin, bile acids and glucagon-like peptide 1 (GLP-1), amongst many others. Ghrelin, [109, 110] FXR-mediated bile acid signaling [111], and GLP-1 [112] have been specifically targeted in the last decade with respect to their potential as therapeutic agents to reduce the burden of obesity and diabetes. Ghrelin, bile acids, and GLP-1 have also been individually hypothesized to be solely responsible for the powerful body weight-lowering and anti-diabetic outcomes associated with bariatric surgery [113, 114]. Each of the changes in these specific hormones is touted as metabolically beneficial for the bariatric surgery recipient, but in the context of pregnancy may not be explicitly advantageous for the growing fetus. In fact, perturbations to each of these hormones, independent of bariatric surgery, can lead to gestational conditions resulting in adverse fetal outcomes and/or fetal demise.

Circulating ghrelin levels are significantly reduced in both the humans and rodents following bariatric surgery [115, 116]. Ghrelin is produced in the gastric mucosa of the greater curvature that is massively resected during VSG and thus ghrelin is low in particular following VSG [117]. Ghrelin rises in circulation with prolonged fasting and precipitously drops off following ingestion. It is physiologically activated by octynolation through the enzyme ghrelin O-acyl transferase (GOAT), and exerts its endocrine influences in diverse

tissues as it circulates in plasma in both its “inactive” or desacyl and “active,” acyl forms. In animal gestational models, anti-ghrelin treatment administered to rats during pregnancy reduces the size and weight of the rat litter in comparison to controls [118]. In a similar manner, babies born SGA have lower levels of cord ghrelin [119, 120] than normal-sized babies. We know that ghrelin is reduced during VSG rodent pregnancy [27] and assume this would be true in human bariatric pregnancies; this has not been reported to date.

Another interesting side effect following bariatric surgery is the increased intrahepatic cycling of bile acids, which circulate as hormonal signaling molecules [121–123]. Bile acids are detergents produced by the liver from a backbone of cholesterol and released into the intestine to aid in lipid absorption. Following bariatric surgery, bile acid levels rise precipitously, and the composition of bile acid shifts [122]. Beyond bile acids’ lipid absorptive actions, they signal as hormones via a nuclear-receptor mechanism through FXR and in a receptor-mediated mechanism via TGR5. Substantial work has been done to identify the unique effects of bile acids on glucose homeostasis, body weight regulation, and food intake following bariatric procedures [123, 124]. The direct cause of their rise remains elusive. Unfortunately, in the context of pregnancy, elevations in bile acids are not advantageous but rather, harmful. The abnormal rise of bile acids during pregnancy causes a gestational disorder known as intrahepatic cholestasis of pregnancy (ICP) [125]. Chronic elevation of bile acids in ICP results in serious risks for the pregnancy, including increased incidence of fetal demise, premature births, and SGA infants [126, 127]. In our rodent model of pregnancy, bile acids are elevated in comparison to lean controls (*unpublished data*). Delving deeper, the various negative side effects of ICP overlap directly with the negative effects we have identified in our pre-clinical model of VSG [27, 128].

One of the most consistent hormonal changes to occur after bariatric surgery is the robust increase in circulating GLP1 [32]. GLP1 has broad effects to regulate glucose metabolism, including effects on islet hormone secretion, gastrointestinal motility, and satiety. It is speculated that many of the positive effects of bariatric surgery are due to greater circulating GLP1. Interestingly, females with gestational diabetes, who tend to give birth to LGA babies, have been reported to have low GLP1 levels [129–131]. In contrast, recent studies suggest that higher maternal GLP1 levels during pregnancy are associated with smaller infants; e.g., maternal GLP1 levels in normal-weight gestating females are negatively correlated with fetal abdominal circumferences by ultrasound and neonatal birth weight [132]. In this same study, other gut hormones such as glucose-dependent insulinotropic peptide (GIP), peptide YY (PYY) and ghrelin neither changed during pregnancy nor correlated with maternal or fetal indices [132]. Taken together in the setting of pregnancy the impact of GLP1 may not be uniformly positive. Collectively these data point toward a potentially important role for maternal GLP1 in the growth and development of the fetus and neonatal birth size. Given that both VSG and RYGB result in greatly increased levels of GLP-1 both in fed and fasted conditions [133], it is possible for elevated GLP-1 level to affect body weight outcomes of the offspring of post-bariatric mothers.

