REVIEW

Maternal Micronutrient Deficiencies and Related Adverse Neonatal Outcomes after Bariatric Surgery: A Systematic Review[1,2]

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ABSTRACT

Pregnant and postpartum women with a history of bariatric surgery are at risk of micronutrient deficiencies as a result of the combination of physiologic changes related to pregnancy and iatrogenic postoperative alterations in the absorption and metabolism of crucial nutrients. This systematic review investigates micronutrient deficiencies and related adverse clinical outcomes in pregnant and postpartum women after bariatric surgery. A systematic approach involving critical appraisal was conducted independently by 2 researchers to examine deficiencies of phylloquinone, folate, iron, calcium, zinc, magnesium, iodide, copper, and vitamins A, D, and B-12 in pregnant and postpartum women after bariatric surgery, together with subsequent outcomes in the neonates. The search identified 29 relevant cases and 8 cohort studies. The quality of reporting among the case reports was weak according to the criteria based on the CARE (CAse REporting) guidelines as was that for the cohort studies based on the criteria from the Cohort Study Quality Assessment list of the Dutch Cochrane Center. The most common adverse neonatal outcomes related to maternal micronutrient deficiencies include visual complications (vitamin A), intracranial hemorrhage (phylloquinone), neurological and developmental impairment (vitamin B-12), and neural tube defects (folate). On the basis of the systematically collected information, we conclude that the evidence on micronutrient deficiencies in pregnant and postpartum women after bariatric surgery and subsequent adverse neonatal outcomes remains weak and inconclusive. *Adv Nutr* 2015;6:420–9.

Keywords: maternal nutrition, pregnancy, micronutrients, bariatric surgery, obesity surgery, neonatal complications, gestation, early postpartum

Introduction

Pursuing an adequate maternal nutritional status during pregnancy is crucial to optimize maternal, fetal, and neonatal health. The avoidance of nutritional deficiencies during pregnancy is one of the key messages in the "1000 day" concept. This concept highlights the importance of a lasting foundation for health through adequate nutrition from the start of pregnancy until a child's second birthday (1). The obstetric field is now adressing a clinical concern of nutritional deficiencies in pregnant and postpartum women with previous bariatric surgery (2), who represent a growing population as a consequence of the worldwide obesity epidemic. The complexity of physiologic changes related to the surgery combined with the physiologic changes related to pregnancy may predispose these women to depleted micronutrient concentrations or clinical deficiencies (2).

Restrictive bariatric procedures limit the size of the gastric pouch by the use of a band [laparoscopic adjustable gastric banding (LAGB)][11] or staples (sleeve gastrectomy). The intestinal continuity is kept intact, resulting in a normal digestion and absorption of nutrients. Depleted micronutrient concentrations or deficiencies, however, may occur because of restricted food intake, low nutrient-dense food choices, poor eating habits, and food intolerance (3, 4). Malabsorptive procedures [biliopancreatic diversion (BPD) or Scopinaro procedure] are characterized by bypassing the duodenum and jejunum. The amount of intestine available for absorption is reduced. In mixed procedures

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[11] Abbreviations used: BPD, biliopancreatic diversion; LAGB, laparoscopic adjustable gastric banding; NTD, neural tube defect; RYGB, Roux-en-Y gastric bypass; 25(OH)D, 25-hydroxyvitamin D.

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[Roux-and-Y gastric bypass (RYGB)], both energy intake and absorption are limited. Food intake is reduced by the creation of a gastric pouch, and less intestine, gastric acid, bile, and pancreatic enzymes are available for absorption (4). Frequently reported deficiencies after LAGB are folate and thiamin deficiencies; after BPD are vitamin A, D, and E and phylloquinone deficiencies; and after RYGB are iron, thiamin, vitamin D, folate, and calcium deficiencies (4). Pregnancy is mainly characterized by an increased maternal distribution volume and the increased need for nutrients allowing for the development and growth of the placenta and fetus (5, 6). Maternal kidney function adapts to the clearance of fetal and maternal metabolic waste, resulting in an increased urine excretion of water-soluble vitamins (5). In normal pregnancy, therefore, the need for most micronutrients is increased. Serum concentrations of the water-soluble vitamin B-6, vitamin B-12, folate, and thiamin, together with the fat-soluble vitamin A, phylloquinone, and the inactive form of vitamin D (25-hydroxyvitamin D [25(OH)D]) decrease, whereas vitamin E serum concentrations and the active metabolite of blood vitamin D increase. The need for minerals and trace elements is most often increased during pregnancy. An overview table showing the percentage increase in dietary intakes for micronutrients in pregnant women compared with nonpregnant women is presented in the article by Ladipo (5).

