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Δ/ντς: Φ. Καλφαρέντζος

Η ΕΓΚΥΜΟΣΥΝΗ ΜΕΤΑ ΤΗ ΧΕΙΡΟΥΡΓΙΚΗ
ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΠΑΧΥΣΑΡΚΙΑΣ:
ΘΡΕΠΤΙΚΗ ΚΑΤΑΣΤΑΣΗ ΚΑΙ ΕΚΒΑΣΗ

Nancy Clark Mead
Κλινικός Διαιτολόγος-Διατροφολόγος

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ΠΑΤΡΑ 2014
PREGNANCY FOLLOWING BARIATRIC SURGERY:
NUTRITIONAL STATUS AND OUTCOME

Nancy Clark Mead
Clinical Dietitian-Nutritionist

DOCTORAL DISSERTATION

PATRA 2014
ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

1. Φώτιος Καλφαρέντζος, Καθηγητής Χειρουργικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.

2. Θεόδωρος Αλεξανδρίδης, Καθηγητής Ενδοκρινολογίας-Παθολογίας του Ιατρικού Τμήματος Πανεπιστημίου Πατρών.

3. Γεώργιος Κουρούνης, Ομότιμος Καθηγητής Γυναικολογικής-Μαιευτικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.

ΕΠΤΑΜΕΛΗΣ ΕΞΕΤΑΣΤΙΚΗ ΕΠΙΤΡΟΠΗ

1. Φώτιος Καλφαρέντζος, Καθηγητής Χειρουργικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.

2. Θεόδωρος Αλεξανδρίδης, Καθηγητής Ενδοκρινολογίας-Παθολογίας του Ιατρικού Τμήματος Πανεπιστημίου Πατρών.

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4. Γεώργιος Δεκαβάλας, Καθηγητής Γυναικολογικής-Μαιευτικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.

5. Μιχάλης Σταυρόπουλος, Καθηγητής Χειρουργικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.

6. Γεώργιος Αντωνάκης, Αναπληρωτής Καθηγητής Γυναικολογικής-Μαιευτικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.

7. Βασίλειος Παπαδόπουλος, Επίκουρος Καθηγητής Γυναικολογικής-Μαιευτικής του Ιατρικού Τμήματος του Πανεπιστημίου Πατρών.
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Introduction

Obesity has reached epidemic proportions worldwide and affects people of all ages. The impact of obesity on health is profound as obesity is associated with multiple comorbid conditions. Of particular concern is the fact that the obesity epidemic continues to spiral in an upward trend and a vicious cycle of obesity has been created where obese mothers give birth to obese daughters who become obese adults. Thus obesity is passed on from generation to generation. Much research is being devoted to trying to find ways to stop this vicious cycle of obesity, and the most logical place to start is where it all begins, in the intrauterine environment.

More and more obese women of reproductive age are undergoing bariatric surgery as a permanent solution for sustained weight loss. This means that there will be an increasing number of pregnancies following surgery in the years to come, and we as health professionals must be prepared in order to ensure the best possible outcomes for both mother and child. To this end many studies have appeared in recent years investigating pregnancy outcomes after surgery, and even though most studies indicate positive effects of surgery on the incidence of metabolic complications during pregnancy, there are increasing concerns regarding the possibility of compromised nutritional status of the mother with ensuing adverse consequences in the offspring including intrauterine growth restriction. Therefore, larger and more scrutinizing studies are essential in order to determine potential problems and specific strategies for nutritional management of this extremely sensitive patient group and possible implications for future generations.

This is what provided the inspiration for the present dissertation.
Part I.

Background and Literature Review
I. 1. Definition and classification of obesity

Obesity is a complex multifactorial chronic disease that develops from an interaction of genotype and the environment\(^1\). Our understanding of how and why obesity develops is incompletely understood but involves the integration of social, behavioral, cultural, physiological, metabolic and genetic factors.

Overweight and obesity is defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that presents a risk to health. The most frequently used index for defining obesity is the Body Mass Index (BMI), which is the ratio of body weight in kilograms to height in meters squared (kg/m\(^2\)). As BMI increases so do the health risks and thus, the clinical significance of obesity. All overweight and obese adults (age 18 yrs or older) with a BMI of ≥ 25 are considered at risk\(^1\). At BMI levels of 25-29.9 and 30-34.9, fat distribution as measured by waist circumference, which is the most sensitive index of visceral obesity, is also used to determine relative health risk. The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors including the metabolic syndrome. Waist circumference thus provides a clinically acceptable measurement for assessing a patient’s abdominal fat content and can identify up to 46% of subjects likely to develop metabolic syndrome within the next 5 years\(^2\). High risk cut off points for waist circumference in men and women are >102 cm and > 88 cm, respectively. Classification of obesity based on BMI, waist circumference and associated disease risk is shown in Table 1.

Table 1. Classification of overweight and obesity by BMI, Waist Circumference and Associated Disease Risks\(^1\)

<table>
<thead>
<tr>
<th>Classification of overweight and obesity by BMI, Waist Circumference and Associated Disease Risks</th>
<th>Classification of overweight and obesity by BMI, Waist Circumference and Associated Disease Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m(^2))</td>
<td>Obesity Class</td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0 – 34.9</td>
</tr>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Obesity</td>
<td>35.0 – 39.9</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>≥ 40</td>
</tr>
<tr>
<td></td>
<td>III</td>
</tr>
</tbody>
</table>

*Disease risk for type 2 diabetes, hypertension, and CVD.
I. 2. Prevalence of obesity

I.2.1. Worldwide

Obesity has reached epidemic proportions worldwide and affects people of all ages. The alarming increase in the prevalence of obesity worldwide has led the World Health Organization (WHO) to consider obesity as one of the most serious global health problems of the 21st century\(^3\text{,}^{,4}\). The most recent IASO (International Association for the Study of Obesity)/IOTF (International Obesity Task Force) analysis (2010) estimates that ~ 1.0 billion adults are currently overweight and a further 475 million are obese. Furthermore, IASO/IOTF estimate that up to 200 million school aged children worldwide are either overweight or obese, of whom 40-50 million are classified as obese\(^5\).

Especially alarming is the increase in childhood obesity and in metabolic disease among children including infants\(^6\). According to recent studies, 12% of children are in the 97th percentile for weight, 17% are in the 95th percentile, and 32% are in the 85th percentile\(^7\). Of greatest concern is that almost 10% of infants are above the 95th percentile for body weight\(^7\).

I.2.2. United States

In keeping with worldwide trends, the prevalence of obesity in the United States has increased dramatically over the past 25 years,\(^8\) and obesity continues to be a major public health problem. Nearly two-thirds of the U.S. population is overweight\(^9\) with over 1/3 of the adult population aged 20 years and over considered to be obese in 2009-2010\(^{10\text{,}11}\). Furthermore, among adolescents aged 12-19 years of age, obesity has tripled over the last 3 decades, increasing from 5.0% to 17.6%\(^{12}\).

Although overall obesity rates have plateaued in the US, rates of severe obesity are still increasing and there are now approximately 15 million people in the US with BMI \(\geq 40\text{kg/m}^2\)\(^{10}\). Based on self-reported data from The Behavioral Risk Factor Surveillance System, the incidence of morbid obesity has been increasing at an even more rapid rate than that of obesity. From 2000 to 2005, reports of obesity increased by 24%, but those reporting BMI >40 increased by 50% and BMI >50 by 75%\(^{13}\).

I.2.3. Europe

IASO/IOTF reports that in the European Union’s 27 member states ~ 60% of adults and > 20% of school-aged children are overweight or obese\(^5\). This equates to ~
260 million adults and > 12 million children overweight or obese. IOTF data show a frequency of 10-27% in males and up to 38% in females, and the prevalence of obesity varies among countries. Some countries, including Finland, Greece, Cyprus, the Czech Republic, Slovenia and Malta have rates even higher than those in the US. IOTF/IASO data from Greece for the years 2001-2003 show obesity to be present in 27.9% of men and 25.6% of women.

I.2.4. Women of reproductive age

The obesity epidemic, particularly its impact on children and adolescents, has resulted in an increasing number of obese reproductive-aged women (14). The recent National Health and Nutrition Examination Survey found that in the US, more than 1/3 of women are obese, > ½ of pregnant women are overweight or obese, and 8 % of reproductive-aged women are extremely obese (BMI ≥ 40) (15). In 2009, 26% of US adult women reported a body mass index (BMI) in the obese range (≥ 30kg/m²) (16) and, inevitably, the number of women entering pregnancy in obese status is also increasing (17). According to WHO, the prevalence of obesity in pregnancy ranges from 1.8-25.3% (4) and affects at least 1 in 5 pregnancies (18). In the United States, the incidence of obesity among pregnant women ranges from 18.5% to 38.3%, according to the cohort studied and the cutoff point used to define overweight (19). Pregravid overweight is therefore one of the most frequent high-risk obstetric situations. In the UK half of all women of childbearing age are either overweight or obese (20), with 18% being obese at the start of pregnancy (21). A survey performed in Greece in 1983 and again in 1998 showed the incidence of overweight and obesity before pregnancy to be 12% and 2.1% in 1983 and 15.3% and 4.7% respectively in 1998 (17) with an overall prevalence of obesity among adult women of 15-20% and a rising trend of obesity in adult women over the last decades (22,23).
I.3. Health Impact of Obesity

I.3.1. General

Obesity has been associated with an increased hazard ratio for all-cause mortality \(^{(24)}\), as well as significant medical and psychological co-morbidity. Indeed, obesity is not only a chronic medical condition but should be regarded as a bona fide disease state \(^{(25)}\). All overweight and obese adults with a BMI of \(\geq 25\) are considered at risk for the development of obesity-related comorbidities \(^{(1)}\).

Many of the complications of obesity are thought to be mediated in part by inflammation and its sequelae \(^{(26)}\). Obesity is associated with a metabolic environment characterized by multiorgan inflammation, insulin resistance, hyperlipidemia and vascular dysfunction \(^{(6)}\). Insulin resistance and consequent hyperinsulinemia can result in such conditions as hypertension, hyperlipidemia, degenerative heart disease, hyperuricemia and glucose intolerance or diabetes type 2. Hyperleptinemia, increased PAI-1 concentrations, micro- or macro-proteinuria and endothelium dysfunction have also been reported. This group of disorders has been collectively described as “metabolic syndrome” \(^{(3)}\).

Other obesity associated diseases include cardiovascular disease (CVD) and cardiac dysfunction, venal insufficiency or venous stasis disease, respiratory diseases such as obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (OSA + OHS), asthma; nonalcoholic fatty liver disease (NAFLD); myoskeletal disorders, osteoarthritis, gastrointestinal disorders such as gastroesophageal reflux disease (GERD), gallstones; reproductive disorders and gynecological abnormalities, and some of the most common cancers including breast and colon cancer; severe urinary incontinence; debilitating arthritis; and severely impaired quality of life \(^{(1,27)}\). An even more disturbing trend is the dramatic increase in metabolic disease among children, including infants \(^{(6)}\) as being obese in early childhood strongly predicts a life time of health problems in adults including CVD and DB \(^{(28-31)}\).

Among the health problems associated with obesity those related to reproduction include sexual dysfunction, infertility, adverse maternal and fetal complications as well as adverse neonatal and childhood outcomes. The heightened inflammatory response of obesity may also be involved in mediating adverse clinical outcomes during pregnancy where this metabolic environment of inflammation and insulin resistance presents a challenge to both mother and the developing fetus.
I.3.2 Obesity and Reproductive Health

The relationship between obesity and reproductive function is complex and incompletely understood. However, it is well established that obesity before and during pregnancy constitutes a major risk factor for both maternal and fetal complications \(^{(32,33)}\).

**Obesity before pregnancy**

**Fertility status and sexual function**

Obese women have reduced fertility as compared to women with normal body weight, this being observed in both natural conception \(^{(34,35)}\) and conception achieved by assisted reproduction techniques (ARIs) \(^{(36)}\). They also require higher doses of gonadotrophins and more days of ovarian stimulation to achieve desired pregnancy rates when receiving infertility treatments \(^{(35)}\). Subfertility observed in obese women is partly attributed to the decrease in frequency or complete absence of ovulation \(^{(32,33)}\), the prevailing cause of which is polycystic ovary syndrome (PCOS), which is characterized by central visceral obesity in 40\% of cases \(^{(37)}\). Obesity also potentially adversely affects the endometrium, implantation and early fetal development \(^{(14)}\). The impact of adipose and enteric signaling on reproductive function has been addressed in a recent review by Gosman et al \(^{(14)}\), which provides preliminary insight into the roles of the 2 largest endocrine organs, bowel and adipose tissue, as potential signal mediators between energy balance and female reproduction. Adverse reproductive sequelae and alterations in the hypothalamic-pituitary-ovarian (HPO) axis are recognized in obese women \(^{(38-42)}\) including longer and more irregular menstrual cycles, as well as decreased reproductive hormone excretion and corpus luteum function.

**Obesity during pregnancy**

Overweight and obese women, as well as normal weight women with excessive weight gain during pregnancy, are at increased risk of several pregnancy complications, including gestational diabetes mellitus (GDM), gestational hypertension, pre-eclampsia, thromboembolism, and cesarean delivery \(^{(8,43-47)}\). Maternal obesity also confers an increased risk of fetal growth abnormalities and birth defects, intrauterine growth restriction, macrosomia and fetal death, as well as increased risks for the future health of the child \(^{(3,6,8)}\). It must also be stressed that all of these risks increase as the degree of obesity increases, and even small increments in weight gain can make a difference.
Unfortunately, women who are overweight before pregnancy are far more likely to exceed the weight gain recommendations during pregnancy and to expect an even greater risk of adverse complications (48). Some of the adverse obstetric complications associated with obesity are outlined below:

1. Maternal complications

   a. Miscarriage

   Although excess bodyweight has been correlated with increased risk for first trimester miscarriage, the results of various studies are controversial and far from being conclusive (46,49,50). Nevertheless, at least 3 cohort studies suggest that obesity is an independent risk factor for spontaneous abortion among women who undergo fertility treatment (49,51,52) as well as women who conceive naturally (50).

   b. Metabolic disorders

   **Gestational Diabetes**

   Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that begins or is first recognized during pregnancy. GDM affects 3-10% of pregnancies, representing >200,000 cases annually in the U.S. (33,53). The risk of GDM is higher among women who are obese, and the recent dramatic increase in obesity prevalence in the U.S. mirrors a worrisome rise in the prevalence of GDM (54). Future individual health and societal medical costs could be substantial as obesity and GDM not only increase the risk of adverse pregnancy and infant outcomes (55,56) but are also associated with a higher risk of developing type 2 diabetes later in life in both the mother and child (57-59).

   Although many factors contribute to the onset of GDM, such as ethnic origin, age and family history, obesity constitutes an independent risk factor as the incidence of GDM is 2- to 3-fold higher in obese and overweight as compared to normal weight women (33). Based on a recent meta-analysis (54), the unadjusted ORs of developing GDM were 2.14 (95% CI 1.82–2.53), 3.56 (3.05–4.21), and 8.56 (5.07–16.04) among overweight, obese, and severely obese women, respectively, compared with normal-weight pregnant women. Similarly, in a recent prospective multicentre study of > 16,000
patients, a BMI of 30-39.9 was associated with an increased risk of GDM compared to women with BMI < 30 (odds ratio OR, 2.6 and 4.0, respectively) (8,37). Moreover, obesity and diabetes play independent roles in determining fetal size with obese women as well as women with GDM at increased risk for fetal macrosomia.

Hypertensive disorders

During pregnancy obese women face an increased risk of developing hypertension and pre-eclampsia. Gestational hypertension is defined as systolic blood pressure of 140mm Hg or greater or diastolic blood pressure of 90mm Hg or greater with onset after 20 weeks’ gestation (60). Obese parturients are 2.5-3.2 times more likely to develop a hypertensive disorder during pregnancy than normal weight pregnant women (46). Gestational hypertension is associated with marked changes in renal function that may lead to excessive extracellular fluid retention. About 25% of women with gestational hypertension will develop preeclampsia, which is characterized by proteinuria (>300 mg in a 24-hour urine sample). Specifically, women with BMI >30 have a 2- to 3-fold higher risk for developing pre-eclampsia, while morbidly obese women (BMI≥40) are 3.3 times more prone to developing pre-eclampsia, and this risk doubles for an increase in BMI prior to pregnancy by 5-7 kg/m2 (3,46,61). Of further note is that pre-eclampsia is associated with increased risk for coronary heart disease in later life (62). Preeclampsia accompanied by grand mal seizures is a condition called eclampsia (60) which is also more prevalent in obese women.

c. Thromboembolism

Pregnancy per se constitutes a prothrombotic state characterized by an increase in platelet concentration of coagulation factors I, VII, VIII and X, a decrease in protein S and inhibition of fibrinolysis (63). These changes in combination with other risk factors, such as advanced maternal age, high parity, cesarean section, pre-eclampsia and obesity, result in increased risk for venous thrombosis. According to several studies, obesity (BMI>30kg/m2) doubles the risk of thrombosis by increasing the concentration of factors VIII and IX, but not of fibrinogen (64).
d. Preterm delivery

Current evidence indicates that obesity during pregnancy may lead to an increase in induced preterm delivery, in particular of very pre-term (<32 weeks) infants (43,65), but not spontaneous preterm birth (66), which is usually encountered in women with low BMI (67,68). Nevertheless, the data are still inconclusive (69). Although some studies have reported a higher rate of preterm delivery for obese women, one large study of >2900 obese women showed that pre-pregnancy obesity was actually associated with a lower rate of spontaneous preterm birth (66).

e. Cesarean delivery

Studies suggest a 2-fold increase in the risk for cesarean section in obese women even without additional risk factors (33). A recent multicenter study (47) showed CD rate to be 20.7% in women with BMI < 30, 33.8% in women with BMI 30-34.9, and 47.4% with BMI 35-39.9. C-section in this group is of great concern, as women who are overweight or obese are more susceptibility to perioperative complications, such as excessive blood loss, deep venous thrombosis, wound infection, endometritis, postpartum urine infection as well as increased operative time and difficulties in anesthesia management, especially in the presence of sleep apnea (8). Fetal macrosomia increases the risk for cesarean delivery or, increased vaginal lacerations with vaginal delivery (70). Other potential intrapartum complications include difficulty estimating fetal weight (even with ultrasonogram) and inability to obtain interpretable external fetal heart rate and uterine contraction patterns (8).

2. Fetal complications

Maternal obesity is associated with increased risk for perinatal mortality, fetal growth abnormalities, including intrauterine growth restriction and macrosomia, and occurrence of genetic disorders (3,6,8,33,65,71-73). In the metabolic environment of the obese gravidae, the fetoplacental unit develops under conditions of both excess nutrients and inflammation. Because the placenta regulates nutrient flow from mother to fetus, it likely occupies a central role in mediating the adverse obstetric risks associated with pregnancy (6). The placenta is the primary organ for nutrient exchange during pregnancy, and an abnormal placental development has been associated with virtually every adverse
obstetric outcome including abnormalities in fetal growth, pre-eclampsia, preterm labor, and still birth (74-77). Obese gravidae demonstrate metabolic, inflammatory and vascular abnormalities even when there are no associated medical conditions, suggesting that obesity in and of itself is a contributor to these adverse obstetric outcomes (78). Mechanisms underlying these increased risks are incompletely understood, but insights from both animal models and humans suggest placental inflammation and placental dysfunction as possible contributing factors. The most common complications for the fetus are intrauterine death, genetic disorders and macrosomia. When counseling obese women about potential pregnancy complications, it is important to inform them of associated fetal risks including prematurity, still birth, congenital abnormalities (e.g. neural tube defects), macrosomia and childhood and adolescent obesity (8). Finally, maternal obesity results in increased admission rate of offspring to neonatal intensive care units (NICU) (33,79).

a. Fetal death

Fetal death constitutes a dramatic development of any pregnancy, especially when it takes place in late pregnancy. In some studies, an up to 5-fold increase in intrauterine death as well as increased infant mortality rate has been recorded in obese women (80). There also appears to be a correlation between maternal BMI and infant mortality rate (81). A large Swedish cohort study reported a greater risk of antepartum stillbirth among obese patients than women with BMI <20 kg/m² (65).

b. Congenital anomalies

Prenatal screening for congenital anomalies becomes problematic in obese women due to the difficulty of interpreting blood serum indices as well as the inability to display fetal anatomy on ultrasonogram (33) which lowers detection rates (82). These difficulties could, at least in part, explain the increased incidence of congenital anomalies in fetuses of obese women. Nonetheless, there are data supporting an actual association between maternal obesity and genetic disorders (79,82). Specifically, the fetuses of obese mothers have a higher risk of developing abnormalities of the neural tube, as for example spinal bifida, cardiovascular abnormalities, as well as abnormalities of the abdominal wall such as omphalocele. These abnormalities are more prevalent in offspring of women with
type 2 diabetes and folic acid deficiency, disorders that often coexist with obesity. Nevertheless, data have established that the risk of neural tube defects among obese pregnant women is double that of pregnant women of normal weight even after correcting for diabetes as a potential confounding factor \(^{(83-85)}\). Finally, it has been shown that obese women have an increased risk of delivering infants with neural tube defects regardless of folic acid supplementation, and it may be that their needs are even higher than what is now recommended; however, the benefit of administration of folic acid doses higher than 400μg/d has not been studied in obese pregnant women without diabetes \(^{(8)}\).

c. Abnormal fetal growth

**Macrosomia**

Macrosomia, also known as big baby syndrome, is usually defined as a fetus or infant that weighs above 4000 grams or 4500 grams regardless of gestational age. Large for gestational age (LGA) is defined as a weight (or length, or head circumference) that lies above the 90\(^{th}\) percentile for that gestational age. It is an indication of high prenatal growth rate and is often used synonymously with macrosomia.

The association between maternal obesity and fetal macrosomia is well established \(^{(86,87)}\). In fact, there is a linear association between maternal prepregnancy BMI and mean birth weight \(^{(88)}\). A large multicenter study in women with BMI 30-39.9 kg/m\(^2\) showed increased fetal macrosomia (OR 1.7 and 1.9) compared to BMI < 30 kg/m\(^2\) \(^{(46)}\). Multiple studies have shown that both maternal obesity and excessive weight gain during pregnancy are associated with macrosomic or LGA infants \(^{(44,86)}\). Maternal weight and insulin resistance before pregnancy affect fetal growth, as is reflected in birth weight \(^{(89)}\). Obesity and insulin resistance alter placental function, which during the last weeks of pregnancy, increases the availability of glucose \(^{(90)}\). Thus, maternal hyperglycemia induces fetal hyperglycemia and, as a consequence, hypertrophy/hyperplasia of the fetal pancreas and hyperinsulinemia. Insulin has a direct effect on cell division that leads to macrosomia. Therefore, women with diabetes are at high risk of delivering macrosomic babies. Furthermore, obese women, even with normal glucose tolerance levels, have a 2-fold higher risk of giving birth to macrosomic babies since both conditions are independently correlated to macrosomia \(^{(3)}\). Given that the incidence of obesity is approximately 10-fold that of GDM, it is evident that maternal lifestyle exerts a great
influence on the incidence of fetal macrosomia. Once again, there seems to be a quantitative relationship between maternal BMI and risk of delivering a macrosomic/LGA neonate \(^{(86)}\). Fetal macrosomia is also associated with depressed 5-minute Apgar scores and increased rates of admission to NICU \(^{(91)}\). Furthermore, in the long term these LGA infants are at increased risk of childhood and adolescent obesity \(^{(45,92,93)}\). Finally, macrosomia is associated with higher risk of other obstetrical events, such as shoulder dystocia, clavical fractures, and injury of the branchial plexus \(^{(33,91)}\). For these reasons, although the diagnosis of fetal macrosomia is imprecise, prophylactic cesarean delivery may be considered for suspected fetal macrosomia with estimated fetal weights > 5000g in women without diabetes and >4500g in women with diabetes \(^{(91)}\).