Fetal-placental changes during VSG during pregnancy and early postnatal life: using a rodent model.

Using our rat model of maternal VSG coupled with pregnancy [27, 84], we examined the *in utero* environment of our VSG model, identifying several possible mechanisms by which the fetus may suffer detriment [128]. We found that the immune system in the pregnant VSG dam is altered, having lower T-cells and higher IgG in circulation [128]. In the placenta of VSG dams, there were more apoptotic cells and an elevation of inflammatory markers. Furthermore, the VSG placental barrier is more permissive to moderately-sized molecules than in Sham controls, and may not protect the fetus as effectively. We also identified hormone changes in the VSG dams, including a reduction in circulating leptin when compared to both lean or obese controls, and a reduction in leptin receptor expression in the placenta. Lastly, testosterone was elevated in VSG dams, while androgen receptor expression was reduced in the placenta [128].

We next asked if the immune system of the postnatal offspring was affected by maternal immune changes. At PND21, B lymphocytes in the peripheral blood were reduced while total IgG was elevated in offspring of VSG dams compared to the offspring of Sham dams [134]. At the same time point, markers of inflammation in the brain were elevated, including *Il1b* and microglial marker, IBA1 [134]. Later at PND60, these differences are not found; however, there were markers of increased immune activity in the spleen, including increased levels of T cell markers and increased expression of *Il1b* [134]. These data suggest that the immune system of VSG offspring may have been compromised at birth, but during postnatal development may become hyper-reactive. This line of work requires further study.

Transgenerational consequences of maternal bariatric surgery in rodent and human offspring.

Given that healthcare providers suggest postponing pregnancy for 12–18 months for women after bariatric surgery, prospective, longitudinal studies that report outcomes in offspring conceived after surgical weight loss are sparse. Of the studies that exist, both positive and negative outcomes have been found. In a study of pregnancies before and after BPD/DS, researchers found a reduced risk for obesity in offspring of pregnancies complicated by prior surgical weight loss and a variety of epigenetic marker changes in immune and inflammatory gene regions [135]. The authors interpreted these changes as positive. However, BPD/DS is a malabsorptive bariatric surgery where high calories are still consumed; its resulting physiology is different substantively from the other mainstream surgical weight loss procedures. Another small study of 13 children born to mothers after RYGB, a substantial number of the children born were obese coupled with a variety of vitamin deficiencies, macronutrient malnutrition and substantially elevated sodium intake [136]. In a Swedish study of sibling pairs, one born before maternal BPD/DS and the other between 1 and 11 years after, differently methylated CpG sites in genes involved with insulin receptor signaling, T2DM signaling, and leptin signaling in obesity were identified suggesting targeted changes in methylation may occur during *in utero* development following bariatric surgery [137]. Though the fetal weights of matched offspring born after

for metabolic, behavioral and cognitive changes as a result of parental bariatric surgery are important since many times both spouses obtains the surgery. Considering that both the mother and fetus are vulnerable populations during a pregnancy, understanding the effect of these surgeries on future generations is necessary to best support those choosing to improve their health through these life-altering options.