To the best of our knowledge, there are no systematic reviews on micronutrient deficiencies and related adverse outcomes in pregnancies after bariatric surgery, despite a growing clinical concern for the nutritional monitoring and follow-up of these high-risk pregnancies. Therefore, a systematic review was performed that aimed to identify original research reporting on micronutrient deficiencies in pregnant and postpartum women with bariatric surgery, together with the clinical impact on the neonate.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines have been applied appropriately. An internal review protocol was developed to make the review process applicable for 2 independent researchers (GJ and CM).

Criteria for considering studies for inclusion. The target population consisted of pregnant and postpartum women with a history of bariatric surgery. The postpartum period is defined as the period beginning immediately after birth and extending for ~6 wk. The intervention under study was bariatric surgery. This includes a variety of surgical procedures for the treatment of obesity, including the purely restrictive, the purely malabsorptive, and the combined procedures. The primary outcomes are depleted maternal concentrations or deficiencies of phylloquinone, folate, iron, calcium, zinc, magnesium, iodine, copper, and vitamins A, D, and B-12. The choice for these micronutrients was based on a nonsystematic descriptive overview study by Kaska et al. (7), with the exception of vitamin D, which was added because of the relevant prevalence of deficiencies postoperatively and its important role in pregnancy (8). Secondary outcomes were fetal and neonatal complications related to low maternal micronutrient concentrations or deficiencies after bariatric surgery. Original research studies, including nonrandomized and randomized controlled trials, cohort studies, case-control studies, and case series, were considered for this review. Case reports were also considered as relevant because the overview study by Kaska et al. (7) referred to many case-report studies.

Search methods for identification of studies. First, a database search was conducted in PubMed, Embase, and the Cochrane Library by using the following search terms: (vitamins OR vitamin* OR micronutrient* OR folate OR cobalamin OR zinc OR magnesium OR iodide OR iron OR copper) AND (pregnancy OR pregnan* OR gestation*) AND [bariatric surgery OR gastroenterostomy OR (obesity AND surgery) OR gastric by-pass]. Second, the reference lists of relevant publications identified in the first step of the search strategy were screened for additional relevant publications ("snowballing"). The last search was performed on 12 March 2015.

Data collection and analysis. All studies identified were screened for the following inclusion criteria: *1*) reported concentrations of folate, phylloquinone, iron, calcium, zinc, magnesium, iodine, copper, and vitamins A, D and B-12; *2*) performed in pregnant and postpartum women with previous bariatric surgery; *3*) published in English; *4*) published during the past 25 y (1990 to March 2015); and *5*) were original research studies.

Critical appraisal of the selected studies. Because no relevant specific scoring system for case reports was available to our knowledge, a self-developed scoring system was used to critically evaluate the quality of the case reports. The reporting guidelines for case reports [CARE (CAse REporting) guidelines] were first consulted (9). From there, it was decided to formulate 6 specific criteria that seemed to be clinically relevant and necessary in order to obtain a clear and comprehensive view on the cases. The following criteria were formulated and assessed for the specific reports: time between procedure and pregnancy, micronutrient status and supplement intake before pregnancy, supplement intake during pregnancy, laboratory values, and any clinical follow-up in case of adverse pregnancy outcome.

For the cohort studies, the Cohort Study Quality Assessment list of the Dutch Cochrane Center was used (10). The criteria were sample description, selection bias, definition of the exposure, definition of outcomes, length of follow-up, selective loss to follow-up, and confounding factors. Two independent authors (GJ and CM) were responsible for the search and quality appraisal. In case of disagreement or doubt, a third (AB) and fourth (RD) reviewer were consulted.