**Microsomia**

Microsomia is a term that refers to babies that are small for gestational age (SGA) or of low birth weight (LBW). SGA is defined as a weight (or length, or head circumference) that lies below the 10th percentile for that gestational age. SGA is an indication of low prenatal growth rate or intrauterine growth restriction and although is a more accurate indicator of fetal growth, is often used synonymously with LBW, which is defined as a birth weight < 2500grams regardless of gestational age. Paradoxically, the obese gravidae is at increased risk for SGA infants as well as LGA infants, both of which are associated with an increase in the risk of lifelong metabolic complications including coronary artery disease, diabetes and obesity \(^{(94-98)}\).

3. **Long-term complications**

   a. **For the mother**

   Overweight and obese women are more likely to maintain excess weight with each successive pregnancy and continue at a higher weight throughout their lifetime \(^{(48,67,68,99)}\) thus increasing their risk for serious lifelong health problems. One important example of this is that women who develop gestational diabetes have a 50% likelihood of developing type 2 diabetes within the 10 years following their pregnancy.
b. For the offspring

Maternal obesity in and of itself irrespective of neonatal birth weight constitutes an increased risk for health problems in the offspring, including reduced cognitive development at early ages (11-22 months)\(^{(100)}\), as well as childhood obesity and the appearance of metabolic syndrome and CVD later in life\(^{(101-103)}\). Maternal obesity and diabetes, as well as nutritional status during pregnancy and lactation have profound long-term effects on the systems that regulate energy balance in the offspring\(^{(104)}\). Mounting evidence indicates that early programming events as well as the intrauterine environment contribute significantly to the dramatic increase in juvenile obesity and diabetes. Clinical studies have demonstrated that both pregnancy (i.e. maternal nutrition or GDM) and early post natal (i.e. diet and energy availability) environments significantly influence body weight and energy homeostasis in adulthood\(^{(105-110)}\).

Neonatal birth weight also plays a role in future health as both SGA and LGA infants are more likely to become obese and insulin resistant as adults\(^{(3,110-112)}\). There are many pathophysiological mechanisms that could help to explain this phenomenon. In addition to genetic factors, which are undoubtedly responsible to a certain degree for the tendency of both mother and child to be overweight, the impact of the environment must be taken into account since mother and child typically share the same eating habits\(^{(113)}\). Moreover, the increase in food intake during pregnancy has a quantitative effect on the fetus, promoting the development of adipose tissue\(^{(101)}\) and the increase likelihood of delivering an infant with macrosomia. A non-balanced diet during pregnancy thus contributes to abnormal fetal development which, in turn, results in increased morbidity during childhood, adolescence and adulthood, a phenomenon known as “fetal programming” or “developmental origin of adult disease”\(^{(114)}\). The fetal adjustment to the uterine environment leads to permanent changes in phenotype (i.e. physical structure, physiology and metabolism) which might not be fully functional in extra-uterine conditions. In order to explain this phenomenon, particularly the connection between fetal development and type 2 Diabetes, the hypothesis of the “thrifty phenotype” was formulated\(^{(96)}\). According to this theory, poor nutrition during intrauterine life, as reflected in LBW, results in adverse physiological or morphological characteristics (“developmental plasticity”) in certain organs (e.g. pancreas), while it respects others (e.g. brain). When the individual faces environmental changes in postnatal life, such as an increase in calorie intake, these adaptive changes are no longer favorable and lead to
In addition to type 2 diabetes, the “thrifty phenotype” hypothesis possibly accounts for such diseases as hypertension, hyperlipidemia, atherosclerosis, cardiovascular disease and stroke, their common denominator being insulin resistance. Insulin resistance also appears to be involved in the increased risk for delivery of LGA infants to obese and diabetic mothers, GDM being one of the greatest risk factors for macrosomia. These insightful observational human studies led to mechanistic animal studies showing that DNA modification during development alters future gene expression both centrally and peripherally and affects food preference, satiety, energy expenditure, spontaneous activity, and substrate storage versus oxidation.

In conclusion, maternal obesity constitutes a serious health risk for mother and fetus, the impact of which increases with the degree of obesity. The increasing prevalence of maternal obesity before and during pregnancy results in a vicious circle of obesity in subsequent generations. A systematic effort for weight reduction is imperative in order to avoid transmitting obesity from generation to generation. Achieving this goal will most likely result in a sharp decrease in fetal and neonatal morbidity and mortality and improve the outcome of offspring and of future generations. Possible relationships between maternal diet and fetal macrosomia are shown in Figure 1.

**Figure 1.** Possible relationships between maternal diet and fetal macrosomia.
I.4. Management of Obesity

Obtaining normal weight before pregnancy is an ideal goal since it is of paramount importance not only for conception but for the outcome of pregnancy, as well (119). However, treatment of obesity before pregnancy is a difficult task. Many pregnancies are not planned and, even when they are, very few women consult a specialist on how to lose weight, the main reason being that the majority of women are reluctant to postpone their family planning in order to achieve the target weight despite the fact that weight loss before pregnancy results in better chance for conception and increases the percentage of live births for obese women (32). Treatment of obesity before pregnancy is a difficult task. It is essential, however, that obese women be fully informed about the risks of obesity and the benefits of weight loss. If a woman does enter pregnancy in an obese state, weight management is of paramount importance for delivery outcome as well as maternal and neonatal health (120-121).

Obesity can be managed by both conservative and surgical means depending on whether a woman is pregnant or not. During pregnancy conservative management is, of course, the only option for obesity management. Before pregnancy, however, obesity management can also be achieved by surgical means which provide a more permanent solution to the problem (32,122), and the number of obese reproductive-aged women undergoing bariatric surgery is continually increasing (123-125).

I.4.1. Conservative Management of obesity

Conservative management of obesity includes improved lifestyle by balanced diet, physical exercise and behavior modification. In such cases a low calorie diet is recommended and although there are no specific recommendations regarding the ideal macronutrient composition, protein needs must be adequately covered (0.8-1 g/kg ideal or adjusted body weight/ day). Acceptable macronutrient distribution in adults ranges from 10-35% protein, 45-65% carbohydrates and 20-35% fat (126). The percentage of carbohydrates and fat may vary from very low fat to very low carbohydrate according to metabolic response, individual preferences and compliance. A low-calorie diet with reduced glycemic load and an adequate amount of proteins and mono-unsaturated fatty acids (MUFAs) has been shown to reduce hyperinsulinemia in 6 months (122). For most women an individualized dietary plan of 1200-1500 kcals based on sound nutrition principles is sufficient to promote the retention of lean body mass (LBM) while
facilitating weight reduction when combined with physical activity, in particular aerobic exercise, and behavior modification \(^{(125)}\). Aerobic exercise, in particular, aids in weight loss as well as retention of LBM. Finally, behavior and lifestyle modification are essential in order for weight loss to be maintained over time.

Medical treatment can be considered a second line option and includes the use of antidiabetic drugs, such as glibenclamide and metformin, which might prove to be beneficial and have not proven harmful. Other drugs which have been used include appetite suppressants such as sibutramine, a combined centrally acting serotonin-norepinephrine reuptake inhibitor, drugs which cause malabsorption of carbohydrates, such as acarbose, and orlistat, a pancreatic lipase inhibitor which leads to fat malabsorption \(^{(125)}\). Unfortunately, when drug usage stops, weight regain almost always occurs. Criteria for medical treatment include BMI \(\geq 30\)kg/m\(^2\) with no comorbidities or BMI > 27 with comorbid conditions \(^{(1)}\). Other criteria include failure to manage weight with more conservative behavioral methods, severity of associated comorbidities, absence of contraindications (such as depression or ischemic heart disease), and the need for short-term weight loss to reduce operative risk \(^{(1,125)}\). Promising pharmacology (including biological) treatments are on the horizon, but are still in the research stage \(^{(27)}\). One promising strategy in drug development for the treatment of obesity is the use of adipokine and enterokine targets, especially those that modify appetite. Agents under trial include recombinant leptin, ciliary neurotrophic factor, oxyntomodulin, peptide YY\(3-36\) and octreotide \(^{(14)}\). The endocrinologic understanding of obesity and its comorbidities has expanded greatly with the discovery of adipokines, secreted by fat, and enterokines, secreted by the gut, with a wide range of effects on metabolic processes including those on appetite, energy metabolism, insulin action, lipid metabolism, blood pressure and coagulation.

Conservative management of obesity can effectively induce 5%-10% weight loss and improve health in severely obese individuals \(^{(27,125,126)}\) resulting in cardiometabolic benefit. Unfortunately, conservative management of obesity is not effective over the long term in most cases of severe obesity, in which case surgery provides the only durable option.

During pregnancy, however, conservative management is the only option, and it is strictly recommended for overweight and obese pregnant women to limit weight gain to a minimum (7-11.5 and 5-9 kg, respectively) \(^{(119)}\). This can be achieved by a balanced diet
of high nutritional value, which results in both weight control and normal embryo growth, in combination with physical exercise, specifically aerobic exercise of medium intensity (32,127), such as ≥ 30 minutes/day of moderate walking or swimming (129), which will most likely improve fetal health (32). It has also been shown that exercise decreases the risk for developing pre-eclampsia, glucose intolerance and gestational diabetes mellitus (GDM) (130).

In 2009, the Institute of Medicine (IOM) published revised pregnancy weight gain guidelines that are based on pre-pregnancy body mass index (BMI) ranges recommended by the World Health Organization. These ranges are independent of age, parity, smoking history, race and ethnic background (119,131) and are presented in Table 2. The target range for optimum weight gain is associated with a full-term, healthy baby, weighing an average of 3.1 to 3.6 kg (132), and the pattern of weight gain appears to be even more significant than the absolute weight gain (120). It is worthy of note that recommended weight gains for overweight and obese women in pregnancy is the amount estimated to account for the weight of the fetus and the maternal support tissue. Lower gains, even in obese women, are associated with an increased risk of intrauterine growth retardation (133). On the other hand, higher gains are also associated with greater risk of adverse complications (8,43-48). Thus, the pattern as well as the total amount of weight gain should be monitored carefully by the nutrition professional, and appropriate dietary recommendations made as needed.

Unfortunately, women who are overweight before pregnancy are far more likely to exceed the weight gain recommendations during pregnancy.

Table 2. Recommendations for total and rate of weight gain during pregnancy, according to pre-pregnancy body mass index (119).

<table>
<thead>
<tr>
<th>Pre-pregnancy BMI (kg/m²)</th>
<th>Total weight gain (kg)</th>
<th>Rates of weight gain in 2nd and 3rd trimesters (kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>Underweight: &lt;18.5</td>
<td>12.5-18.0</td>
<td>0.51 (0.44-0.58)</td>
</tr>
<tr>
<td>Normal weight: 18.5-24.9</td>
<td>11.5-16.0</td>
<td>0.42 (0.35-0.50)</td>
</tr>
<tr>
<td>Overweight: 25.0-29.9</td>
<td>7.0-11.5</td>
<td>0.28 (0.23-0.33)</td>
</tr>
<tr>
<td>Obese: ≥ 30.0</td>
<td>5.0-9.0</td>
<td>0.22 (0.17-0.27)</td>
</tr>
</tbody>
</table>

Calculations assume a 0.5-2.0 weight gain in the first trimester.

20
I.4.2. Surgical Management

Although nonsurgical management of obesity can effectively induce 5-10% weight loss and improve health in obese individuals, its effects are usually very short-term since most individuals with severe obesity will regain the weight over time, and bariatric surgery has proven to be the only effective strategy for sustained weight loss among the severely obese (1,27,123,134,135). Furthermore, despite promising pharmacological treatments, bariatric surgery remains superior to nonsurgical treatments in terms of short-term benefit in surrogate markers of metabolic disease and also provides more permanent solutions to weight loss in the event that the above-mentioned measures have failed (27). An enriched evidence base, expanding eligible patient populations, and safer, innovative surgical treatments for obesity will likely result in a greater number of obese patients undergoing surgery. Despite the fact that overall obesity rates and bariatric surgical procedures have plateaued in the U.S., rates of severe obesity are still increasing and only 1% of the clinically eligible population receives surgical treatment for obesity (136). Bariatric surgery as an option for weight loss in reproductive aged women is escalating; already, the number of obese reproductive-aged women undergoing bariatric surgery has increased dramatically over the past few years. Over 80% of bariatric surgical patients are female and over half of all bariatric procedures performed in 2004 were performed in women of reproductive age (123-125).

Indications and eligibility for bariatric surgery according to the most recent AACE/TOS/ASMBS guidelines (27) are presented below:

- Patients with a BMI ≥ 40 kg/m2 without coexisting medical problems and for whom bariatric surgery would not be associated with excessive risk should be eligible for one of the procedures (Grade A; BEL 1).
- Patients with a BMI ≥35 kg/m2 and one or more severe obesity-related co-morbidities, including T2D, hypertension, hyperlipidemia, obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (a combination of OSA and OHS), nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), pseudotumor cerebri, gastroesophageal reflux disease (GERD), asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life, may also be offered a bariatric procedure.
Patients with BMI of 30-34.9 kg/m² with diabetes or metabolic syndrome may also be offered a bariatric procedure, although current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit.

There is insufficient evidence for recommending a bariatric surgical procedure specifically for glycemic control alone, lipid lowering alone, or cardiovascular disease risk reduction alone, independent of BMI criteria (Grade D).

There is also emerging data on bariatric surgery in specific patient populations, including those with mild to moderate obesity, type 2 diabetes (T2D) with Class I obesity (BMI 30-34.9 kg/m²), and patients at the extremes of age.

Before surgery a thorough preoperative evaluation is essential and should include complete medical history and physical examination, routine labs as well as levels of nutrients such as Fe, B12, folic acid and vitamin D, complete nutritional evaluation, endocrine evaluation, psychosocial-behavioral evaluation, pregnancy counseling, and informed consent. Preoperative weight loss can reduce liver volume and may help improve the technical aspects of surgery in patients with an enlarged liver or fatty liver disease and is therefore encouraged before surgery (Grade B; BEL 1; downgraded due to inconsistent results). Preoperative weight loss or medical nutritional therapy may also be used in selected cases to improve comorbidities, such as reasonable preoperative glycemic targets (Grade D) (27).

**Types of procedures and mechanisms of action**

There are currently many different types of bariatric procedures performed today which are briefly described below (27,134,137-140). As the metabolic effects of various bariatric operations become better understood, the traditional classifications of procedures as “restrictive”, “malabsorptive”, or “combination” procedures have become less functional and less widely accepted (27); however, these classifications have been used below for convenience.

**Restrictive procedures**

Restrictive procedures involve creation of a small gastric pouch, which decreases the size of the gastric reservoir, thereby reducing the amount of food that can be consumed at one time and inducing early satiety.
Restrictive procedures currently in use include:

- Laparoscopic adjustable gastric banding (LAGB): In this procedure, an inflatable silicone band is placed around the stomach near its upper end, creating a small pouch and a narrow passage into the larger remainder of the stomach (Figure 2).

- Sleeve gastrectomy (SG): This is a newer procedure shown in Figure 3, in which the stomach capacity is restricted by stapling and dividing it vertically and removing more than 85% of the stomach. Thus, part of the procedure is not reversible. The stomach that remains is relatively long and narrow and has a capacity of 50-100ml. SG has demonstrated benefits comparable to other bariatric procedures and is no longer considered investigational (141). A national risk-adjusted database positions SG between the laparoscopic adjustable gastric band (LAGB) and laparoscopic Roux-en-Y gastric bypass (RYGB) in terms of weight loss, co-morbidity resolution, and complications (142). Although SG is considered a restrictive procedure, it does involve a partial gastrectomy and therefore may work through hormonal mechanisms (e.g. grehlin) as well as the main mechanism of restriction.

- Mixed restrictive-malabsorptive procedures

  Mixed restrictive-malabsorptive procedures include a food volume restriction component as well as some degree of malabsorption.

  - Roux-en-Y gastric bypass (RYGB): In this procedure, a gastric pouch of ~15-20ml is created, thus restricting the amount of food a patient is able to consume, especially in the early postoperative phase. The degree of malabsorption varies depending on limb lengths and primarily involves micronutrients. (Figure 4)

  - Mini gastric bypass (MGB) or Single anastomosis gastric bypass: In this procedure a long narrow gastric pouch is created which restricts food volume. The degree of malabsorption depends on remaining limb lengths and includes malabsorption of micronutrients as well as some macronutrients, primarily fat. (Figure 5)
**Malabsorptive procedures**

Malabsorptive procedures alter the anatomy, bypassing segments of the gastrointestinal tract, thereby reducing the secretory and absorptive surface area necessary for nutrient utilization and metabolism. The malabsorptive procedures have a much smaller element of restriction and rely primarily on malabsorption of fat for long-term maintenance of weight loss. Malabsorption involves micronutrients as well as macronutrients, primarily fat but also complex carbohydrates and protein, as well, due to the longer length of bypassed intestine and the resultant shorter common limb of 50-100 cm.

- Biliopancreatic diversion (BPD) and variants of BPD (Fig. 6)
- Biliopancreatic diversion with duodenal switch (BPD/DS) (Fig. 7)

The hormonal mechanisms of action involved in each type of procedure are complex and beyond the scope of this dissertation. Several reviews on the relative merits of these procedures are also available. Metabolic complications involving macro- and micronutrients are more common among patients who undergo restrictive-malabsorptive or malabsorptive surgical procedures (RYGB, BPD, BPD/DS) than those who have restrictive procedures (VBG, LAGB)\(^{(134,137-140,143)}\).

Diagrams of the various procedures are shown in figures 2-7.

**Figure 2.** Adjustable gastric banding  
**Figure 3.** Sleeve gastrectomy
Figure 4. Roux-en-Y gastric bypass

Figure 5. Mini gastric bypass

Figure 6. Biliopancreatic diversion

Figure 7. Biliopancreatic diversion with duodenal switch
Choice of procedure

According to the latest AACE/TOS/ASMBS Bariatric Surgery Clinical Practice Guidelines\(^{(27)}\), the best choice for any bariatric procedure (type of procedure and type of approach) depends on the individualized goals of therapy (e.g., weight loss and/or metabolic [glycemic] control), available local-regional expertise (surgeon and institution), patient preferences, and personalized risk stratification (Grade D). At this time, there is still insufficient evidence to generalize in favor of one bariatric surgical procedure for the severely obese population (Grade D). In general, laparoscopic bariatric procedures are preferred over open bariatric procedures due to lower early postoperative morbidity and mortality (Grade B; BEL 2). Laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG), laparoscopic Roux-en-Y gastric bypass (RYGB), and laparoscopic biliopancreatic diversion BPD, BPD/duodenal switch (BPD-DS), or related procedures are primary bariatric and metabolic procedures that may be performed in patients requiring weight loss and/or metabolic control (Grade A; BEL 1). Physicians should exercise caution when recommending BPD, BPD-DS, or related procedures because of the greater associated nutritional risks related to the increased length of bypassed small intestine (Grade A; BEL 1). Investigational procedures may be considered for selected patients based on available institutional review board (IRB) approved protocols, suitability for clinical targets and individual patient factors, and only after a careful assessment balancing the importance for innovation, patient safety, and demonstrated effectiveness (Grade D).

Postoperative evaluation and follow-up

In order to ensure success after surgery, not only in terms of weight loss, but in terms of overall health, lifelong postoperative monitoring is essential, especially following malabsorptive procedures. In the early postoperative phase follow up visits are usually scheduled at one, three and six months following surgery. After this time, depending on the type of procedure, visits are usually scheduled at one year and yearly thereafter, often with additional visits after malabsorptive procedures or if any problems occur at any time. Routine postoperative follow-up schedules have been published in recent guidelines\(^{(27,140,143)}\) and include complete medical and laboratory evaluation at each visit as well as evaluation and education by a nutrition professional regarding protocol-derived staged meal progression, adequacy of nutrient intake and compliance
with supplementation guidelines. Medications may be adjusted if necessary. Routine labs include complete blood count (CBC), complete biochemical blood analysis, and measurement of the levels of specific micronutrients including folic acid, vitamin B12, and vitamin D. Bone density measurements are also recommended starting at 2 years postoperative. Weight loss is monitored at each visit and patient goals are discussed. Other parameters are evaluated as needed. Finally, when bariatric surgery is performed in women of child-bearing age, special attention must be given to the possibility of ensuing pregnancy so that necessary precautions may be taken.
I.5. Nutritional Issues and Concerns

1.5.1. Bariatric Surgery (general)

a. Preoperative nutritional concerns

Although obesity is considered a disease of macronutrient excess, micronutrient deficiency is quite common among the obese population (139-145). The two most common deficiencies reported in preoperative candidates are vitamin D and Fe. In fact, there is an inverse association between levels of 25(OH)D and BMI > 30kg/m² (146), and vitamin D deficiency has been reported in 60-80% of obese patients before surgery (143). Not surprisingly, low preoperative vitamin D levels have been reported to increase the risk for postoperative vitamin D deficiency (147). Iron deficiency has been reported in nearly 50% of preoperative patients (143,148), especially in patients of younger age. In particular, premenopausal women are at increased risk of deficiency because of menstrual losses.

Other nutrients sometimes cited as being deficient in preoperative obese patients include vitamin B₁₂, folate and thiamin (143,148-150) as well as sporadic reports of low Zn, Se, and vitamins A, E, and C (143). Considering the fact that deficiencies of these same nutrients often occur postoperatively, it is extremely important to correct them before surgery in order to ensure best possible postoperative management and outcome (143,148-150). There is general agreement that all patients scheduled for bariatric surgery should receive daily multivitamin and multitrace mineral supplements (27,138,139,140,143). Furthermore, it is recommended that appropriate laboratory tests be performed preoperatively if possible, especially for certain nutrients including iron, folate, vitamin B₁₂ and vitamin D.

b. Postoperative nutritional concerns

In order to prevent the development of nutritional deficiencies, routine postoperative supplementation and regular monitoring of nutrient levels is essential.

Short-term nutritional complications

In the immediate postoperative phase the most important nutritional concerns include adequate fluid and protein intake as well as micronutrient supplementation. During this stage the administration of liquid protein supplements is usually necessary to
meet the body’s increased needs at a time when food volume is quite small and weight loss is rapid. Under normal circumstances, nutrient deficiencies during this period are uncommon due to supplementation and previous body stores; however, since food intake is minimal, if severe gastrointestinal symptoms are present, nutritional complications can occur and require immediate attention. Perhaps the most dangerous and potentially devastating micronutrient deficiency occurring in the early postoperative phase is thiamin deficiency \(^{(138,151)}\), which occurs primarily in patients who experience persistent vomiting \(^{(152)}\). Thiamin deficiency after bariatric surgery may manifest clinically in 2 main forms—Wernicke-Korsakoff syndrome and beriberi. Wernicke encephalopathy (WE), which can occur within 1 month postsurgery \(^{(153,154)}\) is characterized by ophthalmoplegia, ataxia, and apathetic mental confusion (Korsakoff’s psychosis). Misdiagnosis and administration of intravenous dextrose without thiamin as first line of therapy can further exacerbate cytotoxicity of the brain \(^{(155)}\). Beriberi is a thiamin deficiency that can affect various organ systems, including the heart, gastrointestinal tract, and peripheral and central nervous systems. Beriberi can be divided into “wet” and “dry” forms. “Wet beriberi” is sometimes referred to as “bariatric beriberi” in this clinical setting and manifests as a high-output congestive heart failure syndrome characterized by an enlarged heart with normal sinus rhythm and dependent edema \(^{(143)}\). Thus, it is highly recommended that all patients who have previously undergone bariatric surgery and have a history of vomiting be administered 100mg of thiamin with the first bag of dextrose-free IV fluid upon presentation to an acute care setting to prevent permanent neurologic sequelae.