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LITERATURE CITED

1. Collaborators GBD, et al., Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*, 2017 377(1): p. 13–27. [PubMed: 28604169]
2. Riley L, Wertz M, and McDowell I, Obesity in Pregnancy: Risks and Management. *Am Fam Physician*, 2018 97(9): p. 559–561. [PubMed: 29763261]
3. Catalano PM and Shankar K, Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. *BMJ*, 2017 356: p. j1. [PubMed: 28179267]
4. Burstein E, et al., Pregnancy outcome among obese women: a prospective study. *Am J Perinatol*, 2008 25(9): p. 561–6. [PubMed: 18770493]
5. Willis K, Lieberman N, and Sheiner E, Pregnancy and neonatal outcome after bariatric surgery. *Best Pract Res Clin Obstet Gynaecol*, 2015 29(1): p. 133–44. [PubMed: 25225055]
6. Santoro N, et al., Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. *J Clin Endocrinol Metab*, 2004 89(6): p. 2622–31. [PubMed: 15181033]
7. Teitelman M, et al., The Impact of Bariatric Surgery on Menstrual Patterns. *Obesity Surgery*, 2006 16(11): p. 1457. [PubMed: 17132411]
8. Yessoufou A and Moutairou K, Maternal diabetes in pregnancy: early and long-term outcomes on the offspring and the concept of “metabolic memory”. *Exp Diabetes Res*, 2011 2011: p. 218598. [PubMed: 22144985]
9. Madan J, et al., Maternal obesity, gestational hypertension, and preterm delivery. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2010 23(1): p. 82–88. [PubMed: 19903115]
10. Lopez-Jaramillo P, et al., Obesity and Preeclampsia: Common Pathophysiological Mechanisms. *Frontiers in Physiology*, 2018 9(1838).
11. Deshmukh VL, Jadhav M, and Yelikar K, Impact of HIGH BMI on Pregnancy: Maternal and Foetal Outcome. *The Journal of Obstetrics and Gynecology of India*, 2016 66(1): p. 192–197.
12. Fernández Alba JJ, et al., Indications of caesarean section in overweight and obese versus normal-weight pregnant women: a retrospective cohort study. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2018 31(3): p. 357–363. [PubMed: 28118780]
13. Schauer PR, et al., Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. *N Engl J Med*, 2017 376(7): p. 641–651. [PubMed: 28199805]
14. Elder KA and Wolfe BM, Bariatric surgery: a review of procedures and outcomes. *Gastroenterology*, 2007 132(6): p. 2253–71. [PubMed: 17498516]
15. Angrisani L, et al., IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures. *Obes Surg*, 2018 28(12): p. 3783–3794. [PubMed: 30121858]
16. Young MT, Phelan MJ, and Nguyen NT, A Decade Analysis of Trends and Outcomes of Male vs Female Patients Who Underwent Bariatric Surgery. *J Am Coll Surg*, 2016 222(3): p. 226–31. [PubMed: 26782151]

17. Maggard MA, et al., Pregnancy and fertility following bariatric surgery: a systematic review. JAMA, 2008 300(19): p. 2286–96. [PubMed: 19017915]
18. American College of O and Gynecologists ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol, 2009 113(6): p. 1405–13. [PubMed: 19461456]
19. Parent B, et al., Bariatric Surgery in Women of Childbearing Age, Timing Between an Operation and Birth, and Associated Perinatal Complications. JAMA Surg, 2017 152(2): p. 128–135. [PubMed: 27760265]
20. Buchwald H and Oien DM, Metabolic/bariatric surgery worldwide 2011. Obes Surg, 2013 23(4): p. 427–36. [PubMed: 23338049]
21. Angrisani L, et al., Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. Obes Surg, 2017.
22. Dogan K, et al., Effectiveness and Safety of Sleeve Gastrectomy, Gastric Bypass, and Adjustable Gastric Banding in Morbidly Obese Patients: a Multicenter, Retrospective, Matched Cohort Study. Obes Surg, 2015 25(7): p. 1110–8. [PubMed: 25408433]
23. Anderson B, et al., Biliopancreatic diversion: the effectiveness of duodenal switch and its limitations. Gastroenterol Res Pract, 2013 2013: p. 974762. [PubMed: 24639868]
24. Buchwald H, et al., Bariatric surgery: a systematic review and meta-analysis. JAMA, 2004 292(14): p. 1724–37. [PubMed: 15479938]
25. Arterburn D and Gupta A, Comparing the Outcomes of Sleeve Gastrectomy and Roux-en-Y Gastric Bypass for Severe Obesity. JAMA, 2018 319(3): p. 235–237. [PubMed: 29340659]
26. Pournaras DJ, et al., Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg, 2012 99(1): p. 100–3. [PubMed: 22021090]
27. Grayson BE, et al., Improved rodent maternal metabolism but reduced intrauterine growth after vertical sleeve gastrectomy. Sci Transl Med, 2013 5(199): p. 199ra112.
28. Ressler IB, Grayson BE, and Seeley RJ, Metabolic, behavioral, and reproductive effects of vertical sleeve gastrectomy in an obese rat model of polycystic ovary syndrome. Obes Surg, 2014 24(6): p. 866–76. [PubMed: 24408363]
29. Grayson BE, et al., Bariatric surgery emphasizes biological sex differences in rodent hepatic lipid handling. Biol Sex Differ, 2017 8: p. 4. [PubMed: 28149499]
30. Stefater M, et al., Sleeve Gastrectomy Induces Loss of Weight and Fat Mass in Obese Rats, But Does Not Affect Leptin Sensitivity. Gastroenterology, 2010 138(7): p. 2426–2436 e3. [PubMed: 20226189]
31. Stefater MA, et al., Sleeve Gastrectomy in Rats Improves Postprandial Lipid Clearance by Reducing Intestinal Triglyceride Secretion. Gastroenterology, 2011 41(3): p. 939–949.e4.
32. Chambers AP, et al., Weight-Independent Changes in Blood Glucose Homeostasis After Gastric Bypass or Vertical Sleeve Gastrectomy in Rats. Gastroenterology, 2011 141(3): p. 950–8. [PubMed: 21699789]
33. Deitel M, et al., Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. J Am Coll Nutr, 1988 7(2): p. 147–53. [PubMed: 3361039]
34. Marceau P, et al., Outcome of pregnancies after biliopancreatic diversion. Obes Surg, 2004 14(3): p. 318–24. [PubMed: 15072650]
35. Gosman GG, et al., Reproductive health of women electing bariatric surgery. Fertil Steril, 2010 94(4): p. 1426–31. [PubMed: 19815190]
36. Pasquali R, Metabolic Syndrome in Polycystic Ovary Syndrome. Front Horm Res, 2018 49: p. 114–130. [PubMed: 29894990]
37. Legro RS, et al., Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. J Clin Endocrinol Metab, 2010 95(12): p. 5305–13. [PubMed: 20826578]
38. Mayer SB, Evans WS, and Nestler JE, Polycystic ovary syndrome and insulin: our understanding in the past, present and future. Womens Health (Lond), 2015 11(2): p. 137–49. [PubMed: 25776288]
39. Nestler JE, et al., Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators

- as the signal transduction system. *J Clin Endocrinol Metab*, 1998 83(6): p. 2001–5. [PubMed: 9626131]
40. Pasquali R, et al., Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *Eur J Endocrinol*, 2011 164(1): p. 53–60. [PubMed: 20956435]
 41. Skubleny D, et al., The Impact of Bariatric Surgery on Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis. *Obes Surg*, 2016 26(1): p. 169–76. [PubMed: 26431698]
 42. Li YJ, Han Y, and He B, Effects of bariatric surgery on obese polycystic ovary syndrome: a systematic review and meta-analysis. *Surg Obes Relat Dis*, 2019 15(6): p. 942–950. [PubMed: 31113751]
 43. Machado Junior AS, et al., The Effect of Sleeve Gastrectomy on the Hormonal Profile of Patients with Polycystic Ovary Syndrome. *Obes Surg*, 2019 29(8): p. 2415–2419. [PubMed: 30953337]
 44. Dilday J, et al., Sleeve Gastrectomy for Obesity in Polycystic Ovarian Syndrome: a Pilot Study Evaluating Weight Loss and Fertility Outcomes. *Obes Surg*, 2019 29(1): p. 93–98. [PubMed: 30112604]
 45. Sermondade N, et al., Female obesity is negatively associated with live birth rate following IVF: a systematic review and meta-analysis. *Hum Reprod Update*, 2019 25(4): p. 439–451. [PubMed: 30941397]
 46. Luke B, et al., Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod*, 2011 26(1): p. 245–52. [PubMed: 21071489]
 47. Doblado MA, et al., In vitro fertilization after bariatric surgery. *Fertil Steril*, 2010 94(7): p. 2812–4. [PubMed: 20667406]
 48. Tan O and Carr BR, The impact of bariatric surgery on obesity-related infertility and in vitro fertilization outcomes. *Semin Reprod Med*, 2012 30(6): p. 517–28. [PubMed: 23074010]
 49. Milone M, et al., Does Bariatric Surgery Improve Assisted Reproductive Technology Outcomes in Obese Infertile Women? *Obes Surg*, 2017 27(8): p. 2106–2112. [PubMed: 28233264]
 50. Committee on Practice, B.-O., ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol*, 2018 131(2): p. e49–e64. [PubMed: 29370047]
 51. Plows JF, et al., The Pathophysiology of Gestational Diabetes Mellitus. *Int J Mol Sci*, 2018 19(11).
 52. Aerts L, Holemans K, and Van Assche FA, Maternal diabetes during pregnancy: consequences for the offspring. *Diabetes Metab Rev*, 1990 6(3): p. 147–67. [PubMed: 2091909]
 53. Lopez-Soldado I and Herrera E, Different diabetogenic response to moderate doses of streptozotocin in pregnant rats, and its long-term consequences in the offspring. *Exp Diabetes Res*, 2003 4(2): p. 107–18. [PubMed: 14630572]
 54. Bennett WL, et al., Impact of bariatric surgery on hypertensive disorders in pregnancy: retrospective analysis of insurance claims data. *BMJ*, 2010 340: p. c1662. [PubMed: 20388692]
 55. Rottenstreich A, et al., Maternal and Perinatal Outcomes After Laparoscopic Sleeve Gastrectomy. *Obstet Gynecol*, 2018 131(3): p. 451–456. [PubMed: 29420411]
 56. Ibiebele I, et al., Perinatal outcomes following bariatric surgery between a first and second pregnancy: a population data linkage study. *Bjog*, 2019.
 57. Lesko J and Peaceman A, Pregnancy outcomes in women after bariatric surgery compared with obese and morbidly obese controls. *Obstet Gynecol*, 2012 119(3): p. 547–54. [PubMed: 22353952]
 58. de Alencar Costa LA, et al., Maternal and perinatal outcomes after bariatric surgery: a case control study. *J Perinat Med*, 2016 44(4): p. 383–8. [PubMed: 26352065]
 59. Kjaer MM and Nilas L, Pregnancy after bariatric surgery--a review of benefits and risks. *Acta Obstet Gynecol Scand*, 2013 92(3): p. 264–71. [PubMed: 23066836]
 60. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*, 2019 133(1): p. e1–e25. [PubMed: 30575675]
 61. Rana S, et al., Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circ Res*, 2019 124(7): p. 1094–1112. [PubMed: 30920918]
 62. American College of O and Gynecologists' B-O Committee on Practice, Practice Bulletin No. 173: Fetal Macrosomia. *Obstet Gynecol*, 2016 128(5): p. e195–e209. [PubMed: 27776071]