Results

Search strategy

Figure 1 presents the flow chart of the literature search and study selection. The review included 25 articles: 17 case-report studies presenting 29 relevant cases and 8 cohort studies.

Quality appraisal of the selected studies

Case reports. Data presented by Pelizzo et al. (11, 12) appear to derive from the same case in their 2 reports [2013 (case 2) and 2014 (case 1)]. The time interval between procedure and conception is not reported in 5 of 29 cases. More than half of the cases do not provide information on micronutrient serum concentrations (n = 21 of 30 cases) and supplement intake (n = 17 of 30 cases) before pregnancy. Supplement intake is often summarized without specifications about dosage and time frame. Information about supplement intake during pregnancy is provided more often and is more detailed (n = 24 of 30 cases), as are laboratory values (n = 22 of 30 cases). Clinical follow-up in case of deficiencies and adverse outcomes is often restricted to neonates only.

Cohort studies. Four cohort studies had a retrospective design (13–16), 2 included both retrospective and prospective data (17, 18), and 2 included only prospective data (19, 20). It is not clear whether the study by Nomura et al. (15) was

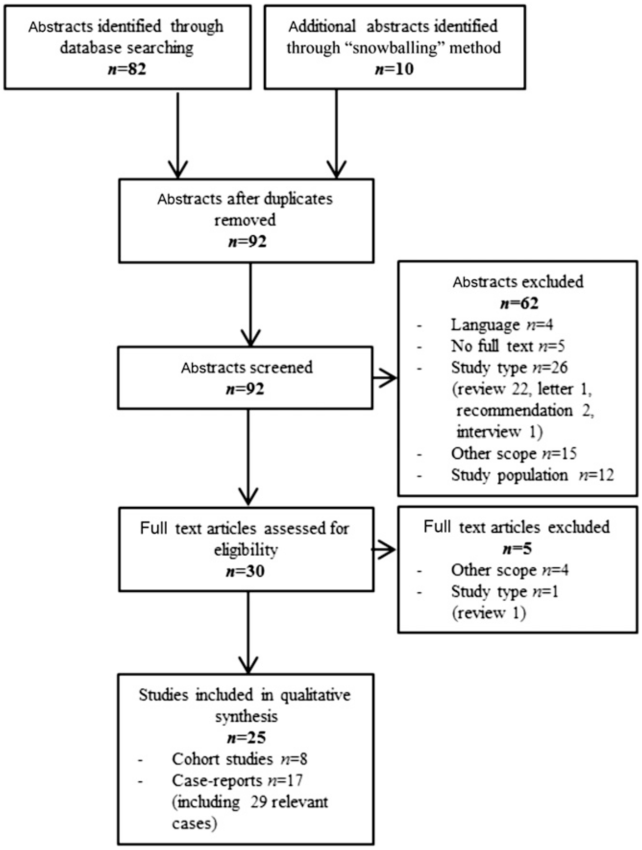

FIGURE 1 Participant flow chart.

performed prospectively or retrospectively. The 2 prospective cohort studies were based on the same research population. The background characteristics of the study populations were mostly clearly described, but the inclusion and exclusion criteria of the historical cohorts was not always clearly defined (n = 6 of 8 studies). The type of surgery is well defined in most studies (n = 7 of 8 studies); however, in the study by Gadgil et al. (16), the authors had insufficient knowledge to judge whether insurance claims deviated from the standard classification of bariatric procedures. The Materials and Methods sections in 7 of 8 cohort studies do not provide clear information on the biochemical variables that were determined, the methods used for analyzing, and the reference values used to define a deficiency. Numbers and reasons for drop-out were specified in only 3 of 8 studies (13, 19, 20), indicating that these were the only studies in which a selective loss to follow-up can be excluded. The adjustment for potential confounding factors is only well specified in the study by Gadgil et al. (16) (n = 1 of 8 studies).

Primary and secondary outcome measures

Intracranial hemorrhages have been reported in neonates after BPD (21, 22) and LAGB (22, 23), possibly related to low phylloquinone serum concentrations and disturbed clotting function. These bleedings resulted in lifelong consequences, including psychomotor and mental retardation, and in 4 cases in perinatal death. A prospective follow-up study reported no adverse outcomes in 49 pregnant women with bariatric surgery in the short term, although almost 88% of the women during the first pregnancy trimester and ~50% of the women at birth had low phylloquinone concentrations (<0.8 nmol/L) (19).