Other nutritional concerns in the early postoperative period include dehydration and electrolyte imbalance due to inadequate fluid intake most often aggravated by vomiting and/or diarrhea. Severe dehydration can lead to renal damage if not corrected. Protein deficiency can also occur in the early postoperative period following malabsorptive procedures if protein intake is extremely low. Early occurrences of protein malnutrition are typically due to patient-related factors such as poor eating habits, intolerance and socioeconomic status \(^{(143)}\). Finally, a frequent finding in the early postoperative period is excessive hair loss, which is observed to some degree in most patients during the third to sixth postoperative months due primarily to the stress of surgery and rapid weight loss. After weight loss stabilizes and providing that the patient adheres to nutritional guidelines, is otherwise doing well and has no genetic or pathological reason for hair loss, the problem resolves itself without extra
supplementation. In the early postoperative phase protein supplements are provided in liquid or powder form and vitamin-mineral supplements should be prescribed in liquid or chewable form for best tolerance and maximum absorption.

**Long-term nutritional complications**

To understand the potential long-term nutritional consequences of bariatric surgery, it is important to understand the anatomical differences among various procedures. Approximately 30% of bariatric surgery patients will develop a nutrition-related complication, typically a macronutrient or micronutrient deficiency or both, at some point following their operation\(^{(139)}\). Specific nutrition-related complications include anemia (Fe, folate, vitamins B\(_{12}\), A and E, Cu and Zn), metabolic bone disease (Ca, vitamin D), protein-energy malnutrition, steatorrhea, polyneuropathy and myopathy (thiamin, Cu, vitamins B\(_{12}\) and E), visual disturbances (vitamins A and E, thiamin), skin rash (Zn, EFAs, vitamin A) and a variety of potentially clinically silent micronutrient deficiencies. Overall, the most common deficiencies after bariatric surgery are Fe, Ca, vitamin D and vitamin B\(_{12}\). The etiology of most nutritional deficiencies following bariatric surgery is multifactorial, with contributions from reduced dietary intake, altered dietary choices, and malabsorption. The number and severity of the deficiencies are determined by the type of bariatric surgery performed, the dietary habits of the patient, and the presence of other surgery-related GI complications such as nausea, vomiting, or diarrhea\(^{(138-141,143)}\).

Restrictive procedures reduce the volume of food intake but do not alter the anatomy of the GI tract. Therefore, nutritional complications are less common but do occur, usually as a result of very low dietary intake, and in most cases are easily corrected by oral supplementation.

Malabsorptive procedures, on the other hand, alter the anatomy, bypassing segments of the GI tract, thereby reducing the secretory and absorptive surface area necessary for nutrient absorption, utilization and metabolism making the appearance of nutrient deficiencies more frequent and often more severe\(^{(138,139,140,143,156)}\). Table 3 shows the main sites of absorption for various nutrients.
Table 3. Sites of micronutrient absorption within the gastrointestinal tract (138)

<table>
<thead>
<tr>
<th>Site of absorption</th>
<th>Micronutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Copper, iodine</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Iron, zinc, copper, selenium, vitamins A, E, and K, thiamin, riboflavin, folate, niacin, biotin, calcium</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Zinc, selenium, iron, calcium, chromium, manganese, vitamins A, D, E, and K, thiamin, riboflavin, pyridoxine, folate, niacin, vitamin C, pantothenate</td>
</tr>
<tr>
<td>Ileum</td>
<td>Vitamins C, D, K, B₁₂, and folate</td>
</tr>
</tbody>
</table>

After operations, such as RYGB, that result in the nutrient stream bypassing the distal stomach, duodenum and proximal jejunum, malabsorption of Fe, Ca, folate and vitamin B₁₂ may be expected (139). The malabsorptive procedures, which result in the nutrient stream bypassing part of the ileum as well, place patients at additional risk of protein deficiency as well as fat-soluble vitamins, essential fatty acids, Cu and Zn.

Figure 8 shows the primary sites of absorption for various nutrients where the shaded areas indicate segments of the GI tract that are bypassed in the RYGB procedure.

Although some deficiencies may develop quickly, most are insidious in onset and may not be readily apparent clinically. Therefore, all bariatric surgery patients should adhere to lifelong vitamin and mineral supplementation and monitoring for deficiencies. It must also be noted that many over-the-counter multivitamin and mineral supplements do not provide adequate amounts of certain nutrients such as vitamin B₁₂, Fe or fat-soluble vitamins and patients will require additional doses of prophylactic supplementation life-long to maintain optimal micronutrient status (138,143).
Figure 8. The primary sites of absorption for various nutrients \(^{157}\).

**Deficiencies of specific nutrients and current recommendations for supplementation**

**Vitamin B12 and folate**

Vitamin B\(_{12}\) (cobalamin) and folate (folic acid) are both involved in the maturation of red blood cells. Over time, a deficiency in either vitamin B\(_{12}\) or folate can lead to macrocytic or megaloblastic anemia, a condition characterized by the production of fewer, but larger, immature, abnormal, undifferentiated red blood cells with a decreased ability...
to carry oxygen. Most (95%) cases of megaloblastic anemia are attributed to vitamin B₁₂ or folate deficiency (158).

**Vitamin B₁₂**

Vitamin B₁₂ deficiency is usually defined by vitamin B₁₂ levels less than 200 pg/ml and has been reported to range from 12-75% following RYGB with most studies citing approximately 35% (159-165). The incidence following BPD procedures is generally lower and ranges from 7-21% (159,166,167). Several factors precipitate deficiency of B₁₂ following gastric bypass surgery including limited intake of animal proteins due to intolerance, decreased cleavage of the vitamin from protein in foods due to a decrease in gastric secretions, and inadequate secretion and function of intrinsic factor which is necessary for absorption in the terminal ileum (139,168,169).

Because LAGB pts have an artificial restriction, yet complete use of the stomach, and BPD patients do not have as great a restriction in stomach capacity and parietal cells as RYGB pts, the reduction in HCl and subsequent vitamin B₁₂ deficiency is not as prevalent in these 2 procedures (143). A lack of B₁₂ deficiency among BPD and BPD/DS patients might also result from a better tolerance of animal proteins in a larger pouch, greater pepsin/gastric acid production to release protein-bound B₁₂, and increased availability and interaction of IF with the pouch contents (143). Finally, vitamin B₁₂ deficiency may also occur due to bacterial overgrowth in the defunctionalized ileal segment due to lack of protective digestive secretions (170).

Manifestations of B₁₂ deficiency include macrocytic anemia, leucopenia, glossitis, thrombocytopenia, paresthesia, and irreversible neuropathies (171). Neurologic sequelae, including subacute combined degeneration of the dorsal and lateral spinal columns are rare complications of vitamin B₁₂ deficiency but may occur (139). As it may take years for vitamin B₁₂ stores to be depleted, it is important to monitor levels annually, particularly in patients who have undergone procedures that exclude the lower part of the stomach (27,139,140,143). It has been demonstrated that the maintenance of B₁₂ needs can be met by the administration of pharmalogic doses of B₁₂ via oral or other nonparenteral routes (172).

The minimal dose of vitamin B₁₂ required for bariatric surgery patients is 350mcg/d and can be administered parenterally or orally (27,143). Higher doses of 1000μg and 2000μg have also been suggested for optimal hematologic and neurologic responses. Even in patients who lack gastric intrinsic factor, at high doses of 1000 and 2000μg/d, oral vitamin B₁₂ is absorbed in sufficient quantities by passive diffusion in the ileum and
is as effective as parenteral therapy in normalizing serum vitamin B$_{12}$ levels (167). Intranasal vitamin B$_{12}$ is also available. Parenteral (intramuscular or subcutaneous) B12 supplementation, 1000-3000 μg every 6 to 12 months, is indicated if B$_{12}$ sufficiency cannot be maintained using oral or intranasal routes (27,143).

**Folate**

Folate deficiency, usually defined as levels <3ng/ml, has been reported in up to 38% of gastric bypass patients (173). Most studies, however, report little or no folate deficiency even after malabsorptive procedures except in cases of non-compliance (160,165,174). The causes cited include decreased food intake, deficiency of vitamin B$_{12}$, which is required as a coenzyme to convert folate to its active form, and surgical bypass of the primary site of absorption (138,143,173). On the other hand, even though folate is primarily absorbed in the proximal segment of the intestine, after surgery it can be absorbed along the entire small intestine through adaptive mechanisms. For this reason, folate deficiency is uncommon and is generally thought to be caused by decreased intake rather than malabsorption (139). Deficiency symptoms include megaloblastic anemia, thrombocytopenia, leucopenia, glossitis, and elevated homocysteine levels (140,143,175,176). When folate deficiency is detected it is easily corrected with daily oral supplementation, usually with a multivitamin supplement alone. Folic acid supplementation (400 μg/d) should be part of a routine mineral-containing multivitamin preparation (27,143).

**Thiamin (Vitamin B$_{1}$)**

Although acute thiamin deficiency primarily occurs in the early postop period, if persistent vomiting appears later on a possible thiamin deficiency should not be ruled out. Over the long term the use of a daily multivitamin should prevent thiamin deficiency in those bariatric patients who are otherwise doing well. It has also been suggested that alterations in gut ecology and bacterial overgrowth may increase risk of thiamin deficiency Lakhani and coworkers (177).

Routine thiamine screening is not recommended following bariatric surgery, but should be considered in postbariatric surgery patients with rapid weight loss, protracted vomiting, parenteral nutrition, excessive alcohol use, neuropathy or encephalopathy, or heart failure (27). Patients with severe thiamine deficiency (suspected or established) should be treated with intravenous thiamine, 500mg/d, for 3 to 5 days, followed by 250
mg/d for 3 to 5 days or until resolution of symptoms. Mild deficiency can be treated with intravenous thiamine, 100mg/d, for 7-14 days. In recalcitrant or recurrent cases of thiamine deficiency without one of the above risks, the addition of antibiotics for small intestine bacterial overgrowth should be considered \(^\text{140,143}\).

**Fat-soluble vitamins**

Fat malabsorption is an expected consequence of the BPD as well as very very long limb (VVLL) gastric bypass procedures \(^\text{165}\). Indeed, it appears to be the principle means by which these operations promote sustained weight loss \(^\text{139,143}\). The length of the common channel regulates the degree of fat malabsorption- a channel of at least 100cm seems to be tolerated best. When fat malabsorption is severe and cannot be controlled by dietary and medical maneuvers, surgical revision may be required. After malabsorptive procedures such as the BPD and BPD/DS fat malabsorption may be as high as 72\% \(^\text{143}\).

Deficiency of fat-soluble vitamins- A, D, E, K- when they occur, typically complicate the course of patients who have undergone malabsorptive procedures who also present with other signs and symptoms of malabsorption \(^\text{139}\). As the malabsorptive effects of surgical procedures increase, so does the likelihood of fat-soluble vitamin malabsorption related to the bypassing of the stomach, absorption sites of the intestine, and poor mixing of bile salts \(^\text{143}\). Therefore, persistent steatorrhea after BPD/BPDDS should prompt an evaluation for nutrient deficiencies\(^\text{27}\).

**Vitamin D**

Vitamin D has received much attention in recent years due not only to its known health benefits on calcium and bone metabolism but to many other nonskeletal health benefits as well, including a reduction in the risk of some common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease and infectious diseases \(^\text{146}\). The primary function of vitamin D is in conjunction with calcium in bone metabolism where their roles are interdependent. Low vitamin D levels are associated with a decrease in dietary calcium absorption but are not always accompanied by a reduction in serum calcium. As blood calcium ions decrease, parathyroid hormone levels increase, and the body is induced into a state of secondary hyperparathyroidism \(^\text{178}\), which allows the kidney and liver to convert 7-dihydroxycholecalciferol into the active form of vitamin D, 1, 25-dihydroxycholecalciferol, and stimulates the intestine to increase absorption of calcium. If dietary calcium is not available or intestinal absorption is impaired by vitamin D
deficiency, calcium homeostasis is maintained by increases in bone resorption and conservation of calcium by way of the kidneys. Therefore, calcium deficiency (low serum calcium) would not be expected until osteoporosis has severely depleted the skeleton of calcium stores with a concurrent increase in the risk of pathologic fractures (146).

In addition to skeletal disorders, calcium and vitamin D deficits increase the risk of malignancies (in particular, of the colon, breast, and prostate gland), chronic inflammatory and autoimmune disease (e.g., diabetes mellitus type 1, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis) and metabolic disorders (metabolic syndrome and hypertension), as well as peripheral vascular disease (179,180).

Deficiency of vitamin D is defined as 25(OH)D levels below 20ng/ml, and insufficiency is defined as levels 20-29ng/ml. For maximum health benefits the ultimate goal is to maintain levels above 30ng/ml (146). Vitamin D status is of particular interest in patients following bariatric surgery first of all because vitamin D deficiency is found so widely in the obese population in general, and secondly, because the absorption of calcium and vitamin D is reduced after many surgical procedures. Calcium is absorbed preferentially in the duodenum and proximal jejunum, and vitamin D is absorbed preferentially in the jejunum and ileum. Therefore, malabsorption of calcium may be expected after both RYGB and BPD procedures whereas malabsorption of vitamin D is more of a concern after malabsorptive BPD/DS procedures (143).

Vitamin D deficiency has been reported in up to 50-70% of patients following malabsorptive procedures (181-183). Decreased dietary intake of calcium and vitamin D-rich foods, related to intolerance can also increase the risk of deficiency after all surgical procedures. In addition, inadequate exposure to sunlight as well as a generalized bone response to weight loss may also contribute to the development of postoperative vitamin D and calcium deficiencies (140,146,184). Semiannual monitoring of serum bone alkaline phosphatase, Ca, P, 25-(OH)D, and PTH levels is recommended as is periodic (~every 2 years) monitoring of bone density (27,139,146).

Recommendations for calcium and vitamin D supplementation to prevent bone loss in patients after bariatric surgery vary (27,140,143,146,185,186). Daily supplementation with ~1200-2000 mg of elemental calcium and 800IU-1600IU vitamin D daily is usually recommended, but more aggressive supplementation is needed if deficiency is found. Calcium is usually recommended in the citrate form for optimal absorption rather than the commonly prescribed carbonate salts because citrate is better absorbed in the absence of
stomach acid, a condition normally found after bariatric surgery. Other studies support the use of even higher doses of vitamin D than those normally recommended to facilitate maintenance of normal vitamin D status after gastric bypass \(^{(187,188)}\). Carlin et al \(^{(187)}\) reported that 50000 IU of vitamin D (ergocalciferol) in a weekly dose corrected vitamin D depletion in most gastric bypass subjects, attenuated cortical bone loss, and improved hypertension. Goldner et al \(^{(188)}\) evaluated vitamin D supplementation at 800, 2000, and 5000 IU of cholecalciferol per day in gastric bypass patients and concluded that the highest dose resulted in the best improvement of serum 25(OH) D without causing hypercalcemia. In cases of severe vitamin D malabsorption, oral doses of vitamin D2 or D3 may need to be as high as 50,000 units 1 to 3 times weekly to daily, and more recalcitrant cases may require concurrent oral administration of calcitriol (1,25-dihydroxyvitamin D) \(^{(27)}\).

Since the primary source of vitamin D is exposure to sunlight \(^{(146,189,190)}\), it could also be suggested that patients try to get at least some sun exposure on a daily basis. Furthermore, it must be appreciated that in the absence of sun exposure it is difficult, if not impossible, to obtain an adequate amount of vitamin D from dietary sources without supplementation to satisfy the body’s requirement.

**Vitamin A**

Vitamin A deficiency has been reported 11-53% of patients following RYGB \(^{(191,192)}\) and 50-70% of patients following BPD procedures with an increasing incidence over time \(^{(181)}\). Numerous factors contribute to a high risk of vitamin A deficiency in gastric bypass surgery patients including oxidative stress, lipid malabsorption, insufficient intake of lipids and food sources of vitamin A, and presence of nonalcoholic fatty liver disease \(^{(193)}\). Rare cases of night blindness and xerophthalmia have been reported in biliopancreatic bypass and gastric bypass patients who failed to take vitamin supplements \(^{(194,195)}\). Routine screening for vitamin A deficiency, which may present as ocular complications, is recommended after purely malabsorptive bariatric procedures, and supplementation alone or in combination with other fat-soluble vitamins (D,E, and K) may be indicated in this setting \(^{(27)}\).

**Vitamin E**

Research on vitamin E status in bariatric surgery subjects is sparse but symptomatic deficiency is uncommon. At 1-4 y after gastric bypass surgery, 4-22% of
subjects have been found to have low serum vitamin E levels\(^{(174,196)}\), but no clinical manifestations of deficiency were reported\(^{(174,181,197)}\). Hematologic abnormalities or visual disturbances may be seen in vitamin E deficiency, which is easily corrected with oral supplements if detected.

**Vitamin K**

In addition to its role in blood clotting, Vitamin K has an additional role in regulation of osteocalcin and bone formation. Low plasma levels of vitamin K have been reported in up to 50% of subjects 3 years after gastric bypass, but no clotting abnormalities were indicated\(^{(138)}\) and up to 68% 4 years after malabsorptive surgery\(^{(181)}\). Sources of vitamin K are either diet or bacterial production in the colon, both of which can be affected after bariatric surgical procedures. Bruising and bleeding may be seen in vitamin K deficiency. In the clinical setting, vitamin K should be supplemented orally or im when INR values rise above 1.4, as the measurement of vitamin K levels and effects on vitamin K induced proteins are research procedure\(^{(140)}\).

**Deficiency of trace minerals**

Several trace element deficiencies have been identified after bariatric surgery, as the main sites of nutrient absorption are bypassed. The most common trace mineral deficiencies are of Fe, primarily in premenopausal women, followed by zinc, copper and selenium.

**Iron**

Iron deficiency is defined as a decrease in the total iron body content and is usually defined by low iron levels in combination with low ferritin levels as well as low hemoglobin and hematocrit values although exact values indicating deficiency seem to vary\(^{(143)}\). Iron deficiency anemia occurs when erythropoiesis is impaired as a result of the lack of iron stores, and is a common postoperative finding in the bariatric surgery setting\(^{(143)}\). Iron deficiency has been reported in 20-49% of patients following RYGB\(^{(162,165,198-202)}\), and development of microcytic anemia secondary to Fe deficiency ranges from 17 to 50%\(^{(144,203)}\). Other factors which play a role in the development of Fe deficiency are female gender, young age, poor preoperative iron status, vitamin B\(_{12}\) deficiency, and time after surgery\(^{(198)}\). Risk increases over time; in fact, iron deficiency and subsequent anemia
may develop years after the surgery. Skroubis et al.\textsuperscript{(165)} studied gastric bypass patients postoperatively for 5 y and documented increasing Fe deficiency with low ferritin levels.

The pathogenesis of Fe deficiency following bariatric surgery is multifactorial, including decreased production of hydrochloric acid in the stomach, which is necessary for dietary Fe in the ferric form to be converted to ferrous state, reduced intake of Fe-rich foods, particularly red meat, which is poorly tolerated after bariatric surgery, and decreased absorption due to bypassing of duodenum and proximal jejunum which are the primary sites of Fe absorption\textsuperscript{(138,143)}. Occasionally, occult or overt blood loss from a gastrointestinal source such as anastomotic ulcer may also contribute. This possibility should be considered particularly if deficiency is difficult to correct. When deficiency is severe, blood transfusion may be needed\textsuperscript{(198)}.

Anemia without evidence of blood loss warrants evaluation of nutritional deficiencies, as well as age appropriate causes during the late postoperative period, and iron status should be monitored in all bariatric surgery patients\textsuperscript{(27)}. In the absence of anemia, iron deficiency is usually asymptomatic. Fatigue and a diminished capacity to exercise, however, are common symptoms of anemia, and patients after RYGB are routinely recommended to take prophylactic oral iron supplements\textsuperscript{(204)}. Treatment regimens include oral ferrous sulfate, fumarate, or gluconate to provide up to 150-200 mg of elemental iron daily. Unfortunately, even upon correct administration of iron tablets, oral replacement therapy (usually with up to 300mg of elemental iron per day in three or four iron tablets)\textsuperscript{(143)} often fails to correct the deficiency in a large proportion of patients\textsuperscript{(137,205-207)}. Taking Fe supplements between meals with food sources containing vitamin C will enhance absorption\textsuperscript{(143)}. However, some patients may require intravenous Fe in the form of iron-dextran or iron-sucrose (ferric gluconate or ferric sucrose) several times a year to prevent microcytic anemia if oral treatment is ineffective\textsuperscript{(198,205)}. Appropriate follow-up of hematological and iron parameters is needed to ensure Fe is adequately replaced and that oral supplementation is effective in maintaining iron status, especially in menstruating women, pregnant women and adolescents\textsuperscript{(137,143,205-208)}.

Nutritional anemias resulting from malabsorptive bariatric surgical procedures might also involve deficiencies in vitamin B\textsubscript{12}, folate, protein, copper, selenium, and zinc and should be evaluated when routine screening for iron deficiency anemia is negative.
**Zinc**

Zinc (Zn) deficiency has also been reported in postoperative bariatric surgery patients (209). Zn deficiency is most often a result of malabsorption as Zn is absorbed in the duodenum and proximal jejunum and is dependent on fat for absorption (181). Manifestations of Zn deficiency include hair loss, pica, significant dysgeusia, diarrhea, emotional disorders, weight loss, intercurrent infection, bullous-pustular dermatitis, and hypogonadism and erectile dysfunction in males (150). Routine screening for zinc deficiency should be performed after malabsorptive bariatric surgical procedures and Zn should be routinely supplemented following BPD and BPD/DS (27).

**Copper**

Copper (Cu) is essential for the production of red blood cells, and for the maintenance of the structure and functioning of the nervous system. Cu deficiency in adults can manifest in hematologic and neurologic symptoms, the most common being normocytic anemia and myeloneuropathy (210,211). Cu malabsorption may be expected after bariatric surgery since it is primarily absorbed in the stomach and proximal duodenum. Copper supplementation (2mg/d) should be included as part of routine multivitamin with mineral preparation. Routine copper screening is not indicated following bariatric surgery but should be evaluated in patients with anemia, neutropenia, myeloneuropathy, and impaired wound healing. In severe deficiency, treatment can be initiated with IV copper (2 to 4 mg/d) for 6 days. Subsequent treatment or treatment of mild to moderate deficiency can usually be achieved with oral copper sulfate or gluconate 3 to 8 mg/d until levels normalize and symptoms resolve. Patients being treated for zinc deficiency or using supplemental zinc for hair loss should receive 1 mg of copper for each 8 to 15 mg of zinc as zinc replacement can cause copper deficiency (27).

**Selenium**

There is insufficient evidence to support routine selenium screening or supplementation after bariatric surgery. However, selenium levels should be checked in patients with a malabsorptive bariatric surgical procedure who have unexplained anemia or fatigue, persistent diarrhea, cardiomyopathy, or metabolic bone disease (27).
Macronutrient deficiencies

Protein

Protein-energy malnutrition is one of the most serious nutritional complications of bariatric surgery. This complication may be a consequence of reduced intake of high protein foods such as red meat, which is poorly tolerated after bariatric surgery, or the development of other GI problems such as anorexia, nausea and diarrhea, that result in poor oral intake of energy as well as micro and macronutrients. Signs and symptoms of protein-energy malnutrition include excessive weight loss, alopecia (hair loss), muscle wasting and edema. Protein malnutrition may be difficult to diagnose; however, diminished visceral protein markers such as serum levels of albumin and pre-albumin may be helpful. It is important to recognize, however, that in the acutely ill patient, levels may be low due to their acute-phase reactant property. Protein malnutrition usually occurs during the first or second postoperative year after malabsorptive procedures, but may also be seen following other bariatric operations in patients with dysfunctional eating habits or protracted vomiting.