63. Belogolovkin V, et al., Impact of prior bariatric surgery on maternal and fetal outcomes among obese and non-obese mothers. *Arch Gynecol Obstet*, 2012 285(5): p. 1211–8. [PubMed: 22057892]
64. Patel JA, et al., Pregnancy outcomes after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*, 2008 4(1): p. 39–45. [PubMed: 18201669]
65. Weintraub AY, et al., Effect of bariatric surgery on pregnancy outcome. *Int J Gynaecol Obstet*, 2008 103(3): p. 246–51. [PubMed: 18768177]
66. Sheiner E, et al., Pregnancy after bariatric surgery is not associated with adverse perinatal outcome. *Am J Obstet Gynecol*, 2004 190(5): p. 1335–40. [PubMed: 15167839]
67. Boots CE, Bernardi LA, and Stephenson MD, Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. *Fertil Steril*, 2014 102(2): p. 455–9. [PubMed: 24907916]
68. Bellver J, et al., Obesity and the risk of spontaneous abortion after oocyte donation. *Fertil Steril*, 2003 79(5): p. 1136–40. [PubMed: 12738508]
69. Fedorcsak P, et al., Impact of overweight and underweight on assisted reproduction treatment. *Hum Reprod*, 2004 19(11): p. 2523–8. [PubMed: 15319380]
70. Goldman RH, et al., Reproductive Outcomes Differ Following Roux-en-Y Gastric Bypass and Adjustable Gastric Band Compared with Those of an Obese Non-Surgical Group. *Obesity Surgery*, 2016 26(11): p. 2581–2589. [PubMed: 27052316]
71. Akhter Z, et al., Pregnancy after bariatric surgery and adverse perinatal outcomes: A systematic review and meta-analysis. *PLoS Med*, 2019 16(8): p. e1002866. [PubMed: 31386658]
72. Cnattingius S, et al., Maternal obesity and risk of preterm delivery. *JAMA*, 2013 309(22): p. 2362–70. [PubMed: 23757084]
73. Marchi J, et al., Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. *Obes Rev*, 2015 16(8): p. 621–38. [PubMed: 26016557]
74. Simmons LE, et al., Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. *Semin Perinatol*, 2010 34(6): p. 408–15. [PubMed: 21094415]
75. Roos N, et al., Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. *Bmj*, 2013 347: p. f6460. [PubMed: 24222480]
76. Chevrot A, et al., Impact of bariatric surgery on fetal growth restriction: experience of a perinatal and bariatric surgery center. *Am J Obstet Gynecol*, 2016 214(5): p. 655 e1–7. [PubMed: 26627725]
77. Dixon JB, Dixon ME, and O'Brien PE, Birth outcomes in obese women after laparoscopic adjustable gastric banding. *Obstet Gynecol*, 2005 106(5 Pt 1): p. 965–72. [PubMed: 16260513]
78. Josefsson A, et al., Bariatric surgery in a national cohort of women: sociodemographics and obstetric outcomes. *Am J Obstet Gynecol*, 2011 205(3): p. 206 e1–8. [PubMed: 21596369]
79. Lapolla A, et al., Pregnancy outcome in morbidly obese women before and after laparoscopic gastric banding. *Obes Surg*, 2010 20(9): p. 1251–7. [PubMed: 20524157]
80. Burke AE, et al., Reduced incidence of gestational diabetes with bariatric surgery. *J Am Coll Surg*, 2010 211(2): p. 169–75. [PubMed: 20670854]
81. ACOG Practice Bulletin No. 204: Fetal Growth Restriction. *Obstet Gynecol*, 2019 133(2): p. e97–e109. [PubMed: 30681542]
82. Kjaer MM and Nilas L, Timing of pregnancy after gastric bypass-a national register-based cohort study. *Obes Surg*, 2013 23(8): p. 1281–5. [PubMed: 23462860]
83. Santulli P, et al., Obstetrical and neonatal outcomes of pregnancies following gastric bypass surgery: a retrospective cohort study in a French referral centre. *Obes Surg*, 2010 20(11): p. 1501–8. [PubMed: 20803358]
84. Spann RA, et al., Rodent Vertical Sleeve Gastrectomy Alters Maternal Immune Health and Feto-placental Development. *Clin Sci (Lond)*, 2017.
85. Ciangura C, et al., Clinical Practice Guidelines for Childbearing Female Candidates for Bariatric Surgery, Pregnancy, and Post-partum Management After Bariatric Surgery. *Obesity Surgery*, 2019 29(11): p. 3722–3734. [PubMed: 31493139]