The prevalence of maternal vitamin A deficiency at birth was found to be 58% in the study by Devlieger et al. (20). Cases of women who were deficient in vitamin A have been reported mainly after BPD procedures and resulted in maternal night blindness, preterm birth, and vision complications in the neonate (24–27). Cabano et al. (28) also presented a case of neonatal aortic dilatation that was linked to depleted neonatal vitamin A concentrations.

The prevalences of maternal vitamin B-12 and folate deficiency at birth were found to be 48% and 0%, respectively, in the cohort study by Devlieger et al. (20). One pregnancy was terminated after diagnosis of a neural tube defect (NTD). In the cohort study by Bebber et al. (13), which consisted of 39 pregnancies after RYGB, the prevalences of vitamin B-12 and folate deficiency at birth were found to be 53% and 16%, respectively. No adverse clinical outcomes were reported. Vitamin B-12 deficiency in pregnancy after bariatric surgery did not always result in complications in the mother and child (29). Maternal vitamin B-12 deficiency can result in clinical neurological disease and developmental delay in the neonate (11, 12, 24, 30–34). Maternal deficiency in vitamin B-12 may affect the amount of vitamin B-12 in breast milk, as reported in 2 exclusively breastfed children of mothers with a history of RYGB (30, 31). Pelizzo et al. (11, 12) described 4 NTDs, of which 3 presented in a folate-deficient woman with RYGB and 1 in a folate-deficient woman with BPD. Another case of depleted maternal folate and vitamin B-12 concentrations accompanied with the presence of NTDs was described by Moliterno et al. (34). Low iron concentrations were found in ~10 cases independently of the type of procedure, and no significant maternal and neonatal adverse outcomes were reported (11, 12, 24, 25, 33, 35).

No studies were found on depleted calcium, zinc, magnesium, iodine, and copper concentrations in pregnant and postpartum women with previous bariatric surgery. One case report found no significant nutritional deficiencies in a pregnant patient after RYGB (36).

Dao et al. (14) compared 21 pregnancies within the first year after RYGB with 13 pregnancies after the first year after RYGB. No significant differences were found in maternal nutritional status. On the other hand, a higher need for intravenous iron therapy was seen in women who became pregnant ≥4 y after surgery than in women who became pregnant <4 y after surgery (15) (**Tables 1** and **2**).

Discussion

This systematic review, which is, to our knowledge, the first on this subject, revealed that the literature on micronutrient concentrations during pregnancy after bariatric surgery is limited to 29 relevant cases and a small number (n = 8) of retrospective and prospective cohort studies. The overall level of evidence was low, and studies often did not provide

TABLE 1 Overview of case reports: maternal nutrient deficiencies after bariatric surgery and short- and long-term effects on the neonate[1]