Protein deficiency is usually defined as serum albumin < 3.5 g/dl and severe protein deficiency as serum albumin < 2.5 g/dl. Mild protein deficiency is easily corrected with increased protein in the diet and nutritional education. Severe deficiency requires additional protein supplements and may require hospitalization and administration of enteral or parenteral nutrition. Severe protein malnutrition is also usually accompanied by anemia and micronutrient deficiencies as well as hepatic insufficiency in some cases.

Strong evidence cannot be found in the literature to support the theory that the malabsorptive components of bariatric surgery alone cause protein deficiency. Protein malnutrition (PM) is usually associated with other contemporaneous circumstances that lead to decreased dietary intake, including anorexia, prolonged vomiting, diarrhea, food intolerance, depression, fear of weight regain, alcohol/drug abuse, socioeconomic status, or other reasons that might cause a patient to avoid protein and limit caloric intake. All postoperative patients are, therefore, at risk of developing primary PM and/or protein-energy malnutrition (PEM) related to decreased oral intake. BPD and BPD/DS patients are at risk of secondary PM/PEM because of the greater degree of malabsorption produced by these procedures. After the second postoperative year, the frequency of
severe protein deficiency decreases possibly due to increased intake of animal protein foods after the initial phase of anorexia, nausea and intolerance. The pathogenesis of PM after BPD is multifactorial. Operation-related variables include stomach volume, intestinal limb length, individual capacity of intestinal absorption and adaptation, as well as the amount of endogenous nitrogen loss. Patient-related variables include customary eating habits, ability to adapt to the nutrition requirements, and socioeconomic status. Early occurrences of PM are typically due to patient-related factors, and recurrent late episodes of PM are more likely to be caused by excessive malabsorption as a result of surgery. Correction in these cases typically requires elongation of the common limb (212). By varying the length of the intestinal limbs and common channel, protein malabsorption can be increased or decreased (167). Whether or not intestinal adaptation plays a role and to what extent is unknown (143). However, after BPD procedures protein malabsorption may be as high as 25-30% (213). Thus, protein intake and nutritional status must be monitored life-long in these patients.

Protein deficiency is not common after RYGB (160,162,165,214,215), but following BPD, the incidence is reported to range from 4-21% (167,216-218). In severe cases, treatment may require enteral nutrition of parenteral nutrition supplementation, revision, or even reversal of the surgery (139,140,216). Recommendations for protein intake after surgery vary and should be individualized depending on patient body weight as well as the type of operation and the postoperative phase. Signs and symptoms of nutrient deficiencies as well as diagnosis and treatment are presented in Table 4 and the latest recommendations for nutritional supplementation of patients after different types of bariatric surgical procedures are shown in Table 5.
<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Symptoms</th>
<th>Diagnosis/ Confirmation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Weakness, decreased muscle mass, brittle hair, generalized edema</td>
<td>Serum albumin and prealbumin levels, serum creatinine</td>
<td>1st phase: Protein supplements 2nd phase: Enteral or parenteral nutrition, reversal of surgical procedure</td>
</tr>
<tr>
<td>Folate</td>
<td>Macrocytic (megaloablastic) anemia, cheilosis, glossitis, palpitations, fatigue, neural tube defects</td>
<td>Blood cell count, elevated MCV, decreased RBC folate, decreased folic acid levels, increased homocysteine</td>
<td>Oral folate 400 µg/d (included in multivitamin) Abstinence from alcohol Oral folate 1000 µg/d Up to 5 mg/d may be needed with severe malabsorption &gt; 1000µg/d can mask hematologic effects of B12 deficiency</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Pernicious anemia/ megaloblastic anemia, paleness with slightly icteric skin and eyes, tingling in fingers and toes, fatigue, vertigo, tinnitus, sore tongue, ataxia, depression, irritability, dementia, psychosis</td>
<td>Blood cell count, elevated MCV, low serum B12 levels</td>
<td>JCEM- 1st phase: Oral crystalline B12, 350µg/d/ 2nd phase: 1000-2000 µg/ 2-3 months im Aills-1000ng/wk IM for 8 wks, then 1000µg/no for life or 350-500 µg oral crystalline B12</td>
</tr>
<tr>
<td>Thiamin (B1)</td>
<td>Anorexia, gait ataxia, paresthesia, muscle cramps, irritability Wet beriberi: high output heart failure with dyspnea due to peripheral vasodilatation Dry beriberi: symmetric motor and sensory neuropathy with pain, paresthesia, loss of reflexes Wernicke-Korsakoff syndrome</td>
<td>Decreased serum or urinary thiamin excretion, decreased RBC transketolase</td>
<td>With hyperemesis parenteral doses of 100 mg/d for first 7 d, followed by daily oral doses of 50mg/d until complete recovery; simultaneous therapeutic doses of other water-soluble vitamins; magnesium deficiency must be treated simultaneously</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Epithelial changes, atrophic glossitis, neuropathy with severe deficiency, depression, confusion, microcytic, hypochromic anemia, platelet dysfunction, hyperhomocysteinemia</td>
<td>Decreased plasma pyridoxal phosphate, complete blood count, increased homocysteine</td>
<td>Vitamin B6 50 mg/d; 100-200 mg if deficiency related to medication use</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Xerophtalmia, loss of nocturnal vision, decreased immunity</td>
<td>Decreased vitamin A levels- critical range plasma retinol &lt;100µg/dL</td>
<td>1st phase: Oral vitamin A 5000-10000 IU/d 2nd phase: Oral vitamin A- 5000 IU/d</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Hypocalcemia, rachitic tetany, tingling, cramping, metabolic bone disease- osteomalacia</td>
<td>Decreased 25(OH)D levels &lt; 20-30 mg/ml, increased PTH, increased ALP, decreased or normal serum Ca</td>
<td>JCEM: 1st phase: Oral vitamin D 50000 IU/d 2nd phase: Calcitriol ? oral vitamin D 1000 IU/d Aills: 50000IU/wk D2 orally or IM for 8 wks</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Hyporeflexia, gait disturbances, ophthalmoplegia, RBC hemolysis, neurologic damage, nyctalopia, muscle weakness</td>
<td>Decreased plasma α-tocopherol</td>
<td>Optimal dose not clearly identified. Potential antioxidant benefits with 100-400 IU/d</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Hemorrhage from deficiency of prothrombin and other factors, easy bruising, bleeding gums, delayed blood clotting, osteoporosis</td>
<td>Increased prothrombin time, reduced clotting factor, increased partial thromboplastin time</td>
<td>Parenteral dose of 10mg. For chronic malabsorption, 1-2mg/d, orally or 1-2mg/wk parenterally</td>
</tr>
<tr>
<td>Calcium</td>
<td>Hypocalcemia, tetany, tingling, cramping, neuromuscular hyperexcitability, metabolic bone disease- osteoporosis</td>
<td>Decreased total and ionized calcium levels, increased PTH, decreased 25(OH)D, bone densitometry</td>
<td>Calcium citrate- 1200-2000 mg, oral vitamin D</td>
</tr>
<tr>
<td>Iron</td>
<td>Decreased work ability, palpitations, fatigue, koilonychias, pica, brittle hair, anemia</td>
<td>Blood cell count, serum iron, iron binding capacity, ferritin</td>
<td>1st phase: Ferrous sulfate 300 mg 2-3 times/d, taken with vitamin C 2nd phase: Parenteral iron administration</td>
</tr>
<tr>
<td>Zinc</td>
<td>Hypoguesia, alterations in sense of smell, poor appetite, poor wound healing, irritability, impaired immune function, diarrhea, hair loss, muscle wasting, dermatitis</td>
<td>Decreased plasma &amp; serum zinc, decreased RBC or WBC zinc, decreased ALP</td>
<td>60 mg elemental zinc orally, twice daily</td>
</tr>
<tr>
<td>Copper</td>
<td>Fatigue, myocardial disease, ataxia, decreased sensation in extremities, muscle weakness, anemia with neutropenia, myelopathy</td>
<td>Normocytic to macrocytic anemia with neutropenia, low levels of ceruloplasmin</td>
<td>3-5mg/d to correct deficiency, 1mg Cu for each 8-15mg of Zn</td>
</tr>
<tr>
<td>Selenium</td>
<td>Cardiomyopathy, arrhythmia, muscle weakness, pseudoalbinism, low thyroid function, impaired immunity</td>
<td>Glutathione peroxidase activity in RBCs</td>
<td>200µg/d orally, IV if necessary, vitamins E, C, and A help uptake</td>
</tr>
</tbody>
</table>
### Table 5. Suggested Postoperative Nutrient Supplementation after different bariatric surgical procedures (adapted from 27,143).

<table>
<thead>
<tr>
<th>Supplement</th>
<th>AGB</th>
<th>SG</th>
<th>RYGB</th>
<th>BPD - BPD/DS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin-mineral supplement</td>
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<tr>
<td>• A high-potency vitamin containing 100% of DV for at least 2/3 of nutrients/ should contain at least 18mg Fe, 400 μg folic acid, Se and Zn</td>
<td>1/day</td>
<td>2/day</td>
<td>2/day</td>
<td>2/day</td>
<td>• Begin on day 1 after hospital discharge</td>
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<tr>
<td>• Begin with chewable or liquid</td>
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<tr>
<td>• Avoid time-released supplements/ enteric coating</td>
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<tr>
<td>• May improve GI tolerance when taken close to food</td>
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<tr>
<td>• Specialized bariatric formulations are available</td>
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<tr>
<td>Additional vitamin B₁₂ (μg)</td>
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<tr>
<td>• Available forms include sublingual tablets, liquid drops, mouth spray, or nasal gel/spray</td>
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<td></td>
<td></td>
<td>1000μg/mo.</td>
<td>• Begin 0-3 mo after surgery</td>
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<tr>
<td>• Intramuscular injection</td>
<td></td>
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<td>• Supplement as needed for normal range levels</td>
</tr>
<tr>
<td>• Oral tablet (crystalline form)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Supplementation after AGB, SG and BPD/DS may be required</td>
</tr>
<tr>
<td>Additional elemental calcium</td>
<td>1200-1500mg</td>
<td>1200-1500mg</td>
<td>1200-1500mg</td>
<td>1800-2400mg</td>
<td>• May begin on day 1 after hospital discharge or within 1 mo after surgery.</td>
</tr>
<tr>
<td>• Choose calcium citrate with vitamin D3</td>
<td></td>
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<td></td>
<td></td>
<td>• Promote intake of dairy beverages &amp;/or high Ca foods in addition to supplements - note recent reports linking Ca supplementation with increased MI risk in postop women.</td>
</tr>
<tr>
<td>• Begin with chewable or liquid form</td>
<td></td>
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<td></td>
<td>• Combined dietary and supplemental Ca intake &gt;1700mg may be required to prevent bone loss during rapid weight loss</td>
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<tr>
<td>• Split into 500-600 mg doses throughout the day</td>
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<tr>
<td>• Suggest a brand with Mg, esp. for BPD/DS</td>
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<tr>
<td>• Do not combine Ca with Fe containing supplements to maximize absorption and minimize GI intolerance</td>
<td></td>
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<tr>
<td>• Wait ≥2 h after MVI or Fe</td>
<td></td>
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<tr>
<td>Additional elemental iron (above that provided by mvi)</td>
<td>Add $\geq 18$-27 mg/d</td>
<td>Add $\geq 18$-27 mg/d</td>
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<tr>
<td>• Begin with liquid or chewable/ no enteric coating</td>
<td></td>
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<tr>
<td>• Do not mix Fe and Ca supplements, take $\geq 2$ hrs. apart</td>
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<tr>
<td>• Avoid excessive intake of tea due to tannin interaction</td>
<td></td>
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<tr>
<td>• Encourage foods rich in heme iron</td>
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<tr>
<td>• Vitamin C may enhance absorption of non-heme iron</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Fat-soluble vitamins</th>
<th>10,000IU</th>
<th>2000IU</th>
<th>300μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vitamin A</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Vitamin D</td>
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<tr>
<td>• Vitamin E</td>
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<td></td>
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<tr>
<td>• Vitamin K</td>
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<table>
<thead>
<tr>
<th>Optional B complex</th>
<th>1/d</th>
<th>1/d</th>
<th>1/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Note $&gt; 1000$μg of supplemental folic acid, provided in combination with multivitamins, could mask B12 deficiency</td>
<td></td>
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</tr>
</tbody>
</table>

| Protein            | $\geq 60$g | $\geq 60$g | 60-80g | 60-120g |

<table>
<thead>
<tr>
<th>Important points to consider:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Time after surgery</td>
</tr>
<tr>
<td>• Type of surgery</td>
</tr>
<tr>
<td>• Overall energy intake</td>
</tr>
</tbody>
</table>

May begin 2-4 weeks after surgery

**Vitamin A:***
- Care in pregnant women to avoid over-supplementation in retinol form

**Vitamin D:**
- Higher levels may be necessary- the latest 2013 Guidelines recommend 3000IU after all types of surgery with titration to blood level $> 30$ng/ml 25(OH)D.

May begin on day 1 after hospital discharge
I.5.2. Nutritional concerns in pregnancy (general)

Numerous factors interact to determine the progress and outcome of pregnancy. Although much remains to be learned about the role of nutrition in modifying this process, it is well accepted that the nutritional status of the pregnant woman affects the outcome of her pregnancy. This is especially true with respect to the birth weight of her infant, a factor closely related to infant mortality, and the infant’s risk of long-term adverse health outcomes, such as hypertension, obesity, glucose intolerance, and cardiovascular disease (219).

Low birth weight (<2500g), whether due to intrauterine growth retardation (IUGR) or prematurity, is a major factor in infant deaths; and infant mortality is 40 times greater in LBW infants that in neonates of normal weight (130). Furthermore, LBW is associated with certain long-term health problems, such as developmental and learning disabilities on the one hand, and excessive weight gain and obesity in childhood on the other (130). Although LBW is usually associated with low maternal body weight and insufficient weight gain in pregnancy, obese gravidae are also at increased risk for delivering small for gestational age (SGA) or LBW babies. Poor gestational nutrition, regardless of maternal body weight, is also implicated in LBW. On the other hand, fetal macrosomia (birth weight > 4000g or 4500g) is also associated with maternal obesity and excessive weight gain in pregnancy as well as childhood obesity and metabolic disease in later life. It thus becomes apparent that an optimum goal of pregnancy is delivering a baby of normal birth weight.

Two indicators of maternal nutritional status have consistently been shown to correlate with infant birth weight: maternal size and the amount of weight gained during pregnancy. Regarding maternal size, it has been shown that both maternal and fetal risks are increased in very small women as well as in women who are obese. Similarly, both too much and too little weight gain put mother and fetus at increased risk. For these reasons pre-pregnancy weight and monitoring of weight gain during pregnancy are extremely important. Recommended weight gain during pregnancy has been previously addressed.

However, maternal weight and weight gain during pregnancy are not the only issues involved in maternal and neonatal outcomes. Equally important is the nutritional status of the mother before conception and the quality of nutrition during pregnancy. Numerous studies have been performed, particularly in poverty-stricken, underdeveloped countries where pre pregnancy nutritional status is likely to be inferior. The findings of
many of these studies suggest that the worse the nutritional condition of the mother entering pregnancy, the more severely the growing fetus is affected and the more valuable an improved prenatal diet, nutritional supplementation or both, are to her pregnancy course and outcome (220).

A balanced diet with appropriate increases in the intake of energy, protein and certain micronutrients that results in appropriate weight gain during pregnancy generally supplies the required nutrients needed for pregnancy. If a woman starts her pregnancy in a good nutritional state and adheres to a healthy diet most needs can be covered by increases in normal food intake without supplementation other than folic acid and iron which are recommended in all pregnancies. However, many physicians prescribe a prenatal vitamin-mineral supplement because of the uncertainty of the woman’s nutritional status and intake even though the Institute of Medicine did not find sufficient evidence to recommend routine use of vitamins other than folate and iron, except in high-risk pregnancies (i.e., those involving undernourished, substance-abusing, or teenaged mothers, a short interval between pregnancies, a history of an LBW infant, multiple gestations, etc.) (221). Prenatal evaluation of nutritional status as well as close monitoring of weight gain, dietary intake and laboratory tests during pregnancy is recommended to ensure the best possible outcome.

**Physiologic Changes of Pregnancy**

Many physical and biochemical changes occur in normal pregnancy that must be taken into account when evaluating weight gain and laboratory indices of nutritional status (130).

**Blood volume and composition:**

Blood volume expands by 50%, resulting in a decrease in hemoglobin levels, blood glucose values, and serum levels of albumin, other serum proteins, and water-soluble vitamins. The decline in serum albumin levels contributes to a tendency for extracellular water to accumulate during pregnancy. The decrease in water-soluble vitamin concentrations makes determination of an inadequate intake or a deficient nutrient state difficult. By contrast, serum concentrations of fat-soluble vitamins and other lipid fractions, such as triglycerides, cholesterol, and free fatty acids, increase. More details on normal ranges of various nutrients during pregnancy can be found elsewhere (222).
**Cardiovascular and pulmonary function:**

To provide for the increased cardiac output that accompanies pregnancy, slight cardiac hypertrophy occurs, along with an increased pulse rate. In most women, blood pressure decreases during the first two trimesters because of peripheral vasodilation. It then returns to normal in the third trimester. Maternal oxygen requirements increase, and the threshold for CO₂ is lowered, making the pregnant women feel dyspneic. Adding to this feeling of dyspnea is the fact that the growing uterus pushes the diaphragm upward, making breathing more difficult. Fortunately, more efficient gas exchange occurs in the lungs (130).

**Gastrointestinal function:**

During pregnancy, the function of the gastrointestinal system changes in several ways that affect nutritional status. Early on, nausea and vomiting may occur, followed by a return of appetite that, in some, may be ravenous. Cravings for and aversions to foods may be accompanied by a decreased ability to taste saltiness. This may, in fact, be a physiologic mechanism for increasing salt intake (223). At the same time that an increased progesterone level relaxes the uterine muscle to allow expansion with fetal growth, gastrointestinal motility also diminishes, to allow for increased absorption of nutrients. This often results in constipation. Additionally, a relaxed lower esophageal sphincter can cause regurgitation and heartburn (130).

**Renal function:**

Increased blood volume produces a high glomerular filtration rate. It appears that the renal tubules are unable to adjust completely, and a percentage of nutrients that would have been reabsorbed in the non-pregnant woman are excreted in the urine. Increased amounts of amino acids, glucose, and water-soluble vitamins may appear in the urine. This may be a reason for the increased number of urinary tract infections seen in pregnant women. The ability to excrete water is lowered, and edema in the legs and ankles is common and normal. This edema is not associated with perinatal mortality when other symptoms of preeclampsia- hypertension and proteinuria- are absent. In fact, if it is not associated with other symptoms of preeclampsia the presence of mild edema is associated with slightly larger babies and a lower rate of prematurity (224).
Placenta:

Not only is the placenta the principal site of production for several hormones responsible for regulating fetal growth and development of maternal support tissues, but it is also the conduit for exchange of nutrients, oxygen, and waste products. Any damage to or inadequacy in the placenta compromises its ability to nourish the fetus, regardless of how well-nourished the mother is, or how optimal her dietary intake. Placental size and the number of placental cells have been found to be 15% to 20% below normal in infants experiencing IUG failure. A small placenta has a relatively smaller surface area for the transfer of nutrients to the fetus. The placental surface area may be the means by which maternal nutrition affects birth weight (225).

Nutritional Requirements during pregnancy

Pregnancy is a time for growth and additional demand for nutrients, which can usually be met by increasing servings of food from normal well-balanced diet with a variety of foods according to the Dietary Guidelines. Table 6 shows the current recommended dietary intakes for women of reproductive age and the corresponding increases for pregnancy and lactation (126,226). Factors that may increase nutritional requirements above the estimated demands of pregnancy include poor nutritional status, young maternal age, multiple pregnancy, closely spaced births, breast-feeding during pregnancy, continued high level of physical activity, certain disease states, and the use of cigarettes, alcohol, and legal or illegal drugs. To this list may be added pregnancies occurring after any type of surgery causing decreased nutrient intake and/or malabsorption, including bariatric surgery. Dietary intake of iron, folate, zinc, protein, and calcium should be carefully assessed for adequacy (120). Supplementation is justified when evidence suggests that the inadequate intake or malabsorption of specific nutrients can increase the risk of an adverse effect on the mother, fetus, or pregnancy outcome.
Table 6. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes of Selected Nutrients (126,226,235)

<table>
<thead>
<tr>
<th></th>
<th>Folate µg/d</th>
<th>Vitamin B₁₂ µg/d</th>
<th>Thiamin mg/d</th>
<th>Vitamin C mg/d</th>
<th>Vitamin A µg/1IU/d</th>
<th>Vitamin D µg/d</th>
<th>Vitamin E µg/d</th>
<th>Vitamin K µg/d</th>
<th>Ca mg/d</th>
<th>Fe mg/d</th>
<th>Zn µg/d</th>
<th>Cu µg/d</th>
<th>Se µg/d</th>
<th>Protein g/kgIBW/d</th>
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<tbody>
<tr>
<td><strong>Females</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8g/kgIBW/d</td>
</tr>
<tr>
<td>14-18 y</td>
<td>400</td>
<td>2.4</td>
<td>1.0</td>
<td>65</td>
<td>700</td>
<td>15/600</td>
<td>15</td>
<td>75</td>
<td>1300</td>
<td>15</td>
<td>9</td>
<td>890</td>
<td>55</td>
<td>46</td>
</tr>
<tr>
<td>19-30 y</td>
<td>400</td>
<td>2.4</td>
<td>1.1</td>
<td>75</td>
<td>700</td>
<td>15/600</td>
<td>15</td>
<td>90</td>
<td>1000</td>
<td>18</td>
<td>8</td>
<td>900</td>
<td>55</td>
<td>46</td>
</tr>
<tr>
<td>31-50 y</td>
<td>400</td>
<td>2.4</td>
<td>1.1</td>
<td>75</td>
<td>700</td>
<td>15/600</td>
<td>15</td>
<td>90</td>
<td>1000</td>
<td>18</td>
<td>8</td>
<td>900</td>
<td>55</td>
<td>46</td>
</tr>
</tbody>
</table>

| **Pregnancy**  |             |                  |              |                |                   |                |                |                |         |         |         |         |         | 0.8g/kg + 25g    |
| 14-18 y        | 600         | 2.6              | 1.4          | 80             | 750               | 15/600         | 15             | 75             | 1300    | 27      | 12      | 1000    | 60      | 71               |
| 19-30 y        | 600         | 2.6              | 1.4          | 85             | 770               | 15/600         | 15             | 90             | 1000    | 27      | 11      | 1000    | 60      | 71               |
| 31-50 y        | 600         | 2.6              | 1.4          | 85             | 770               | 15/600         | 15             | 90             | 1000    | 27      | 11      | 1000    | 60      | 71               |

<table>
<thead>
<tr>
<th><strong>Upper Limit (UL)</strong></th>
<th>800-1000</th>
<th>1800-2000</th>
<th>2800-3000*</th>
<th>50/2000*</th>
<th>800-1000</th>
<th>2500</th>
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<thead>
<tr>
<th><strong>Lactation</strong></th>
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</thead>
<tbody>
<tr>
<td>14-18 y</td>
<td>500</td>
<td>2.8</td>
<td>1.4</td>
<td>115</td>
<td>1200</td>
<td>15/600</td>
</tr>
<tr>
<td>19-30 y</td>
<td>500</td>
<td>2.8</td>
<td>1.4</td>
<td>120</td>
<td>1300</td>
<td>15/600</td>
</tr>
<tr>
<td>31-50 y</td>
<td>500</td>
<td>2.8</td>
<td>1.4</td>
<td>120</td>
<td>1300</td>
<td>15/600</td>
</tr>
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*as preformed Vitamin A
*up to 4000IU (IOM)
Energy

Additional energy is required during pregnancy to support the metabolic demands of pregnancy and fetal growth. The total energy needs during pregnancy range between 2,200 and 2,900 kcal/d for most women\(^\text{132,227}\). However, the mother’s age, pre pregnancy BMI, rate of weight gain, and physiologic appetite must be considered when determining individual needs\(^\text{132}\). Based on a review of evidence, an average additional intake of approximately 340 to 452 kcal/day is suggested in the second and third trimesters\(^\text{126}\). For normal weight and overweight women in developed countries, the additional energy need may actually be less than 300kcal/d, especially in sedentary women\(^\text{132}\). However, it should be recognized that, as long as the amount and rate of weight gain are within the desirable range, the range of acceptable energy intakes with good pregnancy outcomes is wide, and that appropriate weight gain and appetite are better indicators of energy sufficiency than the amount of energy consumed\(^\text{130,132}\).