86. Busetto L, et al., Obesity Management Task Force of the European Association for the Study of Obesity Released “Practical Recommendations for the Post-Bariatric Surgery Medical Management”. *Obesity Surgery*, 2018 28(7): p. 2117–2121. [PubMed: 29725979]
87. Dolin CD, et al., Association between time interval from bariatric surgery to pregnancy and maternal weight outcomes. *J Matern Fetal Neonatal Med*, 2019: p. 1–7.
88. Basbug A, et al., Does pregnancy interval after laparoscopic sleeve gastrectomy affect maternal and perinatal outcomes? *J Matern Fetal Neonatal Med*, 2018: p. 1–7.
89. Forbes R, et al., Essential Fatty Acid Plasma Profiles Following Gastric Bypass and Adjusted Gastric Banding Bariatric Surgeries. *Obes Surg*, 2015.
90. Coluzzi I, et al., Food Intake and Changes in Eating Behavior After Laparoscopic Sleeve Gastrectomy. *Obes Surg*, 2016.
91. Carswell KA, et al., The effect of bariatric surgery on intestinal absorption and transit time. *Obes Surg*, 2014 24(5): p. 796–805. [PubMed: 24374942]
92. Aron-Wisnewsky J, et al., Nutritional and Protein Deficiencies in the Short Term following Both Gastric Bypass and Gastric Banding. *PLoS One*, 2016 11(2): p. e0149588. [PubMed: 26891123]
93. Martins Tde C, et al., Severe protein malnutrition in a morbidly obese patient after bariatric surgery. *Nutrition*, 2015 31(3): p. 535–8. [PubMed: 25701346]
94. Nicoletti CF, et al., Protein and amino acid status before and after bariatric surgery: a 12-month follow-up study. *Surg Obes Relat Dis*, 2013 9(6): p. 1008–12. [PubMed: 24321570]
95. Reamon-Buettner SM, Buschmann J, and Lewin G, Identifying placental epigenetic alterations in an intrauterine growth restriction (IUGR) rat model induced by gestational protein deficiency. *Reprod Toxicol*, 2014 45: p. 117–24. [PubMed: 24607647]
96. Love AL and Billett HH, Obesity, bariatric surgery, and iron deficiency: True, true, true and related. *American Journal of Hematology*, 2008 83(5): p. 403–409. [PubMed: 18061940]
97. Rahman MM, et al., Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. *Am J Clin Nutr*, 2016 103(2): p. 495–504. [PubMed: 26739036]
98. Mead NC, et al., Pregnancy outcomes and nutritional indices after 3 types of bariatric surgery performed at a single institution. *Surg Obes Relat Dis*, 2014 10(6): p. 1166–73. [PubMed: 24913588]
99. Shai D, et al., Pregnancy outcome of patients following bariatric surgery as compared with obese women: a population-based study. *J Matern Fetal Neonatal Med*, 2014 27(3): p. 275–8. [PubMed: 23773032]
100. Galazis N, et al., Maternal and neonatal outcomes in women undergoing bariatric surgery: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*, 2014 181: p. 45–53. [PubMed: 25126981]
101. Devlieger R, et al., Micronutrient levels and supplement intake in pregnancy after bariatric surgery: a prospective cohort study. *PLoS One*, 2014 9(12): p. e114192. [PubMed: 25470614]
102. Jans G, et al., Vitamin K1 monitoring in pregnancies after bariatric surgery: a prospective cohort study. *Surg Obes Relat Dis*, 2014 10(5): p. 885–90. [PubMed: 25264330]
103. Rottenstreich A, et al., Maternal nutritional status and related pregnancy outcomes following bariatric surgery: A systematic review. *Surg Obes Relat Dis*, 2019 15(2): p. 324–332. [PubMed: 30658948]
104. Faintuch J, et al., Pregnancy nutritional indices and birth weight after Roux-en-Y gastric bypass. *Obes Surg*, 2009 19(5): p. 583–9. [PubMed: 18953618]
105. Pelizzo G, et al., Malnutrition in pregnancy following bariatric surgery: three clinical cases of fetal neural defects. *Nutr J*, 2014 13: p. 59. [PubMed: 24929556]
106. Gadgil MD, et al., Laboratory testing for and diagnosis of nutritional deficiencies in pregnancy before and after bariatric surgery. *J Womens Health (Larchmt)*, 2014 23(2): p. 129–37. [PubMed: 24102519]
107. Costa MM, et al., Pregnancy after bariatric surgery: Maternal and fetal outcomes of 39 pregnancies and a literature review. *J Obstet Gynaecol Res*, 2018 44(4): p. 681–690. [PubMed: 29349843]