There are many adverse consequences of energy restriction during pregnancy since optimal fetal growth occurs only when the mother is able to accumulate a critical amount of extra body stores during pregnancy. The effect of maternal malnutrition on the development of the fetus is a matter of concern, not only with respect to nutritionally deprived populations, but also with respect to the deliberate practice of restricting food intake to lose weight or prevent weight gain. A once popular concept held that the fetus can protect itself by parasitizing the mother when nutritional status is less than optimal. However, evidence from famines in Holland and Germany during WWII clearly contradict this assumption as the deprived mothers appeared to be proportionately less affected than their infants\(^\text{130}\).

One recognized consequence of energy restriction is the increased production of ketone bodies and their ultimate spillage into the urine. Although it is known that the fetus can metabolize ketone bodies to some degree, the short- and long-term effects of maternal ketonemia are unclear. Both animal and human data indicate that ketone bodies are probably normally presented to the fetal brain at various times during pregnancy. After an overnight fast, maternal ketone body concentrations in the blood are greater in pregnant than in non-pregnant women, and ketonuria is sometimes seen. Extreme levels of ketonemia, however, may be an indicator of maternal malnutrition and may affect fetal neurodevelopment\(^\text{130}\).
**Protein**

Although the need for additional protein to support the synthesis of maternal and fetal tissues is well recognized, the required magnitude of the increase is uncertain. Efficiency of protein utilization in pregnant women appears to be about 70%, the same as that observed in infants. Needs are also variable, increasing as pregnancy proceeds, with greater demands occurring during the second and third trimesters \(^{(130)}\).

The 2002 DRIs list the recommended daily allowances for protein for all age groups during pregnancy and lactation to be 1.1 g/kg per day or an additional 25g/day above the 0.8 g/kg per day for the nonpregnant state \(^{(126)}\). On average, this recommendation equates to approximately 71g, but for women with greater energy needs, the protein needs may need to be adjusted. For a twin pregnancy, an additional 50 g/d above the RDA is suggested during the second and third trimesters \(^{(126)}\). Protein utilization depends on energy intake. Therefore, adequate energy intake is important so that protein may be spared.

Protein deficiency during pregnancy has adverse consequences, but limited intakes of protein and energy usually occur together, making it hard to separate the effects of energy deficiency from those of protein deficiency \(^{(130)}\). Studies have shown that providing extra energy to mothers influences pregnancy outcome as much as providing energy and protein together \(^{(227,228)}\). Thus, it appears that it is usually the energy deficit and not the protein deficit that determines unfavorable pregnancy outcome.

**Vitamins and minerals**

Maintenance of health during the course of pregnancy requires an adequate supply of vitamins and minerals, some of which have particular significance \(^{(130)}\). In some instances, this is accomplished by increasing dietary intake; in others, vitamin-mineral supplementation is initiated. A multivitamin and mineral supplement is recommended for pregnant women who smoke or abuse alcohol or drugs, and women infected with the human immunodeficiency virus, especially women who receive antiretroviral treatment, in whom a supplement containing B-complex, vitamin E, and vitamin C may slow the progression of disease and reduce complications \(^{(132)}\). A multivitamin and mineral supplement is also recommended for women with iron deficiency.
deficiency anemia or poor-quality diets and women who consume animal products rarely or not at all \(^{(132)}\). Vitamin B\(_{12}\) supplementation is recommended for persons who follow a vegetarian diet pattern, including the lacto-ovo vegetarian diet pattern \(^{(132)}\). Women carrying two or more fetuses are also advised to consume a multivitamin and mineral supplement \(^{(132)}\). Additional nutrients that may need to be supplemented include folic acid, iron, zinc, copper, calcium, and vitamin D.

**Vitamins**

**Folic acid**

Folic acid needs increase during pregnancy in response to the demands of maternal erythropoiesis and fetal and placental growth. Folic acid deficiency is marked by a reduced rate of DNA synthesis and mitotic activity in individual cells. Clinical detection of megaloblastic anemia may not occur until the third trimester; however, preliminary morphologic and biochemical signs of deficiency may precede this state.

Perhaps the greatest significance of folic acid and its potential influence on pregnancy outcome is its role in preventing neural tube defects, such as spina bifida and anencephaly. It is crucial to note that, because the neural tube closes by 28 days of gestation supplementation with folic acid should ideally occur prior to conception. Women of childbearing age should be encouraged to include generous amounts of folic acid sources in their diets such as dark green, leafy vegetables, legumes, orange juice, wheat germ, almonds, and peanuts. In addition, women planning a pregnancy should begin periconceptional supplementation with folic acid at levels of 400 to 800 mcg per day \(^{(228)}\).

Women who take folic acid at the time of conception are less likely to give birth to a child with neural tube defects \(^{(229,230)}\). To ensure that blood vitamin levels are adequate at the time of neural tube closure, supplementation should begin at least 1 month before conception. Women who take multivitamins containing folic acid 1 to 2 months before conception have a reduced risk of having a child with orofacial clefts \(^{(132)}\). Research also indicates that abnormal folate metabolism may play a role in Down syndrome and other birth defects \(^{(132)}\). Women who have delivered an infant with neural tube defects may need to consume more than the recommended amount of folate equivalents \(^{(132)}\), but not more than the current tolerable upper limit of 1000 mcg/d as intakes above this amount may mask a vitamin B\(_{12}\) deficiency \(^{(143)}\).
**Vitamin B6**

Vitamin B6 needs are elevated in pregnancy to provide for increased needs associated with synthesis of nonessential amino acids in growth and vitamin B6-dependent niacin synthesis from tryptophan \(^{120}\).

**Ascorbic Acid**

An extra 10 mg/day of vitamin C is recommended for pregnant women. Although ascorbic acid deficiency has not been associated with adverse pregnancy outcome in large population studies, a few studies have suggested an association between low plasma levels of vitamin C and preeclampsia, as well as premature rupture of the membranes \(^{120}\).

**Vitamin A**

Maternal stores of vitamin A are usually adequate to meet the fetal accretion rate. For this reason and because excessive consumption of vitamin A appears to be teratogenic causing birth defects of the head, heart, brain, and spinal cord, the Food and Drug Administration (FDA) and the Institute of Medicine recommend that vitamin A intake be limited \(^{221,232}\). The latest DRI for pregnancy is 750-770μg/d or ~2500IU as preformed vitamin A or retinol and the upper limit has been set at 2800-3000μg or 10,000IU \(^{226}\) since vitamin A supplements above this level have been shown to increase the risk of delivering a baby with a cranial neural crest defect five times over that of women who take 5000 IU or less per day \(^{233}\). These findings do not apply vitamin A in the form of beta-carotene, a precursor of vitamin A found in fruits and vegetables. Vitamin A poses the most danger when taken in these amounts 2 weeks prior to conception and during the first 2 months of gestation.

**Vitamin D**

Vitamin D has long been appreciated for its positive effects on calcium balance during pregnancy. This vitamin and its metabolites cross the placenta and appear in fetal blood in the same concentration as found in maternal circulation. There is increasing interest in vitamin D nutrition during pregnancy because of widespread reports of a high prevalence of low vitamin D status in pregnant women \(^{234}\). Maternal deficiency of vitamin D and the subsequent limitation in placental transport to the fetus
have been associated with neonatal hypocalcemia or enamel hypoplasia, or both, and vitamin D levels are often low in such infants. Other maternal and fetal complications of vitamin D deficiency include a possible association with adverse fetal growth and bone development, pre-eclampsia, gestational diabetes mellitus, and decreased infant immune response\(^{(234)}\). The latest DRI for vitamin D in pregnancy is 15mcg (600IU)/day\(^{(235)}\), which is the same as that for non-pregnant women and is increased compared with previous DRIs with a target of achieving a concentration of > 75nmol/L (or 30ng/ml) which may be protective against lower respiratory infection, wheezing, and eczema in infants\(^{(234)}\). The latest upper limit for pregnancy is 4000IU/d.

**Vitamin E**

Vitamin E needs are believed to increase somewhat during pregnancy, but vitamin E deficiency in humans is rare and has not been linked with either damage to offspring or reduced fertility.

**Minerals**

**Calcium**

The pregnant woman routinely exhibits extensive adjustments in calcium metabolism, largely as a result of the influence of hormonal factors. Human chorionic somatomammotropin from the placenta progressively increases the rate of bone turnover. Estrogen, also largely derived from the placenta, inhibits bone resorption, provoking a compensatory release of parathyroid hormone, which maintains the serum calcium level while enhancing intestinal absorption. The net effect of these changes, which predate fetal skeletal mineralization, is the promotion of progressive calcium retention to meet progressively increasing fetal skeletal demands for mineralization. Fetal hypercalcemia and subsequent endocrine adjustments ultimately stimulate the mineralization process.

Approximately 30 g of calcium is accumulated during pregnancy, almost all of it in the fetal skeleton (25g)\(^{(120)}\). The remainder is stored in the maternal skeleton, presumably held in reserve for the calcium demands of lactation. Most accretion occurs during the latter part of pregnancy, with an estimated average of 300mg per day being deposited during the last trimester.
Due to the increased efficiency of calcium absorption during pregnancy, because of the effect of maternal hormones on increasing the absorption and utilization of calcium, calcium requirements for pregnant women are similar to the requirements for women who are not pregnant\(^\text{120}\). A daily intake of 1,000 mg is recommended for pregnant and lactating women \(\geq 19\) years\(^\text{226}\). Intakes lower than this may cause calcium to leach from the calcium reservoir in the maternal skeleton. The upper limit for calcium intake during pregnancy has been set at 2500mg.

**Iron**

A marked increase in the maternal blood supply during pregnancy greatly increases the demand for iron\(^1\text{30}\). With the availability of this mineral, either from the diet or supplements, total erythrocyte volume increases by 20% to 30%. Active bone marrow may utilize an extra 500mg of elemental iron during pregnancy, and the term fetus and placenta accumulate 250-300mg of elemental iron. Overall, the pregnant women must have between 700 and 800 mg of extra iron, most of which is needed during the last half of pregnancy when the heaviest maternal and fetal demands occur. Averaged over the entire pregnancy, this amounts to a daily increment of 15mg of iron. Only rarely do women enter pregnancy with iron stores sufficient to cover all needs without compromising, maternal well-being. Iron supplementation, usually in the form of ferrous salts, is thus often acknowledged as a necessary means of preventing iron deficiency anemia\(^\text{130}\).

The latest DRI for iron during pregnancy is 27 mg/day in the form of ferrous iron\(^\text{226}\). In order to meet these needs a low-dose supplement is usually recommended at the first prenatal visit\(^\text{132}\). An iron supplement containing 150 mg of ferrous sulfate, 300 mg of ferrous gluconate, or 100mg of ferrous fumarate can fulfill this additional need. Iron deficiency anemia is the most common anemia during pregnancy. If the maternal iron stores are low, 60 to 120 mg of iron may be recommended\(^\text{132,236}\). If the laboratory values indicate macrocytic anemia, vitamin B\(_{12}\) and folate levels should be assessed\(^\text{132}\).

Maternal anemia, defined by a hematocrit value of less that 32% and a hemoglobin level of less than 11g/dl, occurs in some pregnant women who do not use iron supplements. An anemic woman is clearly less able to tolerate hemorrhage with
delivery and is more prone to develop puerperal infection; however, the fetal effects of maternal anemia are poorly understood. Some data suggest that fetal effects are relatively mild, but several reports suggest that pregnancy outcome may be compromised, as it may lead to preterm delivery, LBW and decreased infant Fe stores.

**Zinc and copper**

Iron can interfere with the absorption of Zn and Cu. Therefore, women who take daily supplements with more than 30mg of iron should add 15mg of Zn and 2 mg of Cu (132), amounts which are routinely found in prenatal vitamins.

**Sodium**

Sodium is required during pregnancy for the expanding maternal tissue and fluid compartments and to provide fetal needs. Routine sodium restriction is not recommended (132).

**Fluids:** Adequate fluid intake is extremely important. The recommended daily fluid intake for pregnant women is ~ 35-40 ml/kg of pregravid weight (132).

**Fiber:** Ingestion of fiber is important to speed digestion and prevent constipation and hemorrhoids. The 2002 DRI for adequate intake of total fiber is 28g/d for all age groups during pregnancy (126,132).

Listed below are some of the nutritionally related risk factors during pregnancy (120,132):

- Hb < 11g/dl (first and 3rd trimesters), < 10.5 g/dl (2nd trimester); or Hct <33% (1st and 3rd trimesters), < 32% (2nd trimester)
- Inadequate weight gain: < 0.45kg/mo for very overweight women, < 0.9kg/mo for normal or slightly OW women, < 1.8-3.6kg/mo for women with multiple gestation and underweight women
- Excessive weight gain (> 3kg/mo after 1st trimester), possibly associated with fluid retention
- Ferritin level < 20 mcg/dl
- Serum folate level < 3 mg/dl
- Serum albumin level < 2.5 g/dl
- Total serum protein level < 5.5 g/dl
- Vitamin B_{12} level < 80pg/ml
Finally, although it is clear that prenatal nutrition impacts short- and long-term health, many scientific questions remain unanswered due to the many challenges to performing high quality scientific research in pregnancy. These challenges include the often unknown critical windows of when nutrition may impact development, many physiological changes that occur over the course of normal pregnancy, large individual differences in maternal adaptation to pregnancy, ethical and practical issues of experimenting with human pregnancy, and the lack of a good animal model that can be directly extrapolated to humans.
I.5.3. Nutritional concerns in pregnancy following bariatric surgery

An increasing number of women of child-bearing age are undergoing bariatric surgery as a treatment option for obesity. Consequently, the number of pregnancies following surgery can be expected to increase dramatically over the coming years, and extra attention must be given to the nutritional status of these women both before and during pregnancy for the best maternal and fetal outcomes as well as the health of future generations.

All of the nutritional concerns related to surgery combined with those related to pregnancy must be attended to. Because of the potential impact of surgery on nutritional status, pregnancy after bariatric surgery, depending on the procedure performed and the time interval from surgery to the onset of pregnancy, must be considered high risk and requires close monitoring of maternal weight gain and dietary intake as well as laboratory tests and clinical signs and symptoms indicative of nutritional status. Specific concerns include inadequate weight gain or, in some cases, weight loss, inadequate food intake, often in the presence of gastrointestinal symptoms such as nausea and vomiting, malabsorption depending on type of procedure and the presence of diarrhea, and non-compliance with nutrition guidelines and supplementation. Any findings indicative of adverse effects on maternal health and the growing fetus must be detected and treated early.

During the first 12 months following bariatric surgery, patients are in the most catabolic phase and lose approximately 30% of their body weight. During this phase of rapid weight loss, dietary intake is also limited. Thus, there is a theoretical concern that if pregnancy occurs during the first postoperative year either the mother or fetus, or both may become malnourished. For this reason, it has traditionally been recommended that women delay pregnancy at least one year following restrictive procedures and 1½ years following malabsorptive procedures to avoid nutritional complications during the period of rapid weight loss, although there is no specific recommendation regarding the ideal time interval to wait. On the other hand, when pregnancy occurs after the first postoperative year there is increasing concern regarding the presence of long-term nutritional deficiencies which can develop over time and which may affect both maternal and fetal health. For all of these reasons, irrespective of the time interval following surgery, pregnant women should be evaluated immediately for nutritional deficiencies and informed about the importance of nutrition during
pregnancy including dietary guidelines and the routine use of vitamin and mineral supplements as well as the necessity for closer follow up.

In particular, pregnant women are at increased risk of deficiencies in iron, vitamin B\textsubscript{12}, folic acid, vitamin D and calcium, as well as protein. These are the same nutrients that are of most concern after bariatric surgery. Deficiencies of these nutrients are associated with several maternal and fetal complications, including severe anemia, preterm birth, low birth weight and failure to thrive, neonatal hypocalcemia or rickets, maternal osteomalacia, and congenital abnormalities including fetal mental retardation, and neural tube defects \cite{239}. Therefore, the combination of pregnancy plus surgery is of particular concern, especially after malabsorptive procedures.

Case reports of severe pregnancy complications associated to maternal nutritional deficiencies have been published \cite{240}. However, most of these birth defects are rare, and larger studies or composite materials are required to show the true impact of bariatric surgery \cite{241}. Nonetheless, women of reproductive age with a history of bariatric surgery should be regarded as a high risk group and be counseled on these issues. The impact of surgery on specific reproductive outcome parameters will be addressed in detail below.

It is also important to note that women with a history of oligomenorrhea and androgenicity due to polycystic ovary syndrome before surgery may become fertile during the postoperative period and should be counseled that unexpected pregnancies can occur unless contraceptive methods are employed \cite{139}. Finally, all women of reproductive age undergoing surgery should be informed early on about the importance of nutrition, and when a pregnancy is planned they should be given additional supplementation starting in the preconception period and be checked for nutritional deficiencies.

According to the 2013 update of the AACE/TOS/ASMBS Clinical Practice Guidelines \cite{27}, candidates for bariatric surgery should avoid pregnancy preoperatively and for 12 to 18 months postoperatively (Grade D). Furthermore, women who become pregnant after bariatric surgery should be counseled and monitored for appropriate weight gain, nutritional supplementation, and for fetal health (Grade C; BEL 3). All women of reproductive age should be counseled on contraceptive choices following bariatric surgery (Grade D). Patients with RYGB or malabsorptive procedures should be counseled in non-oral contraceptive therapies (Grade D). Patients who do become
pregnant following bariatric surgery should have nutritional surveillance and laboratory screening for deficiency every trimester, including iron, folate and B\textsubscript{12}, calcium, and fat-soluble vitamins (Grade D). Patients who become pregnant post-LAGB should have band adjustments as necessary for appropriate weight gain for fetal health (Grade B; BEL 2). deficiencies before as well as during pregnancy.

Unfortunately, there are no specific guidelines regarding exact dose of nutrient supplementation during pregnancy after malabsorptive surgery, and the only specific recommendations to date have been suggested by Beard et al\textsuperscript{(237)} for pregnancies following RYGB, which are shown in Table 7.

Table 7\textsuperscript{(237)}. Reproductive management after bariatric surgery

<table>
<thead>
<tr>
<th>Management recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative fertility counseling</td>
</tr>
<tr>
<td>Reliable contraception for 12-18 months</td>
</tr>
<tr>
<td>Nutritional monitoring and supplementation tailored to the type of bariatric procedure performed with specific focus on identifying and treating deficiencies in iron, folate, B12, calcium, and vitamin D both pre- and post-conception</td>
</tr>
<tr>
<td>Recommendations during pregnancy: one standard prenatal vitamin daily, which may include or should be supplemented with the following</td>
</tr>
<tr>
<td>400 μg folate daily for all reproductive-aged women</td>
</tr>
<tr>
<td>50-100 mg elemental iron daily for menstruating and pregnant women</td>
</tr>
<tr>
<td>1000 mg calcium daily for all postoperative patients</td>
</tr>
<tr>
<td>60 g of dietary protein daily for pregnant patients</td>
</tr>
<tr>
<td>Low threshold for suspicion of intestinal obstruction during pregnancy. Image via CT scan and surgical exploration as needed</td>
</tr>
<tr>
<td>Close follow up of weight changes during pregnancy and postpartum</td>
</tr>
<tr>
<td>Cooperation with high-risk obstetrical colleagues in patient management</td>
</tr>
</tbody>
</table>

In conclusion, nutritional supplementation and close monitoring of nutritional status both preconception and during pregnancy is a crucial element of patient care by the bariatric surgeon and high-risk obstetrician.
I.6. Impact of bariatric surgery on health

I.6.1. General health outcomes

Bariatric surgery has been proven an effective weight loss treatment for those who are severely obese. While there are risks involved, the benefits of bariatric surgical procedures in the resolution or marked improvement of specific obesity-related comorbidities far outweigh the risks. Bariatric surgery results in substantial and durable weight loss leading to a significant reduction in health care costs and comorbidities associated with obesity, such as diabetes, hypertension, hyperlipidemia, sleep apnea and certain cancers. A meta-analysis of 22,094 patients after various types of bariatric surgery showed significant excess weight loss (EWL) after all types of surgery, which was greatest after the malabsorptive procedures BPD and DS 70.1% (66.3-73.9%), followed by gastric bypass 61.6% (56.7-66.5) and AGB with EWL 47.5% (40.7-54.2%). The same meta-analysis found that diabetes was completely resolved in 76.8% and resolved or improved in 86.0% of surgical patients. Hyperlipidemia was improved in ≥70%, hypertension was resolved in 61.7% and resolved or improved in 78.5%, and obstructive sleep apnea resolved in 86% of patients. Furthermore, it was shown that resolution of diabetes and hyperlipidemias was most impressive after BPD and DS, 98.9% and 99.1%, respectively, implying mechanisms of action other than weight loss alone, whereas resolution of hypertension seems to be independent of the type of surgery performed. Superior outcomes of diversionary procedures such as GBP and BPD appear to be related to altered hormonal signals associated with obesity and food intake, including adipokines (ASP and adiponectin) as well as inflammatory peptides (CRP, IL-6) and satiety related hormones (leptin and ghrelin), all of which play important roles in the pathophysiology of obesity, insulin resistance, dyslipidemia, and chronic low-grade inflammation. Complete long-term normalization of insulin sensitivity with full restoration of β-cell function has also been demonstrated in severely obese patients with a history of type 2 diabetes after BPD.

Bariatric surgical interventions also appear to have positive influences on other comorbid conditions including GERD, degenerative joint disease, nonalcoholic steatohepatitis, urinary incontinence, and even some cancers. Psychiatric morbidity and quality of life (QOL) are also improved in most cases.
More recently, bariatric surgery has been shown to decrease long-term mortality in postoperative patients when compared to obese controls (249,250). Despite the known immediate and long-term complications of bariatric surgery, overall mortality has improved since 2008. Recent data from the Swedish Obese Subjects (SOS) study, a large prospective observational study of > 2000 bariatric surgical patients demonstrated a mortality hazard ratio (HR) of 0.71 ten years following surgery compared with matched obese controls (251). More recent data from this cohort followed for up to 20 years demonstrated a HR of 0.47 in cardiovascular death (including stroke and myocardial infarction) among surgical subjects compared with obese controls (252). In another cohort, all-cause mortality decreased by 40% 7 years after RYGB, compared with the control group, and cause-specific mortality in the surgery group decreased by 56% for coronary artery disease, by 92% for T2D, and by 60% for cancer (249).

Bariatric surgery also appears to have positive effects on reproductive health, which constitutes an area of intensive ongoing research. An attempt has been made below to evaluate the information available to date.
I.6.2. Reproductive health outcomes

The effect of weight loss through bariatric surgery on fertility and childbirth outcomes has not yet been fully elucidated. Although rates of many adverse maternal and neonatal outcomes may be lower in women who become pregnant after having had bariatric surgery compared with rates in pregnant women who are obese, further data are needed from rigorously designed studies \(^{(253)}\). The literature to date regarding effects of surgery on reproductive health is further discussed below:

**Fertility and sexual function**

There is much ambiguity in the literature regarding fertility and bariatric surgery with data demonstrating both positive and negative associations \(^{(254,255)}\). Although nonsurgical weight loss in morbidly obese women has proven to improve fertility status \(^{(256,257)}\), data on fertility after weight loss by bariatric surgery are still limited. Nevertheless, for the most part studies show increased fertility following bariatric surgery as shown by an increase in spontaneous conception \(^{(38)}\). Although the mechanisms for improved reproductive function are not well understood, it is well-established that bariatric surgery improves the markers of PCOS which influence fertility, such as anovulation, hirsutism, hormonal changes, insulin resistance, sexual activity and libido \(^{(258-260)}\). Furthermore, case series suggest improvement in the ability to conceive after restrictive as well as malabsorptive bariatric surgical procedures \(^{(261-263)}\).

A recent systematic review on the impact of bariatric surgery on female reproduction \(^{(38)}\) presents an overview of reproductive physiology after surgery with specific focus on the hypothalamic-pituitary-ovarian (HPO) axis, reproductive hormone profiles, fertility status, measures of ovarian reserve, pregnancy, efficacy of oral contraceptives and sexual function. It is likely that post-operative alterations in adipocyte and enteric signals contribute significantly to such reproductive changes \(^{(14)}\). However, thus far the literature has not specifically addressed adipose/enteric signal modulation of reproductive function in severely obese women who undergo surgery.

Sexual function may also be improved following the dramatic weight loss after surgery; however, the possibility of detrimental influence afterward can occur \(^{(38)}\). Furthermore, oral contraceptives (OCPs) may not be as effective following surgery due
to unpredictable alterations in the bioavailability of constituent hormones in OCP formulas, especially after gastric bypass and malabsorptive procedures (264). The combination of lower estrogen dosages and postoperative GI disturbances might contribute to an increased risk for unintended pregnancy in the postoperative period (264), and contraception and preconception counseling should be a component of the overall counseling for any reproductive-aged woman undergoing bariatric surgery, especially for adolescents as pregnancy rates after bariatric surgery are double the rate in the general adolescent population (12.8% vs 6.4%) (265).

In conclusion, bariatric surgery seems to improve fertility status, sexuality, pregnancy outcomes and reproductive hormone profile but patients must be cautioned since surgery may also be linked to contraceptive failure with the use of OCP (38).

**Maternal outcomes**

Several large systematic reviews of maternal and obstetric outcomes following obesity surgery have recently been published (241,253,254,266-269). Maternal outcome variables studied include miscarriage, gestational weight gain (GWG), gestational diabetes mellitus (GDM), hypertensive disorders such as pregnancy-induced hypertension (PIH) and pre-eclampsia, and mode of delivery. Some of these findings of these studies are discussed below.

**a. Miscarriage**

The effect of bariatric surgery on miscarriage rates is difficult to evaluate because of small patient numbers and the limited number of studies (35). Two retrospective studies recorded changes in miscarriage rates within subjects before and after BPD. One found no difference in miscarriage rates pre- and post-operatively (21.6% vs. 26%) (263), and another recorded a reduction (17 vs. 11%) (270), although statistical significance was not commented on in either study. It has also been reported that miscarriage rates are significantly higher after various surgical procedures including restrictive and RYGB procedures (38.9% vs 18.8% p<.001) (271).
b. Metabolic complications of pregnancy

The majority of studies included in the major systematic reviews describe decreased rates of gestational diabetes and hypertensive disorders following bariatric surgery, and there seems to be general agreement in the literature that pregnancy after bariatric surgery is associated with a lower risk of metabolic complications during pregnancy.

Gestational diabetes mellitus

Most studies overwhelmingly report a reduced incidence of GDM in pregnancies following all types of bariatric surgery. Ducarme et al (272) showed that the incidence of GDM (0% vs 22.1%, p<0.05) was lower after LAGB than in the obese comparison group. Other studies involving LAGB have also reported a lower risk of GDM in post-surgery pregnancies when compared with obese women (273-275). Two studies after RYGB showed no difference in GDM (276,277), while others involving RYGB or mixed RYGB and restrictive surgery showed a significant decrease in GDM in post-surgery pregnancies when compared with pre-surgery deliveries (271,278,279) or non-operated, BMI-matched control groups (280). Of particular interest is the study by Tamir et al (271) involving 288 paired pregnancies (144 pre surgery, 144 after), in which gestational diabetes was significantly reduced in post-surgery pregnancies (20.8% vs 7.6%, p<0.001). Only one study showed a higher risk of GDM in women after bariatric surgery compared with the background population, 9.4 vs 5% (281).

A limited number of studies have also compared pregnancies among different types of surgery (282,283). In these studies no significant differences in metabolic complications were noted between pregnancies after LAGB and RYGB. No studies to date have compared metabolic complications after restrictive procedures to those seen after malabsorptive BPD/DS procedures. However, since malabsorptive operations may promote insulin secretion and inhibit glucagon production (134), they may be more effective than restrictive procedures in preventing and treating diseases related to glucose metabolism such as GDM. Further studies comparing pregnancies after restrictive and malabsorptive procedures are needed in order to determine if this is indeed the case.

Finally, it must be noted that GDM screening in patients after malabsorptive surgery requires special considerations as dumping syndrome can be
provoked by the standard 75 or 50 g glucose tolerance test \(^{(284)}\). In order to prevent the induction of dumping syndrome, obstetric physicians may choose to screen them for GDM by monitoring home fasting and 2-hour postprandial blood glucose levels for a week at 26-28 weeks of gestation \(^{(285)}\).

**Hypertensive disorders**

Studies comparing pre- and post-bariatric surgery pregnancies consistently show a reduction in risk and rates of hypertensive disorders after obesity surgery. This is a consistent finding after all types of surgery when post- surgery pregnancies are compared to pregnancies in obese women who have not had surgery \(^{(253,267-269,271-273,286,287)}\). Recently, Weintraub et al \(^{(287)}\) found bariatric surgery to be independently associated with a reduction in hypertensive disorders during pregnancy. Furthermore, Tamir et al \(^{(271)}\) found that hypertensive disorders were significantly reduced in the paired postoperative group (31.9% vs 16.6%, \(p=.004\)). Overall, it can be said that studies comparing pre- and postbariatric surgery pregnancies consistently show that the incidence of PIH and pre-eclampsia is lower following surgically induced weight loss than in obese women and may even approach community levels \(^{(253)}\).

c. **Nutritional complications and metabolic profile**

Major reviews on pregnancy following bariatric surgery do not address the issue of nutritional indices during pregnancy in detail, but stress the importance of close monitoring and adherence to supplemental guidelines. There seems to be a general consensus that with proper monitoring and supplementation gastric bypass and LAGB present minimal risk for nutritional problems; however, there is less consensus regarding BPD where information is much more limited \(^{(253,269)}\). Furthermore, the potential for nutritional complications and adverse maternal and fetal outcomes following malabsorptive surgery must not be overlooked, and close monitoring by a multidisciplinary team is essential. Finally, since there are physiological changes during pregnancy which alter the blood levels of some of these parameters, it must be noted that when evaluating laboratory measurements during pregnancy, one must take into consideration what is considered “normal” at this time. This issue has been addressed in detail in a recent publication by the American College of Obstetrics and Gynecology.
Potential nutrition-related complications include anemia, various micronutrient deficiencies, and protein malnutrition.

**Anemia**

Varying degrees of anemia have been reported in pregnant women following bariatric surgery. Patel (277) after RYGB reported that 3 of 26 pts (11.5%) had anemia, defined as Hb < 10g/dl, 2 of whom had had pre-pregnancy iron deficiency anemia, and were treated with IV iron. Wittgrove et al (278) reported that no women presented with clinically significant anemia without stating actual levels or definition of clinically severe anemia. Faintuch et al (288) presented the most detailed information to date regarding nutritional indices after RYGB. They report mean Hb levels of 11.4 ± 1.5 g/dl in 14 pregnant women after RYGB with no cases of severe anemia (Hb < 7.0 g/dl). A recent study by Nomura et al (289) involving 30 pregnancies following RYGB, reported varying degrees of anemia defined as Hb < 11.0 g/dl in 16 women (53.3%) during the first trimester, 23 (76.7%) during the second trimester and 18 (60%) during the third trimester. Two patients presented severe anemia (Hb < 7.0 g/dl) requiring intravenous iron or blood transfusion, and two additional patients received intravenous iron as well. It is also of interest to note that the need for intravenous iron supplementation or packed red cell transfusion for the treatment of iron deficiency anemia was significantly more frequent among women who became pregnant 4 or more years after surgery compared to those who became pregnant less than 4 years following surgery. Finally, Sheiner et al (282) reported anemia (Hb<10) in 22.6% of RYGB patients and Tamir et al (271) after mixed surgeries in 144 postoperative pregnancies reported one case of mild anemia and 2 cases of severe anemia requiring blood transfusion, without stating which procedure had been performed in each case. There are no reports in the literature stating the incidence of anemia in pregnancies following SG or BPD procedures.

**Folic acid and vitamin B₁₂ deficiency**

Folic acid and vitamin B₁₂ levels have been reported in detail in only one study (288) in 14 pregnant women following RYGB. Folic acid levels were higher during pregnancy than before surgery, and vitamin B₁₂ levels decreased although, according to the authors, most patients remained within the acceptable range. Finally, there have
been some isolated case reports of vitamin B12 deficiency, including one in a breastfed infant of an asymptomatic mother \(^{(290)}\).

**Other micronutrient deficiencies**

Calcium levels were reported in one study in pregnancy after RYGB \(^{(288)}\) which showed no decrease during pregnancy; vitamin D levels were not reported. There are no other studies presenting detailed information on Ca and vitamin D status. There are also some isolated case studies reporting vitamin A deficiency following BPD \(^{(291)}\).

**Protein malnutrition**

Protein malnutrition defined by low serum albumin levels (mild \(<3.5\), severe \(<2.5\)) is not referred to in studies of pregnancies after purely restrictive procedures, and in one study after RYGB \(^{(288)}\) serum albumin levels remained within the normal range (4.1±0.4g/dl). In another study following RYGB \(^{(277)}\), additional protein supplementation was recommended to 2 patients without any reference to albumin levels. Protein malnutrition has, however, been reported in pregnant women following malabsorptive procedures. Adami et al \(^{(292)}\) reported that 13 of 64 pregnant women (20%) presented with varying degrees of protein malnutrition in pregnant women following BPD requiring either total or peripheral parenteral nutrition. A few years later, Friedman et al \(^{(270)}\) reported that parenteral nutritional support was needed in 32 of 152 pregnant women (21%), and finally, in a more recent study, Marceau et al \(^{(263)}\) showed that mean serum albumin levels decreased from 4.04 to 3.57 g/dl in postoperative pregnancies with 4 patients (2.5%) presenting with serum albumin levels < 2.6g/dl requiring TPN. Normal serum albumin levels during pregnancy have been reported to range from 2.6-4.5 g/dl and 2.3-4.2 g/dl during the 2\(^{nd}\) and 3\(^{rd}\) trimesters, respectively \(^{(222)}\). Therefore, serum albumin levels must be carefully interpreted and evaluated along with the patient’s clinical status.

**d. Cesarean Delivery**

Overall, bariatric surgery does not appear to reduce the risk of cesarean delivery (CD); on the contrary, the incidence of CD remains high in women following bariatric surgery and is often higher than in non-surgical groups \(^{(253)}\). Studies comparing mode of delivery among obese women before and after surgery are conflicting, with
some describing a decreased risk for CD (268,279) and others describing an increase in CDs after surgery (287). In the review by Maggard et al (253), rates of CD ranged from 0% to 65.8% for post-surgery pregnancy and from 5.6% to 64.5% for comparison groups. Sheiner et al (282) demonstrated a higher CD rate (29.4%) in all groups of bariatric surgery. The authors suggest that caregiver bias may contribute to this elevated CD rate, as there was no known physiological reason necessitating higher CD in women who had previously undergone weight loss surgery. On the other hand, an increase in CDs after bariatric surgery may be attributed to previous cesarean deliveries in this population (287). In any case, obstetricians need to be aware of caregiver bias and avoid operation without clear and definitive indications and also need to be aware that the presence of large areas of redundant skin can result in loss of landmarks and make intraoperative access difficult.

e. Surgical complications

In addition to nutritional complications, case reports and small studies have identified significant late surgery-related complications of previous bariatric surgery that have occurred during pregnancy, including intestinal hernia (most commonly reported), maternal intestinal obstruction, gastrointestinal hemorrhage, perforation and even death (253,263,274,276,277,293). Most cases of intestinal obstruction are due to adhesions from previous surgery, and exploratory laparotomy might be necessary. Computed tomography scan with contrast is suggested to be reliable for diagnosis (269). The incidence of such maternal GI complications related to surgery is infrequent; however, correct diagnosis can be a problem and there should be a high index of suspicion for gastrointestinal surgical complications when pregnant women who have had these procedures present with significant abdominal symptoms (269).

Post-LAGB pregnancies are also not without complications (269). Band complications include slippage and migration, band leakage (266), and gastric prolapse necessitating removal of the gastric band (274). Furthermore, deflation of the band may be needed in up to 70% of cases to allow for adequate nutrient intake or in case of frequent vomiting (268).
Neonatal outcomes

Neonatal outcome variables most often studied include preterm birth (gestational age <37 weeks), birth weight in relation to gestational age, low birth weight (LBW) (<2500g) and macrosomia (>4000g). Other variables sometimes recorded include congenital abnormalities, Apgar score, NICU admission and fetal mortality.

a. Preterm delivery

The preterm delivery rate does not appear to change significantly in pregnancies after bariatric surgery compared with pregnancies prior to surgery (263,271,273,275,287), with BMI-matched controls (273,277) or with pregnancies in non-surgical obese population groups (272,273,275,277,280). However, some studies indicate that the risk of preterm delivery may be higher in post-bariatric surgery pregnancies than in non-operated normal BMI controls (275,280,281,294,295). In one of these studies (281) the risk of preterm rupture of membranes (PROM) was significantly increased in post-surgery pregnancies. Overall, the incidence of preterm delivery after surgery ranges from ~ 6% to 27% as compared to reported incidence in the general U.S. population of 12.8%. A recent nationwide population based matched cohort study by Roos et al (295) reporting on perinatal outcomes of 2534 births to mothers with a history of bariatric surgery (gastric bypass, VBG, and banding) compared with 12,468 matched control births of women of similar age, parity, and early pregnancy BMI, also showed a higher risk of both medically indicated and spontaneous preterm and very preterm birth in the post-surgery group (total 9.7% versus 6.1%), without differentiating among surgeries. Finally, in another recent survey, Josefsson et al (296) found that although there was no significant difference in preterm delivery, gestation was half a week shorter in 126 pregnancies after bariatric surgery compared with pregnancies from the Swedish Medical Birth Register.

b. Neonatal birth weight

Since there is a linear association between maternal pre-pregnancy BMI and mean birth weight, a significant decrease in mean birth weight would be expected following bariatric surgery when compared with preoperative obese controls. This is indeed the case in most studies. Although some studies show no significant difference in birth weight after surgery (284,272-274,294), most show significantly lower birth weight (263,271,275,277,280,287,289,296-298) as well as a lower incidence of macrosomia after bariatric
surgery compared with pre-surgery deliveries \(^{(263,278,287,298)}\), BMI-matched controls \(^{(297)}\), non-operated obese women \(^{(272,275,277,280)}\) or women in the general population \(^{(294,296)}\). This may be an indication of more appropriately grown infants \(^{(123)}\). The reported incidence of macrosomia after surgery ranges from 0-11.6% compared with 14.6-34.8% in control groups, and the difference is especially notable when comparisons are made with obese and severely obese control groups. Comparing pregnancies after restrictive and restrictive-malabsorptive surgery, Sheiner et al \(^{(282)}\) showed no statistically significant differences in macrosomia between groups. Only one study described a higher birth weight and an increased risk of macrosomia after bariatric surgery compared with the general population \(^{(281)}\).

Theoretically, by treating obesity associated with large babies, weight loss surgery may prevent macrosomia in post-op pregnant women \(^{(254)}\), which is especially important as it is well known that macrosomia is associated with adverse health outcomes in later life including obesity and the metabolic syndrome. The decrease in the rates of macrosomia and LGA babies among post-bariatric surgery deliveries suggests that weight loss surgery may be a successful intervention for preventing delivery of large infants \(^{(254)}\).

On the other hand, bariatric surgery may potentially increase the risk for intrauterine growth restriction (IUGR) as indicated by low birth weight (LBW- <2500g) and small for gestational age (SGA < 10\(^{th}\) percentile for weight according to gestational age) infants, due to poor nutritional status in the mother. In this regard it should be noted that anemia is a well-established mechanism for SGA \(^{(299,300)}\). Thus, it would be more likely to observe higher incidence of LBW and SGA after malabsorptive surgery where nutritional deficiencies are more likely. Marceau et al \(^{(263)}\) comparing 162 post-surgery pregnancies after BPD to pre-surgery controls did report higher incidence of SGA in the post-surgery group; however, the difference was not significant (9.6% versus 3.1%), and according to the authors was within the normal regional limit. The incidence of LBW in the same group was rather high at 27.4%, but no comparison was made with the pre-surgery group. Paired data for neonates born to the same mothers before and after BPD \(^{(263,270,301)}\) have also shown that babies delivered at term after surgery weighed less than infants delivered by the same mothers before surgery. It is of further interest to note that in the study of Marceau et al \(^{(263)}\), three of the four infants
born to mothers with severe hypoalbuminemia during pregnancy were small for gestational age.

Increased risk of small for gestational age (SGA) or growth-restricted infants has been indicated after other types of surgery as well, including restrictive procedures and RYGB. These studies compared post-surgery pregnancies with the general population (281,294,296), with non-obese controls (11.5% vs. 0.5%) (277), and with obese pre-surgery paired (271,278) and non-paired (280) pregnancies. Similarly, Roos et al (295) in their large population based cohort study found that the risk of delivering a small for gestational age infant was significantly higher in women with a history of bariatric surgery than in matched controls (5.2% vs 3.0%, p<0.001), and concluded that pregnant women with a history of bariatric surgery should be regarded as a risk group and be counseled about the increased risk of preterm birth and intrauterine growth restriction compared with non-operated pregnant women with similar characteristics. This study did not investigate whether the increased risk for small for gestational age birth was caused by micronutrient deficiencies, nor if it can be reduced by more intensive micronutrient or fetal growth monitoring. Only one small study (13 cases) addressing banding described a reduced risk of LBW (7.7% versus 10.6% p<0.05) compared with obese women (272).

Seven studies reporting on gestational length found no differences among neonates born to women after bariatric surgery relative to controls, either women in BMI-adjusted control groups (272,275,277,284,297) or deliveries before surgery (263,287), possibly indicating normal growth but less adiposity. No studies to date report data on head circumference.

Overall, the literature indicates that pregnancy after bariatric surgery is associated with a lower birth weight, reduced risk of macrosomia and a lower risk of metabolic pregnancy complications. The lower birthweight may induce a higher risk of small-for-gestational age infants (269).

c. Congenital abnormalities

Although there are case reports of congenital abnormalities after bariatric surgery, primarily neural tube defects (NTDs), the incidence does not appear to be increased when compared with the general population (123,281). Most studies reporting on this issue show no difference in the risk of birth defects in infants born after surgery;
however, Weintraub et al \(^{(287)}\) found a higher risk of birth defects after bariatric surgery among 507 neonates after bariatric surgery compared with 301 pre-surgery deliveries. A review by Guelinckx et al \(^{(266)}\) also reported higher congenital malformation rates following BPD, including diaphragmatic hernia, intestinal obstruction and rectal atresia (0.4%), and neural tube defects (NTDs; 0.8%), and another review by Abodeely et al \(^{(267)}\) identified ten cases (1.6%) of congenital defects in infants of women who had undergone bariatric surgery as compared to the general population (0.7%). On the contrary, Sheiner et al in 298 pregnancies after different bariatric procedures \(^{(282)}\) did not show an increased risk of congenital malformations after controlling for diabetes and hypertensive disorders. When evaluating this parameter it should also be kept in mind that obese women in general have a higher risk for delivering infants with congenital malformations. It should also be stressed that folic acid supplementation is required in all women who have undergone weight loss surgery to prevent NTDs. They should be screened for NTDs through second trimester alphafetoprotein and ultrasound. Elevated homocysteine levels have been reported in pregnant women post-LAGB, potentially putting fetuses at an elevated risk for NTDs \(^{(273)}\). Further research is needed to establish the correct pre-conception dosage of folic acid in women who have undergone weight loss surgery.

d. Perinatal mortality

Previous bariatric surgery does not appear to be associated with an increase in perinatal mortality \(^{(123)}\). Sheiner et al \(^{(281)}\) reported no significant difference in perinatal mortality rates in post-surgery patients compared with the general obstetric population (6.6 versus 14.8 in 1000 births) or between restrictive and RYGB procedures. In agreement with these findings, Marceau et al \(^{(263)}\) showed no difference in perinatal mortality (0.6 vs. 1.0%) between surgery and control groups after BPD. Finally, Roos et al in their large population based cohort study \(^{(295)}\) showed no differences in stillbirths of neonatal mortality in post-surgery deliveries.

Overall, there is no strong evidence that adverse neonatal outcomes are higher following gastric bypass procedures compared with obese groups \(^{(253)}\).
**Childhood development**

In addition to the studies investigating paired pregnancy and neonatal outcomes, recent studies have begun to evaluate later childhood development of siblings born before and after BPD type malabsorptive surgery\(^{(301-303)}\). These studies show that mean body weight and BMI percentile as well as the incidence of severe obesity are significantly lower in children born after surgery than in their siblings born before maternal surgery. Barisione et al\(^{(303)}\) also state that the difference in BMI is not significant in young children aged 1 to 6 but becomes apparent at adolescence. Furthermore, Kral et al\(^{(302)}\) observed that the prevalence of overweight was reduced to normal population levels in children 6-18 years of age born after maternal surgery. Finally, Smith et al\(^{(301)}\) studied the cardiometabolic risk factor profile in children born after maternal surgery (AMS) and found that these children had greater insulin sensitivity, improved lipid profile, lower C-reactive protein and leptin levels, and increased levels of ghrelin, suggesting an overall more favorable metabolic profile. They conclude that these results suggest the importance of potentially modifiable epigenetic factors in the cause of obesity attributable to an improved intrauterine environment. In this way surgical weight loss may help to prevent parental transmission of obesity to the next generation\(^{(301-303)}\).

**Conclusions and recommendations**

An increasing number of women of childbearing age are undergoing bariatric surgery procedures and need information and guidance regarding reproductive issues. Optimizing success for a healthy maternal and neonatal outcome requires a multidisciplinary team including surgeons, primary care clinicians, obstetricians, anaesthetists, fertility specialists, nutritionists, psychologists and plastic surgeons as well as patients themselves. Women who have had bariatric surgery generally tolerate pregnancy well\(^{(269)}\).