108. Chakhtoura MT, et al., Hypovitaminosis D in bariatric surgery: A systematic review of observational studies. *Metabolism*, 2016 65(4): p. 574–85. [PubMed: 26805016]
109. Daina A, et al., Rational Design, Synthesis, and Pharmacological Characterization of Novel Ghrelin Receptor Inverse Agonists as Potential Treatment against Obesity-Related Metabolic Diseases. *J Med Chem*, 2018 61(24): p. 11039–11060. [PubMed: 30265805]
110. Helmling S, Jarosch F, and Klussmann S, The promise of ghrelin antagonism in obesity treatment. *Drug News Perspect*, 2006 19(1): p. 13–20. [PubMed: 16550252]
111. De Magalhaes Filho CD, Downes M, and Evans RM, Farnesoid X Receptor an Emerging Target to Combat Obesity. *Dig Dis*, 2017 35(3): p. 185–190. [PubMed: 28249279]
112. Smith NK, et al., GLP-1: Molecular mechanisms and outcomes of a complex signaling system. *Neurochem Int*, 2019 128: p. 94–105. [PubMed: 31002893]
113. Albaugh VL, et al., Role of Bile Acids and GLP-1 in Mediating the Metabolic Improvements of Bariatric Surgery. *Gastroenterology*, 2019 156(4): p. 1041–1051.e4. [PubMed: 30445014]
114. Steinert RE, et al., Ghrelin, CCK, GLP-1, and PYY(3–36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB. *Physiol Rev*, 2017 97(1): p. 411–463. [PubMed: 28003328]
115. Wang Y and Liu J, Plasma ghrelin modulation in gastric band operation and sleeve gastrectomy. *Obes Surg*, 2009 19(3): p. 357–62. [PubMed: 18841429]
116. Frezza EE, Chiriva-Internati M, and Wachtel MS, Analysis of the results of sleeve gastrectomy for morbid obesity and the role of ghrelin. *Surg Today*, 2008 38(6): p. 481–3. [PubMed: 18516524]
117. Chambers AP, et al., The effects of vertical sleeve gastrectomy in rodents are ghrelin independent. *Gastroenterology*, 2013 144(1): p. 50–52 e5. [PubMed: 22995675]
118. Nakahara K, et al., Maternal ghrelin plays an important role in rat fetal development during pregnancy. *Endocrinology*, 2006 147(3): p. 1333–42. [PubMed: 16339208]
119. Yalinbas EE, et al., The Role of Umbilical Cord Blood Concentration of IGF-I, IGF-II, Leptin, Adiponectin, Ghrelin, Resistin, and Visfatin in Fetal Growth. *Am J Perinatol*, 2018.
120. Warchol M, et al., Association of cord blood ghrelin, leptin and insulin concentrations in term newborns with anthropometric parameters at birth. *J Pediatr Endocrinol Metab*, 2018 31(2): p. 151–157. [PubMed: 29320365]
121. Spinelli V, et al., Influence of Roux-en-Y gastric bypass on plasma bile acid profiles: a comparative study between rats, pigs and humans. *Int J Obes (Lond)*, 2016.
122. Myronovych A, et al., Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. *Obesity (Silver Spring)*, 2013.
123. Myronovych A, et al., The role of small heterodimer partner in nonalcoholic fatty liver disease improvement after sleeve gastrectomy in mice. *Obesity (Silver Spring)*, 2014 22(11): p. 2301–11. [PubMed: 25376397]
124. Ryan KK, et al., FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*, 2014 509(7499): p. 183–8. [PubMed: 24670636]
125. Dixon PH and Williamson C, The pathophysiology of intrahepatic cholestasis of pregnancy. *Clin Res Hepatol Gastroenterol*, 2016 40(2): p. 141–53. [PubMed: 26823041]
126. Glantz A, et al., Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology*, 2005 42(6): p. 1399–405. [PubMed: 16317669]
127. Wikstrom Shemer E, et al., Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. *Bjog*, 2013 120(6): p. 717–23. [PubMed: 23418899]
128. Spann RA, et al., Rodent vertical sleeve gastrectomy alters maternal immune health and fetoplacental development. *Clin Sci (Lond)*, 2018 132(2): p. 295–312. [PubMed: 29167317]
129. Kosinski M, et al., Postpartum reversibility of impaired incretin effect in gestational diabetes mellitus. *Regul Pept*, 2013 186C: p. 104–107.
130. Lencioni C, et al., Glucagon-like peptide-1 secretion in women with gestational diabetes mellitus during and after pregnancy. *J Endocrinol Invest*, 2011 34(9): p. e287–90. [PubMed: 21666414]