No randomized controlled trials exist to assess pregnancy outcome; the best available evidence comes from observational cohort, case-control studies and case reports. Furthermore, heterogeneity between the studies regarding study design,
operative intervention and reference populations does not permit a meta-analytic approach (241). The available evidence suggests lower incidence of GDM, PIH, macrosomia with lower mean birth weight and a higher incidence of low birth weight following bariatric surgery. The risk for preterm delivery, congenital anomalies and perinatal death is not increased. Bariatric surgery should not be performed with the intention of treating infertility; however, fertility may improve with rapid postoperative weight loss. There is uncertainty regarding the correct dosage of micronutrient supplementation in these women and additional multivitamin and micronutrients with dietary modifications may be required to suit the needs of patients after gastric bypass and BPD, where additional protein may also be required. Finally, the importance of nutritional status for optimum outcomes must be stressed.

At the present time, both obstetricians and surgeons should consider postbariatric surgery pregnancy women as high risk. Optimal education should be encouraged in these individuals so that they can make well informed decisions about planning pregnancy after weight loss surgery. Detailed knowledge from larger studies regarding benefits and risks for the mother and her offspring is needed to improve the surveillance of these pregnancies and to assist in preventing adverse outcomes (241). Table 7 presents an overall management plan for pregnancy after previous bariatric surgery (269).
Table 8. Management of pregnancy following bariatric surgery.

<table>
<thead>
<tr>
<th>Management of pregnancy following bariatric surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-conception</strong></td>
</tr>
<tr>
<td>• Contraceptive counselling – reliable contraception (preferably, non-oral) to delay pregnancy for approximately 12 months after surgery. Adequate patient education is key.</td>
</tr>
<tr>
<td>• Follow-up with nutritionist/dietitian to monitor nutritional status and weight gain.</td>
</tr>
<tr>
<td>• Folic acid, vitamin B12, calcium and iron supplementation.</td>
</tr>
<tr>
<td><strong>Antenatal care</strong></td>
</tr>
<tr>
<td>• Patients should be managed in a multidisciplinary setting to optimize pregnancy outcome.</td>
</tr>
<tr>
<td>• Keep the bariatric surgeon in the loop.</td>
</tr>
<tr>
<td>• Early antenatal consultation.</td>
</tr>
<tr>
<td>• Offer emotional support.</td>
</tr>
<tr>
<td>• Determine baseline nutritional status and monitor adherence to nutritional supplementation. Tailor nutritional status to individual needs and the type of bariatric surgery (chewable or liquid multivitamin).</td>
</tr>
<tr>
<td>• Regular blood tests may be required following malabsorptive surgery to check for micronutrient deficiency.</td>
</tr>
<tr>
<td>• Weigh the individual at every visit to monitor gestational weight gain (GWG). Active band management following a laparoscopic adjustable gastric band procedure results in the least GWG.</td>
</tr>
<tr>
<td>• Inform anesthetist and pediatric department of maternal bariatric surgery history.</td>
</tr>
<tr>
<td>• Take fasting and 2-hour postprandial glucose monitoring for a week to detect gestational diabetes mellitus as the standard (the glucose tolerance test can induce dumping syndrome).</td>
</tr>
<tr>
<td>• Screen for neural tube defects and arrange serial ultrasound scans focusing on intrauterine growth restriction and malformations.</td>
</tr>
<tr>
<td>• Even if there is slight suspicion of intestinal obstruction, perform clinical examination and imaging studies. Surgical exploration may be required.</td>
</tr>
<tr>
<td>• Assess for thromboprophylaxis.</td>
</tr>
<tr>
<td><strong>Intrapartum</strong></td>
</tr>
<tr>
<td>• There is no medical reason that pregnant women postbariatric surgery require delivery via cesarean section.</td>
</tr>
<tr>
<td>• It is important to anticipate problems and effectively prepare equipment and personnel.</td>
</tr>
<tr>
<td>• Fetal scalp monitoring may be required.</td>
</tr>
<tr>
<td><strong>Postpartum care</strong></td>
</tr>
<tr>
<td>• Adequate pain control, early mobilization, thromboprophylaxis, physiotherapy.</td>
</tr>
<tr>
<td>• Encourage breast feeding.</td>
</tr>
<tr>
<td>• Follow up with nutritionist to ensure a healthy diet and to guide further weight loss, if required.</td>
</tr>
<tr>
<td>• Women considering body contouring surgery postbariatric surgery should wait until they have completed their family as future pregnancies can reverse the effects of cosmetic surgery.</td>
</tr>
</tbody>
</table>
Part II.

Original Research
II.1 Objective

In women of reproductive age obesity is associated with anovulation and decreased fertility, primarily due to polycystic ovary syndrome (3,258,260). In addition, obese pregnant women are at higher risk for obstetric complications including hypertension, pre-eclampsia and gestational diabetes as well as early and late fetal death, congenital abnormalities and fetal macrosomia (3,8). Consequently, it is important for obese women to lose weight before attempting pregnancy (123). Bariatric surgery is the most effective long-term treatment for morbid obesity, and as the rate of obesity continues to rise, so too does the number of operations performed each year. Approximately half of all bariatric surgery patients are women of reproductive age and, thus, there will be an ever increasing number of pregnancies following surgery (237,253).

The counseling and management of women who become pregnant after bariatric surgery present a challenge to both the obstetrician and the surgeon. Studies to date present encouraging data regarding reduction of obstetric complications and improved pregnancy outcomes following surgery (253,267,269,271,282). However, the potential for nutritional complications resulting in adverse perinatal outcomes must not be overlooked, and studies investigating nutritional status and perinatal outcomes in post bariatric surgery pregnancies are lacking. Consequently, there is a need for more studies investigating the nutritional status of these women and their pregnancy outcomes, especially following malabsorptive procedures, where the potential for nutritional complications is greatest.

The objective of the present study is to investigate pregnancy outcomes and nutritional indices following three different types of bariatric surgery performed at our institution - sleeve gastrectomy (SG), a restrictive procedure, Roux-en-Y gastric bypass (RYGB), a combined restrictive-malabsorptive procedure, and our version of biliopancreatic diversion (BPD), which is a malabsorptive procedure.
II. 2. Materials and Methods

This is a retrospective study investigating pregnancy outcomes of 113 women who gave birth to 150 children following BPD, RYGB and SG, at the University Hospital of Patras, Surgical Department, between June 1994 and December 2011. All known singleton pregnancies that were recorded in our bariatric patient database during this time period were included. Multiple sequential pregnancies were included, but multiple gestation pregnancies as well as pregnancies following vertical banded gastroplasty (VBG) were excluded. Pregnancy outcomes were compared among different types of surgery as well as to 20-year overall birth data from our hospital database. In addition, paired comparisons of pre-surgery and post-surgery pregnancy outcomes were made in a subset of these same women who had also given birth before surgery (BS).

Surgical Technique

Surgeries were performed using both open and laparoscopic techniques. The choice of procedure depended upon BMI consensus criteria, metabolic disorders and eating habits as well as the expertise of the surgeon. Representative of malabsorptive procedures is our version of BPD, which is the procedure of choice for patients with body mass index (BMI) ≥ 50kg/m². This procedure includes a gastric pouch of 60ml, a common limb of 100cm, and an alimentary limb of ~400cm with the remainder of the small intestine as the biliopancreatic limb. Other procedures performed included RYGB and SG, and all procedures have been described in detail elsewhere (304,305).

Patient follow-up and data collection

All patients were routinely evaluated at 1, 3, 6 and 12 months after surgery (AS) and yearly thereafter with an additional evaluation at 18 months after BPD. At each follow-up complete medical, laboratory and nutritional evaluations were performed and educational guidelines provided. Routine supplementation included a daily multivitamin-mineral tablet after all procedures, containing 400mcg of folate.
and 6 mcg of vitamin B₁₂, as well as intramuscular (IM) injections of vitamin B₁₂, starting 6 months postoperatively at a dosage of 1000-3000 mcg every 6-12 months depending on laboratory values (160). IM injections as opposed to additional oral supplementation were preferred at our institution as a more reliable method to achieve maximum compliance since economic issues often make compliance with everyday per os supplements a problem. Additional iron (100mg) was also prescribed following RYGB and BPD in premenopausal women, and additional calcium and vitamin D were prescribed in all patients after these 2 procedures (1g + 800 IU and 2g + 1600IU, respectively).

Women of reproductive age were advised to wait one year after SG and RYGB, and 1½ years after BPD before becoming pregnant, and were questioned regarding existing pregnancies or intention to become pregnant. An additional vitamin supplement was recommended after RYGB and BPD during pregnancy as well as extra folic acid, 5mg/day as prescribed by most obstetricians in Greece. Calcium supplements continued as before, iron supplementation was increased as necessary and intramuscular injections of vitamin B₁₂ administered as necessary based on laboratory tests. Protein supplements were prescribed when daily intake was considered inadequate or if serum albumin levels fell below 3.5g/dl. Protein supplements were deemed necessary only after BPD, where the daily protein goal was ~ 100g, adjusted on an individual basis. Supplements contained 20g each of high biological value protein. Information regarding pregnancy and nutritional status was gathered during these routine postoperative visits through the use of questionnaires with follow-up interviews and phone calls. Other pertinent information was obtained from medical records and additional laboratory examinations.

The study was approved by the local Research and Ethics Committee at the University Hospital of Patras.
**Maternal clinical characteristics**

The following maternal characteristics were analyzed: maternal age, BMI before surgery, pre-pregnancy and before delivery, weight gain during pregnancy and the time interval between surgery and the onset of pregnancy. Data regarding pregnancies which occurred before surgery were also collected.

**Laboratory evaluation**

Hematology and biochemical laboratory measurements were obtained before surgery (BS) (I), after surgery (AS) but before pregnancy (II) and during pregnancy (III). Special attention was paid to indices of nutritional status during pregnancy including hemoglobin and hematocrit levels, iron, ferritin, folic acid, vitamin B\textsubscript{12}, albumin, total protein, and calcium. Levels of cholesterol, triglycerides, phosphorus, sodium and magnesium were also recorded.

**Neonatal outcomes and delivery data**

Information was collected regarding type of delivery, gestational age (GA), incidence of preterm deliveries, birth weight (BW), length and head circumference, as well as the incidence of low birth weight (LBW), small for gestational age (SGA) and macrosomia. Preterm was defined as GA < 37 weeks, LBW as <2500 grams, SGA as BW < 10th percentile for GA, macrosomia as > 4000 grams, and large for gestational age (LGA) as BW > 90th percentile for GA\textsuperscript{(306)}.

**Childhood development**

All mothers were contacted and asked to provide information regarding weight, height and age of children born before and after surgery. Reference charts\textsuperscript{(307)} were used to assess BMI percentiles of children under 18 years of age, where obesity is defined as BMI > 90\textsuperscript{th} percentile.
Statistical analysis

All continuous variables are expressed with means and standard deviation. Inferential statistics tests were preceded by Kolmogorov-Smirnof tests of normality. Comparisons of central tendency measures were performed using analysis of variance (ANOVA) tests or their non-parametric forms where appropriate. Where statistical significance was found, appropriate post-hoc tests (Bonferroni or Tamhane’s test) were used to locate the specific pairs of groups that led to the observed significance. Paired measurements were treated with Repeated Measures ANOVA, paired-t-test or Wilcoxon matched-pair signed-rank test depending on the specific nature of the variables under study. Possible significance of differences between qualitative variables was investigated with chi-squared test. All tests were performed using the Statistical Package for Social Sciences, (SPSS) version 20.
II. 3. Results

This is a retrospective study investigating singleton pregnancy outcomes of 113 women who gave birth to 150 children following three different surgical procedures performed at our institution between June 1994 and December 2011. Sixty-four women underwent our version of biliopancreatic diversion (BPD), 35 gastric bypass (RYGB) and 15 sleeve gastrectomy (SG). Pregnancy outcomes were compared among different types of surgery as well as to 20-year data from our hospital database. In addition, paired comparisons of pregnancy outcomes were made in a subset of 36 of these same women who had also given birth to 56 children before surgery (BS).

Clinical characteristics

Clinical characteristics of the groups according to the type of bariatric operation performed are shown in Table 1. Preoperative body weight and BMI as well as pre-pregnancy BMI were higher in the BPD group, but there were no significant differences in weight gain during pregnancy. The time interval from surgery to onset of the first pregnancy was significantly shorter in the SG group.

Table 1. Clinical characteristics according to type of bariatric operation.

<table>
<thead>
<tr>
<th></th>
<th>BPD</th>
<th>RYGB</th>
<th>SG</th>
<th>Total</th>
<th>p value</th>
<th>Sig. pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28.8 ± 5.3</td>
<td>27.0 ± 4.5</td>
<td>26.0 ± 4.4</td>
<td>27.9 ± 5.0</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>before surgery (n=64)</td>
<td>(n=34)</td>
<td>(n=15)</td>
<td>(113)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>143.7 ± 21.9</td>
<td>127.2 ± 21.9</td>
<td>121.9 ± 9.4</td>
<td>135.8 ± 22.5</td>
<td>&lt;0.001</td>
<td>BPD-RYGB</td>
</tr>
<tr>
<td>presurgery (n=64)</td>
<td>(n=34)</td>
<td>(n=15)</td>
<td>(113)</td>
<td></td>
<td></td>
<td>BPD-SG</td>
</tr>
<tr>
<td>BMI presurgery</td>
<td>53.7 ± 8.7</td>
<td>48.0 ± 7.3</td>
<td>43.7 ± 3.2</td>
<td>50.7 ± 8.6</td>
<td>&lt;0.001</td>
<td>BPD-RYGB</td>
</tr>
<tr>
<td></td>
<td>(n=64)</td>
<td>(n=34)</td>
<td>(n=15)</td>
<td></td>
<td></td>
<td>BPD-SG</td>
</tr>
<tr>
<td>BMI prepregnancy</td>
<td>30.7 ± 5.3</td>
<td>29.3 ± 4.6</td>
<td>27.0 ± 3.8</td>
<td>29.8 ± 5.1</td>
<td>0.033</td>
<td>BPD-SG</td>
</tr>
<tr>
<td>BMI predelivery</td>
<td>33.9 ± 5.3</td>
<td>33.3 ± 4.8</td>
<td>31.2 ± 4.1</td>
<td>33.4 ± 5.1</td>
<td>0.176</td>
<td>NS</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>8.6 ± 7.9</td>
<td>10.6 ± 6.7</td>
<td>11.9 ± 10.2</td>
<td>9.5 ± 7.8</td>
<td>0.277</td>
<td>NS</td>
</tr>
<tr>
<td>during pregnancy</td>
<td>(n=64)</td>
<td>(n=34)</td>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery to 1st pregnancy</td>
<td>37.9 ± 23.6</td>
<td>44.1 ± 29.9</td>
<td>23.5 ± 17.6</td>
<td>37.9 ± 25.6</td>
<td>0.033</td>
<td>RYGB-SG</td>
</tr>
<tr>
<td>pregnancy (months)</td>
<td>(n=64)</td>
<td>(n=34)</td>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation (SD). BMI= body mass index (kg/m²)
Laboratory evaluation

Representative laboratory measurements indicating maternal metabolic profile are presented in Table 2. In order to determine if altered laboratory tests during pregnancy were a result only of pregnancy or only of surgery or could be attributed to a combined effect of surgery plus pregnancy, a comparison was made between laboratory values before surgery, after surgery but before the onset of pregnancy, and during pregnancy. Values at all 3 time points are paired for the same mothers and refer only to the first postoperative pregnancy.

Pre-pregnancy hemoglobin (Hb) and hematocrit (Hct) levels were lower than pre-surgery levels following all types of surgery, with a further significant decrease observed during pregnancy in all 3 groups. Hb levels < 10g/dl were seen in 15 BPD patients (24.2%) and 5 RYGB patients (15.6%). Hct levels < 30% were observed in 10 BPD patients (16.1%) and 1 RYGB patient (3.1%). None of the patients had Hb levels < 7g/dl and none received intravenous iron administration. Iron levels in general increased somewhat after surgery with a further increase during pregnancy, which was significant only in the SG group.

Folic acid levels increased following surgery and increased even further during pregnancy. The increase during pregnancy was statistically significant in all groups. Two non-compliant RYGB patients (6.3%) had folic acid levels < 3ng/ml during pregnancy, but none had folic acid levels < 1.9 ng/ml, which is the low-end cut off point at our institution.

There was a decrease in vitamin B$_{12}$ levels following all types of surgery, but no significant further decrease during pregnancy. Levels < 130 pg/ml, which is the low end cutoff for the second trimester of pregnancy (222) were seen in 14 patients during pregnancy- 7 (11.7%) following BPD, 5 (15.6%) after RYGB, and 2 (13.3%) after SG. Of these patients, 8 presented with vitamin B$_{12}$ levels < 100 pg/ml, 3 (5%) after BPD, 3 (9.4%) after RYGB and 2 (13.3%) after SG all of whom were treated with intramuscular injections. None of the patients presented clinical symptomatology.

Mean serum albumin levels decreased significantly following BPD and RYGB between the time of surgery and the onset of pregnancy. During pregnancy a significant decrease was seen following all types of surgery; however, mean serum albumin levels remained within the normal range. Serum albumin levels < 3 g/dl were
seen in a total of 5 patients, all following BPD (8.3%). Only one of these patients (1.7%) presented with albumin < 2.6g/dl. This particular patient had not informed us of her pregnancy and came to the hospital at the end of her pregnancy and was admitted for treatment with total parenteral nutrition (TPN).

Mean calcium levels when corrected for albumin concentration did not change during pregnancy, and parathormone (PTH) levels remained constant. Serum phosphorous levels remained within the normal range in all patients during pregnancy.

There was a small but significant decrease in serum sodium levels during pregnancy in the BPD group but levels remained within the normal range in all patients. There were no significant changes after surgery or during pregnancy in sodium levels in any of the other groups. Potassium and magnesium levels also remained within the normal range in all patients.

There was significant improvement in the metabolic profile of all women regarding blood glucose levels. Preoperatively, a total of 36 patients had fasting glucose levels > 100mg/dl, 21 had levels > 110 mg/dl and 6 had levels > 125 mg/dl. Two of these women had gestational diabetes (GDM) requiring insulin during BS pregnancies whereas no patient had GDM in pregnancies occurring AS.

Finally, regarding blood lipid profile, serum cholesterol levels decreased significantly after BPD and RYGB, and serum triglyceride levels decreased significantly after all types of surgery, including SG. During pregnancy cholesterol and triglyceride levels increased significantly compared to pre-pregnancy levels in the BPD and RYGB groups, but were still within the normal range.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>BPD (n = 62)</th>
<th></th>
<th>Sig pairs</th>
<th>RyGB (n = 32)</th>
<th></th>
<th>Sig pairs</th>
<th>SG (n = 15)</th>
<th></th>
<th>Sig pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>p</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>p</td>
<td>I</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>13.1 ± 1.1</td>
<td>12.2 ± 1.5</td>
<td>11.1 ± 1.3</td>
<td>&lt; 0.001</td>
<td>All</td>
<td>13.1 ± 1.0</td>
<td>12.6 ± 1.4</td>
<td>11.5 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>40.1 ± 3.1</td>
<td>37.4 ± 3.9</td>
<td>33.8 ± 3.6</td>
<td>&lt; 0.001</td>
<td>All</td>
<td>40.1 ± 2.9</td>
<td>38.2 ± 3.7</td>
<td>35.4 ± 4.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fe (μg/dl)</td>
<td>62.4 ± 22.4</td>
<td>68.7 ± 29.9</td>
<td>75.7 ± 30.8</td>
<td>0.014</td>
<td>I-III</td>
<td>63.7 ± 27.3</td>
<td>68.7 ± 32.1</td>
<td>75.4 ± 40.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>58.9 ± 63.9</td>
<td>46.6 ± 58.0</td>
<td>30.9 ± 32.9</td>
<td>0.003</td>
<td>I-III II-III</td>
<td>32.5 ± 28.7</td>
<td>37.7 ± 51.7</td>
<td>25.4 ± 25.3</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>102.5 ± 23.0</td>
<td>82.4 ± 8.5</td>
<td>79.2 ± 10.1</td>
<td>&lt; 0.001</td>
<td>I-II I-III</td>
<td>92.5 ± 12.2</td>
<td>84.8 ± 9.1</td>
<td>80.8 ± 12.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total Protein (g/dl)</td>
<td>7.59 ± 0.60</td>
<td>7.08 ± 0.58</td>
<td>6.51 ± 0.61</td>
<td>&lt; 0.001</td>
<td>All</td>
<td>7.67 ± 0.58</td>
<td>7.30 ± 0.41</td>
<td>6.80 ± 0.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.35 ± 0.38</td>
<td>4.26 ± 0.41</td>
<td>3.81 ± 0.51</td>
<td>&lt; 0.001</td>
<td>I-III II-III</td>
<td>4.64 ± 0.45</td>
<td>4.51 ± 0.32</td>
<td>4.08 ± 0.44</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Folic acid (ng/ml)</td>
<td>5.8 ± 3.0</td>
<td>10.8 ± 5.2</td>
<td>15.8 ± 7.7</td>
<td>&lt; 0.001</td>
<td>All</td>
<td>6.5 ± 4.0</td>
<td>7.7 ± 4.3</td>
<td>13.6 ± 6.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vit. B12 (pg/ml)</td>
<td>428 ± 273</td>
<td>258 ± 162</td>
<td>239 ± 134</td>
<td>&lt; 0.001</td>
<td>I-II</td>
<td>528 ± 433</td>
<td>238 ± 116</td>
<td>270 ± 152</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.36 ± 0.44</td>
<td>9.38 ± 0.54</td>
<td>8.96 ± 0.54</td>
<td>&lt; 0.001</td>
<td>I-III II-III</td>
<td>9.48 ± 0.49</td>
<td>9.48 ± 0.36</td>
<td>9.11 ± 0.49</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Phos. (mg/dl)</td>
<td>3.6 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>3.7 ± 0.6</td>
<td>&lt; 0.001</td>
<td>I-II</td>
<td>3.6 ± 0.7</td>
<td>4.0 ± 0.6</td>
<td>3.8 ± 0.5</td>
<td>0.018</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>44.3 ± 27.7</td>
<td>37.7 ± 18.6</td>
<td>34.3 ± 18.2</td>
<td>NS</td>
<td>II-III</td>
<td>139.3 ± 2.0</td>
<td>140.0 ± 1.6</td>
<td>139.7 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>139.6 ± 2.5</td>
<td>140.4 ± 2.5</td>
<td>139.2 ± 3.1</td>
<td>0.04</td>
<td>II-III</td>
<td>139.3 ± 2.0</td>
<td>140.0 ± 1.6</td>
<td>139.7 ± 2.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2. Maternal biochemical profile according to type of bariatric operation before (I) and after surgery (II) and during pregnancy (III).
<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>PTH= parathormone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K (mEq/L)</strong></td>
<td>4.5 ±0.4</td>
<td>4.4 ±0.4</td>
<td>4.32 ±0.5</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Mg (mg/dl)</strong></td>
<td>1.96±0.2</td>
<td>1.97±0.2</td>
<td>1.97±0.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Chol (mg/dl)</strong></td>
<td>196±38</td>
<td>136±27</td>
<td>150±38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TG (mg/dl)</strong></td>
<td>130±66</td>
<td>80±28</td>
<td>94±42</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation (SD).