131. Bonde L, et al., Reduced postprandial GLP-1 responses in women with gestational diabetes mellitus. *Diabetes Obes Metab*, 2013 15(8): p. 713–20. [PubMed: 23406269]
132. Valsamakis G, et al., The role of maternal gut hormones in normal pregnancy: fasting plasma active glucagon-like peptide 1 level is a negative predictor of fetal abdomen circumference and maternal weight change. *Eur J Endocrinol*, 2010 162(5): p. 897–903. [PubMed: 20194524]
133. Chambers AP, et al., Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. *Am J Physiol Endocrinol Metab*, 2014 306(4): p. E424–32. [PubMed: 24368666]
134. Spann RA, et al., Altered immune system in offspring of rat maternal vertical sleeve gastrectomy. *Am J Physiol Regul Integr Comp Physiol*, 2019 317(6): p. R852–r863. [PubMed: 31692364]
135. Guenard F, et al., Methylation and expression of immune and inflammatory genes in the offspring of bariatric bypass surgery patients. *J Obes*, 2013 2013: p. 492170. [PubMed: 23840945]
136. Gimenes JC, et al., Nutritional Status of Children from Women with Previously Bariatric Surgery. *Obes Surg*, 2018 28(4): p. 990–995. [PubMed: 28980121]
137. Berglind D, et al., Differential methylation in inflammation and type 2 diabetes genes in siblings born before and after maternal bariatric surgery. *Obesity (Silver Spring)*, 2016 24(1): p. 250–61. [PubMed: 26637991]
138. Willmer M, et al., Surgically induced interpregnancy weight loss and prevalence of overweight and obesity in offspring. *PLoS One*, 2013 8(12): p. e82247. [PubMed: 24349234]

Figure 1:

Bariatric surgery results in a variety of changes in the body. These nutrient, hormone and molecular changes can drive pregnancy complications independent of surgery. Therefore it is conceivable that in the context of pregnancy, these changes are problematic