**PTH= parathormone**
**Neonatal outcomes and delivery data**

Table 3 shows the delivery data and neonatal outcomes of infants born after surgery (AS) as well as infants born over the last 20 years at our institution. Comparing outcomes after different types of surgery, there were no differences among surgical procedures regarding gestational age or frequency of preterm delivery. Comparing newborn data to overall hospital data, however, gestational age was significantly lower and the incidence of preterm delivery significantly higher after BPD. Mean birth weight was also lower after BPD when compared with RYGB and SG, and mean birth weight after all procedures was lower than that seen in the general population as represented by overall hospital data. On the other hand none of the infants born following surgery had macrosomia compared with 5.5% in overall hospital births. The incidence of LBW and SGA were also more frequent after both BPD and RYGB when compared to hospital data; however there was no difference in either parameter among surgeries. Finally, the percentage of cesarean deliveries was high following all types of surgery and was significantly higher than in overall hospital deliveries.

Of further interest, regarding neonatal outcomes in relation to the time interval from surgery to the onset of pregnancy, we observed that after BPD 12 women became pregnant before the recommended 18 months, 4 of whom became pregnant before 12 months. A total of 2 babies were preterm- one was normal weight for age and the other was small for gestational age. This case was the mother who had not informed us of her pregnancy and who became pregnant 10 months following BPD. One additional infant was born at 37 weeks and was also small for gestational age. In this case the time from surgery to onset of pregnancy was 13.5 months. These 2 cases demonstrate the importance of waiting the recommended amount of time before conception. After RYGB only 2 women became pregnant before the recommended 12 months. Of these, one delivered preterm, but there was no incidence of low birth weight or small for gestational age. Similarly, after SG 5 women became pregnant before the recommended 12 months, one of whom delivered preterm, but there was no incidence of low birth weight or small for gestational age.
Table 3. Neonatal data following surgery according to type of bariatric operation and comparison to 20-year hospital data.

<table>
<thead>
<tr>
<th></th>
<th>BPD</th>
<th>RYGB</th>
<th>SG</th>
<th>Total</th>
<th>Hospital 1993-2012</th>
<th>Significant pairs/p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>83</td>
<td>45</td>
<td>18</td>
<td>146</td>
<td>22870</td>
<td></td>
</tr>
<tr>
<td>Male n (%)</td>
<td>45 (54.2)</td>
<td>22 (48.9)</td>
<td>10 (55.6)</td>
<td>77 (52.7)</td>
<td>11755 (51.4)</td>
<td>BPD/Hospital &lt;0.05</td>
</tr>
<tr>
<td>Weeks of gestation</td>
<td>37.7 ± 1.9</td>
<td>37.7 ± 2.0</td>
<td>38.4 ± 1.7</td>
<td>37.8 ± 1.9</td>
<td>38.2 ± 0.02</td>
<td>RYGB/Hospital &lt;0.0001</td>
</tr>
<tr>
<td>Preterm delivery n (%)</td>
<td>18 (22.0)</td>
<td>6 (13.6)</td>
<td>1 (5.6)</td>
<td>25 (17.1)</td>
<td>2807 (12.3)</td>
<td>RYGB/Hospital &lt;0.005</td>
</tr>
<tr>
<td>Birth weight (BW) (g)</td>
<td>2677 ± 497</td>
<td>2921 ± 537</td>
<td>2997 ± 320</td>
<td>2792 ± 507</td>
<td>3190.2 ± 28.6</td>
<td>SGA/Hospital &lt;0.05</td>
</tr>
<tr>
<td>LBW (BW &lt; 2500g)</td>
<td>23 (27.7%)</td>
<td>9 (20.0%)</td>
<td>0</td>
<td>32 (21.9%)</td>
<td>2158 (9.4%)</td>
<td>BPD/Hospital &lt;0.0001</td>
</tr>
<tr>
<td>SGA n (%)</td>
<td>8 (9.6)</td>
<td>4 (8.9)</td>
<td>0</td>
<td>12 (8.2)</td>
<td>304 (1.3)</td>
<td>RYGB/Hospital &lt;0.01</td>
</tr>
<tr>
<td>LBW + SGA n (%)</td>
<td>6 (7.2)</td>
<td>4 (8.9)</td>
<td>0</td>
<td>10 (6.8)</td>
<td>3438 (15.0)</td>
<td>RYGB/Hospital &lt;0.001</td>
</tr>
<tr>
<td>BW &gt; 4000 g</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1254 (5.5%)</td>
<td>RYGB/Hospital &lt;0.05</td>
</tr>
<tr>
<td>LGA n (%)</td>
<td>6 (7.2)</td>
<td>6 (13.3)</td>
<td>0</td>
<td>12 (8.2)</td>
<td>3438 (15.0)</td>
<td>SGA/Hospital &lt;0.05</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>48.1 ± 3.3</td>
<td>49.7 ± 2.4</td>
<td>49.6 ± 1.6</td>
<td>48.8 ± 2.4</td>
<td>3438 (15.0)</td>
<td>BPD/RYGB &lt;0.05</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>33.0 ± 2.7</td>
<td>33.7 ± 1.9</td>
<td>34.4 ± 1.4</td>
<td>33.4 ± 2.3</td>
<td>NS</td>
<td>BPD/SG &lt;0.05</td>
</tr>
<tr>
<td>Cesarean delivery n (%)</td>
<td>53 (66.3)</td>
<td>23 (52.3)</td>
<td>12 (66.7)</td>
<td>88 (60.1)</td>
<td>9411 (41.1)</td>
<td>Surgery/Hospital &lt;0.0001</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation (SD)
Preterm = < 37 weeks gestation
LBW = low birth weight
SGA=small for gestational age (birth weight < 10th percentile)
LGA= large for gestational age (birth weight > 90th percentile)
Table 4 presents the paired maternal and neonatal data from the subset of 36 mothers with pregnancies before as well as after surgery. Gestational weight gain was significantly lower in pregnancies after surgery with no cases of gestational diabetes. Neonatal birth weight was significantly lower without an increase in LBW or SGA and there were no significant differences in birth length, head circumference or gestational age.

**Table 4. Maternal and neonatal data from paired before surgery and after surgery pregnancies**

<table>
<thead>
<tr>
<th>Pregnancy data</th>
<th>Before Surgery</th>
<th>After Surgery</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong>=36</td>
<td>n=36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.9 ± 4.5</td>
<td>34.0 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) at start</td>
<td>34.7 ± 9.1</td>
<td>30.4 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg) at start</td>
<td>91.4 ± 23.0</td>
<td>79.4 ± 13.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Weight gain (kg) during pregnancy</td>
<td>14.3 ± 12.7</td>
<td>7.4 ± 8.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Gestational diabetes (cases)</td>
<td>2</td>
<td>0</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal data</th>
<th>Before Surgery</th>
<th>After Surgery</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong>=53</td>
<td>n=39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3346 ± 603</td>
<td>2760 ± 528</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBW (&lt; 2500 g)</td>
<td>4 (7.5%)</td>
<td>8 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>1 (1.9%)</td>
<td>1 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Macrosomia (&gt; 4000 g)</td>
<td>3 (5.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td>9 (17.0%)</td>
<td>3 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Length (cm) O</td>
<td>50.5 ± 2.0</td>
<td>49.6 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>34.1 ± 1.4</td>
<td>34.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Weeks of gestation</td>
<td>38.2 ± 1.8</td>
<td>37.4 ± 1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation (SD)

BMI = Body Mass Index

SGA = Small for gestational age (birth weight < 10th percentile)

LGA = Large for gestational age (birth weight > 90th percentile)
**Childhood development**

Preliminary findings regarding the childhood development of these children are shown in Table 6. No significant differences in current BMI or BMI percentile can be seen in specific age groups. Only when looking at the total number of children can a significant difference be seen, where both BMI and BMI percentile were found to be significantly lower overall in children born after surgery. However, it is interesting to note that 9 children born before surgery, (1 aged 15 years and 8 ≥ 18 years) currently have a BMI ≥ 30kg/m².

**Table 6.** Current data of children born before and after surgery to the same mothers

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Before surgery (BS)</th>
<th>After surgery (AS)</th>
<th>p values BS vs AS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of children (M/F)</td>
<td>BMI ± SD</td>
<td>BMI %ile ± SD (to age 18)</td>
</tr>
<tr>
<td>2-4</td>
<td>12 (9M/3F)</td>
<td>15.4 ± 1.5</td>
<td>36.9 ± 25.1</td>
</tr>
<tr>
<td>4-6</td>
<td>8 (3M/5F)</td>
<td>15.6 ± 3.9</td>
<td>46.9 ± 40.2</td>
</tr>
<tr>
<td>6-8</td>
<td>1 (F)</td>
<td>20.1</td>
<td>80.0</td>
</tr>
<tr>
<td>8-10</td>
<td>4 (1M/3F)</td>
<td>18.4 ± 4.7</td>
<td>42.3 ± 37.5</td>
</tr>
<tr>
<td>10-12</td>
<td>6 (2M/4F)</td>
<td>22.1 ± 2.6</td>
<td>70.8 ± 22.7</td>
</tr>
<tr>
<td>12-15</td>
<td>8 (5M/3F)</td>
<td>26.5 ± 7.3*</td>
<td>77.6 ± 20.5</td>
</tr>
<tr>
<td>15-18</td>
<td>6 (3M/3F)</td>
<td>21.0 ± 3.3</td>
<td>38.2 ± 37.1</td>
</tr>
<tr>
<td>≥ 18</td>
<td>29 (19M/10F)</td>
<td>26.3 ± 4.9*</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>54 (30M/24F)</td>
<td><strong>24.5 ± 5.5</strong></td>
<td><strong>63.0 ± 31.0</strong></td>
</tr>
</tbody>
</table>

*BMI / %ILE 0.7783 / 0.8805 NS  
*BMI / %ILE 0.9360 / 0.7115 NS  
*BMI / %ILE 0.0001 / 0.0195 NS
II. 4. Discussion

The present study compared pregnancy outcomes and nutritional status following three different bariatric surgical procedures performed at a single institution. Several studies have investigated pregnancy outcomes after laparoscopic gastric banding (LAGB) and RYGB. There is only one study presenting pregnancy outcomes following SG, and few studies investigating pregnancy outcomes after BPD and BPD with duodenal switch (BPD/DS). Other studies comparing outcomes between different procedures include only restrictive LAGB and silastic ring vertical gastroplasty (SRVG) procedures, as well as the restrictive-malabsorptive RYGB. There are no other studies comparing pregnancy outcomes following restrictive and BPD-type malabsorptive procedures.

In an attempt to determine if altered laboratory tests during pregnancy were a result only of pregnancy or only of surgery or could be attributed to a combined effect of surgery plus pregnancy, a comparison was made between representative laboratory values before surgery (BS), after surgery (AS) but before the onset of pregnancy, and during pregnancy. To our knowledge this is the only study published to date presenting such results.

We found a significant decrease in Hb and Hct after BPD and RYGB and a further significant decrease during pregnancy after all types of surgery. Since lower Hb and Hct levels are seen during normal pregnancies, this is an expected result. Defining anemia in pregnancy as Hb < 10g/dl, 15% of women after RYGB and 24% after BPD had anemia requiring extra iron supplements, but there were no cases of severe anemia (Hb <7g/dl), and none received IV iron supplementation. Varying degrees of anemia have been reported by others in pregnant women following RYGB. Most found that although mild anemia was relatively frequent (20-60%), severe anemia was rare.

Folic acid is an especially important vitamin during pregnancy due to its role in the prevention of neural tube defects, and therefore, of particular concern following RYGB and BPD. Interestingly, we observed an increase in folic acid levels both following surgery and during pregnancy. The increase during pregnancy was statistically significant in all groups, in our opinion, probably due to the dose as well as adherence to supplementation guidelines. It is important to note that the only 2 women...
who had relatively low folic acid levels during pregnancy were those who were not compliant with supplement recommendations. Despite the fact that the levels were still within the normal range for pregnancy\(^{222}\), the importance of compliance must be stressed, not only after surgery in general, but particularly in women of childbearing age before and during pregnancy.

Vitamin B\(_{12}\) is another vitamin of particular concern following bariatric surgery and therefore also during pregnancy. There are no other studies to our knowledge presenting detailed information of vitamin B\(_{12}\) status. Despite our supplementation practice for vitamin B\(_{12}\), we observed a decrease in vitamin B\(_{12}\) levels following all types of surgery, but no significant further decrease during pregnancy. However, levels below what is considered normal in pregnancy were seen frequently enough to warrant concern. Although none of the patients had clinical symptomatology, this is an indication that vitamin B\(_{12}\) levels should be monitored closely after all types of surgery, especially during pregnancy. It is possible that with daily oral vitamin B\(_{12}\) supplements at a dosage of 1000mcg daily\(^{27}\), as opposed to our routine practice of B\(_{12}\) injections this could have been avoided; however, cost and compliance must be considered and this is an issue warranting further study.

Regarding the issue of protein malnutrition, in agreement with the findings of others\(^{288}\) we found no hypoalbuminemia following RYGB. Of particular concern, however, is protein status following malabsorptive procedures. Two studies of pregnancy following Type I BPD procedure with 250cm alimentary limb including 50cm common channel\(^{270,292}\) reported protein malnutrition requiring parenteral nutrition (PN) in 20% and 21% of pregnant women, respectively. Another study in women after BPD/DS procedure with 250 cm alimentary limb including 100cm common channel\(^{263}\) reported severe hypoalbuminemia (\(< 2.6\text{g/dl}\)) in 2.5% of postoperative pregnancies. In our study, five BPD patients (8.3%) presented with albumin levels \(< 3\text{g/dl}\), which may be considered normal in some cases during pregnancy\(^{222}\), but only one (1.7%) had severe hypoalbuminemia. This particular woman became pregnant only 10 months after surgery, had not informed us of her pregnancy and was admitted to hospital at term, at which time TPN was administered. This case is a prime example of the importance of close follow-up and appropriate postoperative waiting time in this patient group. The other 4 women were advised to consume more dietary protein as well as protein supplements and had no further
problems. Based on these data our version of BPD appears to be associated with a lower incidence of severe hypoproteinemia than the Type I BPD procedure, probably due to the longer alimentary limb with 100cm common channel.

Neonatal outcomes following bariatric surgery were similar to those reported by others for RYGB in terms of mean BW, incidence of small for gestational age (SGA) and frequency of preterm births (276,277,288,289). Data following BPD in our study showed 27.7 % LBW and 7.2 % SGA with no macrosomia. These findings are comparable to those of Marceau (263) following BPD-DS with LBW 27.4% and 9.6% SGA. In this study, 3 of the 4 infants born to mothers with severe hypoalbuminemia during pregnancy were SGA. Similarly, in our experience the infant born to the mother with severe hypoalbuminemia was also SGA. This is an issue that warrants further investigation since LBW and SGA may be associated with adverse health outcomes. In this regard, the routine use of protein supplements in women before conception and during pregnancy may be warranted. On the other hand, the incidence of macrosomia, which is also associated with adverse health outcomes in later life including obesity and the metabolic syndrome, was significantly reduced.

Comparing different types of surgery, we found mean birth weight and length following BPD to be significantly less than that following RYGB or SG. However, the frequency of SGA was similar after BPD and RYGB (9.6% vs. 8.9%, respectively), and there was no significant difference in head circumference or gestational age. When neonatal data was compared to overall 20-year hospital data, average birth weight was significantly lower following all types of surgery, with a significantly higher incidence of LBW and SGA after BPD and RYGB. On the other hand, there was no macrosomia following surgery, and the incidence of LGA was significantly lower following BPD than in the general hospital population. The higher frequency of cesarean deliveries in postoperative pregnancies is in line with published literature and may be due to obstetricians’ bias since there appears to be no known physiological reason necessitating CD in women following bariatric surgery (253).

Looking at paired data for neonates born to the same mothers BS and AS, our findings are in agreement with those of others after RYGB (271,278) and BPD (263,270,301), showing that birth weight of AS infants was less than that of BS infants without any significant differences in gestational age, length, or head circumference, suggesting that the fetal development is not affected by the surgical operation.
Recent studies have begun to appear investigating later childhood development of children born before and after BPD type malabsorptive surgery\textsuperscript{(301-303)}. These studies have shown that mean body weight and BMI percentile as well as the incidence of severe obesity are significantly lower in children born AS. These findings indicate that surgical weight loss may help to prevent parental transmission of obesity to future generations, possibly due to an improved intrauterine environment\textsuperscript{(301-303)}. Our preliminary results agree with these findings; however, a major limitation of our study is that the age ranges thus far are not comparable, and the number of children is still too small to draw any definitive conclusions. Other study limitations include the retrospective nature of the investigation, involving data gathered in some cases after a long period of time, and the small number of patients in the SG group. In addition, further research following BPD and DS procedures in this patient group is definitely warranted and may provide insight into possible advantages of preservation of the antrum and pylorus as in the DS procedure versus the longer alimentary limb as in our BPD procedure. Finally, it must be noted that the results of our study pertain to a patient group with follow up at an institution with bariatric expertise and may or may not be extendable to post bariatric patients having obstetrical care at an institution without bariatric experience, and this is another area that needs closer study.
III. Conclusions and Future Directions

In conclusion, our study showed reasonably good pregnancy outcomes in this sample population after these three types of bariatric surgery provided that nutritional guidelines and supplementation recommendations are followed. However, closer monitoring is required following malabsorptive procedures especially regarding protein nutrition, as hypoproteinemia may have an impact on the incidence of LBW and SGA. For this reason we would suggest that women undergoing malabsorptive procedures wait the recommended period of time, at least 18 months after surgery, and be in good nutritional status before attempting to conceive. In addition, further study with larger samples and better controls are needed regarding nutrient status in this patient group. Although there are detailed updated guidelines regarding vitamin and mineral supplementation after surgery (27), and some recommendations for pregnancy following RYGB (237), more specific guidelines for pregnancy following BPD-type malabsorptive procedures are needed, regarding micronutrient as well as protein supplementation. Based on a compilation of evidence and recommendations from both the obesity surgery and obstetrics literature to date as well as our own experience, it would seem prudent to recommend micronutrient and protein intake at least equivalent to the higher of the two recommendations (surgery alone vs. pregnancy alone) with special attention to women following malabsorptive procedures where additional supplementation, especially of protein, may be warranted. A reasonable recommendation for protein intake would be an amount at least equivalent to the RDA with an additional 25g after RYGB and SG and an additional 30% above this amount after BPD. In all cases, individual adjustment based on current body weight, time following surgery, laboratory exams and overall dietary intake and clinical status is essential.

Finally, as women who become pregnant following bariatric surgery are considered a high risk group, the importance of close monitoring of nutritional status after all types of surgery must be stressed, and further investigation into deficiencies of specific nutrients, including vitamin D, and possible associations with neonatal outcomes is needed.
In closing, an important observation lending support to the positive effects of surgery on pregnancy outcomes is that, although newborns after BPD tended to be leaner than their siblings born before surgery, there did not appear to be any apparent adverse effects on fetal development. This is an important finding, which warrants further study with larger study populations and which, together with data from the continued follow-up of children born before and after surgery into adulthood and future generations, may help to provide insight into mechanisms that may help to arrest the vicious cycle of obesity.
Abstract

**Background:** Nutritional status during pregnancy and the effects of nutritional deficiencies on pregnancy outcomes following bariatric surgery is an important issue that warrants further study.

**Objective:** To investigate pregnancy outcomes and nutritional indices following restrictive and malabsorptive procedures.

**Setting:** University Hospital, Greece.

**Methods:** We investigated pregnancy outcomes of 113 women who gave birth to 150 children following biliopancreatic diversion (BPD), Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) between June 1994 and December 2011. Biochemical indices and pregnancy outcomes were compared among the different types of surgery and to overall 20-year hospital data, as well as to 56 pre-surgery pregnancies in 36 women of the same group.

**Results:** Anemia was observed in 24.2% and 15.6% of pregnancies following BPD and RYGB, respectively. Vitamin B\(_{12}\) levels decreased postoperatively in all groups, with no further decrease during pregnancy; however, low levels were observed not only after BPD (11.7%) and RYGB (15.6%), but also after SG (13.3%). Folic acid levels increased. Serum albumin levels decreased in all groups during pregnancy, but hypoproteinemia was seen only after BPD. Neonates after BPD had significantly lower average birth weight without a higher frequency of low birth weight defined as less than 2500gr. A comparison of neonatal data between babies born before surgery (BS) and siblings born after surgery (AS) showed that AS newborns had lower average birth weight with no significant differences in body length or head circumference and no cases of macrosomia.

**Conclusions:** Our study showed reasonably good pregnancy outcomes in this sample population following all types of bariatric surgery provided nutritional supplement guidelines are followed. Closer monitoring is required in pregnancies following malabsorptive procedures especially regarding protein nutrition.
Περίληψη

Η θρεπτική κατάσταση κατά τη διάρκεια της εγκυμοσύνης και οι συνέπειες διατροφικών ανεπαρκειών στην έκβαση της, που ακολουθεί μια χειρουργική επέμβαση για κλινική σοβαρή παχυσαρκία αποτελεί θέμα που χρήζει περαιτέρω έρευνας.

Σκοπός της συγκεκριμένης μελετής ήταν η διερεύνηση της θρεπτικής κατάστασης και της έκβασης της εγκυμοσύνης, τόσο στις μητέρες όσο και στα νεογνά, σε γυναίκες που είχαν υποβληθεί στο παρελθόν σε περιοριστικές και δυσαπορροφητικές επεμβάσεις για κλινικά σοβαρή παχυσαρκία.

Μελετήθηκαν 113 γυναίκες που γέννησαν 150 παιδιά μετά από χολοπαγκρεατική εκτροπή (BPD), Roux-en-Y γαστρική παράκαμψη (RYGB) και επιμήκη γαστρεκτομή μεταξύ Ιουνίου 1994 και Δεκεμβρίου 2011. Συγκρίθηκαν τα αποτελέσματα των θρεπτικών δεικτών και της έκβασης της εγκυμοσύνης μεταξύ των επεμβάσεων καθώς και με τα 20ετή στοιχεία γεννήσεων του νοσοκομείου μας και τα αποτελέσματα από 56 προεγχειρητικές εγκυμοσύνες σε 36 από τις ίδιες γυναίκες.

Αναιμία παρατηρήθηκε σε 24.2% και 15.6% των κυήσεων μετά από BPD και RYGB, αντίστοιχα. Τα επίπεδα της βιταμίνης B12 μειώθηκαν μεταξύ των γυναικών που είχαν υποβληθεί σε διαφορετικές επεμβάσεις καθώς και μετά από BPD και RYGB (11.7% και 15.6%), αλλά και μετά από SG (13.3%). Τα επίπεδα του φυλλικού οξέος αυξήθηκαν μεταξύ των γυναικών που είχαν γίνει επεμβάσεις καθώς και μετά από SG. Τα επίπεδα της αλβουμίνης μειώθηκαν σε όλες τις ομάδες κατά τη διάρκεια της εγκυμοσύνης, αλλά υποπρωτεϊναιμία παρατηρήθηκε μόνο μετά από BPD (11.7%).

Συμπερασματικά, η δική μας μελέτη έδειξε σχετικά καλή θρεπτική κατάσταση και έκβαση στην έκβαση της εγκυμοσύνης μετά από όλους τους τύπους επεμβάσεων στη συγκεκριμένη πληθυσμική ομάδα, χωρίς να υπάρχει σημαντική διαφορά πολλών θρεπτικών δεικτών κατά τη διάρκεια κύησης, στο μήκος ή στην περίμετρο της κεφαλής και καθόλου μακροσωμία.

Συμπερασματικά, η δική μας μελέτη έδειξε σχετικά καλή θρεπτική κατάσταση και έκβαση στην έκβαση της εγκυμοσύνης μετά από όλους τους τύπους επεμβάσεων στη συγκεκριμένη πληθυσμική ομάδα, χωρίς να υπάρχει σημαντική διαφορά πολλών θρεπτικών δεικτών κατά τη διάρκεια κύησης, στο μήκος ή στην περίμετρο της κεφαλής και καθόλου μακροσωμία.
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