Study (reference)	Procedure	Maternal Nutrient deficiency	Maternal laboratory values[2]	Supplementation	Neonatal complications	Long-term outcome
Bersani et al. (21)	BPD	Coagulopathy Low vitamin K factors	PT: 72.3 (10.15) s INR: 5.7 (0.8 – 1.2) F II: 19.1% (70–140%) F VII: 34.8% (70–140%) F IX: 20% (70–140%) F X: 10% (70–140%) Protein C 50% (70–140%) Protein S 33% (54–110%)	2 × 10 mg/d Konakion (Roche Products Ltd)	Severe coagulopathy	Uncomplicated
Cabano et al. (28)	BPD	None		No vitamin A	Preterm birth Bilateral microphthalmia Respiratory distress Enterocolitis Aortic dilatation	Normal aortic measurements
Campbell et al. (29)	RYGB	Vitamin B-12	138 (228–1514) pg/mL	Stopped (side effects)	Vitamin B-12 deficiency	Uncomplicated
Celiker et al. (30)	RYGB	Vitamin B-12	84 pg/mL (unknown)	Oral multivitamin	Vitamin B-12 deficiency	Delayed gross motor Delayed speech
Cools et al. (24)	BPD	Vitamin A Fe, Ca, Zn	Not reported Not reported	Multivitamins Fe Packed cells	Congenital abnormalities Preterm birth Severe anemia	Retardation Epilepsy Blind Deaf
Cools et al. (24)	BPD	Vitamin A Vitamin D Fe, Zn, Ca, P	Not reported Not reported Not reported	Multivitamins Fe Zn	Preterm birth	Uncomplicated
Cools et al. (24)	BPD	Vitamin B-12 Vitamin A Vitamin D Ca, Se, Fe	Not reported Not reported Not reported Not reported	Parenteral vitamins Packed cells TPN	Preterm birth	Uncomplicated
Cools et al. (24)	BPD	Fe	Not reported	Vitamin B-12 Fe	Cerebral cystic zones	Epilepsy
Eerdekens et al. (22)	AGB	Coagulopathy Low vitamin K factors Phylloquinone	PT: 46.8% (70–150%) aPTT: 29.3 (24–31) s F II: 56% (70–130%) F V: 121% (70–130%) F VII: 40% (70–130%) F IX: 75% (70–130%) F X: 27% (70–130%) 0.2 (0.8–5.3) nmol/L	TPN	Preterm birth Vitamin K deficiency bleeding	Perinatal death
Eerdekens et al. (22)	AGB	None	NA	Not reported	Preterm birth Vitamin K deficiency bleeding	Perinatal death
Eerdekens et al. (22)	AGB	None	NA	Not reported	Subdural hematoma	Delayed gross motor Cerebral palsy
Eerdekens et al. (22)	BPD	None	NA	Not reported	Subarachnoidal bleeding	Mental retardation Cerebral palsy

(Continued)

TABLE 1 (*Continued*)

Study (reference)	Procedure	Maternal Nutrient deficiency	Maternal laboratory values[2]	Supplementation	Neonatal complications	Long-term outcome
Eerdekens et al. (22)	BPD-D	Phylloquinone	0.0008 (0.8–5.3) nmol/L	Not reported	Preterm birth Congenital abnormalities	Perinatal death
Gilchrist et al. (25)	BPD	Vitamin A Vitamin D Vitamin K Fe	0.1 (1.6–2.3) μmol/L 30 (50–300) nmol/L Unknown 3 (10–33) μmol/L	Vitamin A (oral) Fe i.v.	Bilateral microphthalmia Inferior adherent leukoma Optic nerve hypoplasia	Ocular malformations Light-sensitive child
Gomez-Lobo et al. (36)	RYGB	None	Not reported	Prenatal vitamins Ferrous sulfate, 325 mg/d Folic acid	None	None
Grange and Finlay (32)	BPD	Vitamin B-12	73 pmol/L (unknown)	Daily prenatal vitamin incl 8 μg vitamin B-12	Failure to thrive Anemia Neutropenia	Uncomplicated
Gurewitsch et al. (33)	RYGB	Vitamin B-12 Fe Fe saturation	120 (226–966) pg/mL 10 (50–150) μg/dL 2% (15–45%)	Prenatal multivitamin Ferrous sulfate, 325 mg/d vitamin B-12 i.m.	Uncomplicated	Uncomplicated
Huerta et al. (26)	BPD	Vitamin A Vitamin D Vitamin B-12 Zn	<0.2 (0.3–0.9) mg/L 6 (15–57) g/L 153 (160–840) pg/mL 45 (65–256) μg/dL	Not during pregnancy PP: multivitamin PP: ferrous sulfate, 325 mg/d	Premature birth Vitamin A deficiency	Retinal damage
Iavazzo et al. (35)	RYGB	Fe	Not reported	Fe	Preterm birth	Unknown
Iavazzo et al. (35)	AGB	Fe	Not reported	Fe	Preterm birth	Unknown
Iavazzo et al. (35)	AGB	Folate	Not reported	Nutritional supplements	Unknown	Unknown
Moliterno et al. (34)	RYGB	None	NA	Folic acid Vitamin B-12	Open NTD	Uncomplicated
Pelizzo et al. (11)	RYGB	Folate Vitamin B-12 Severe anemia	Not reported	None	NTD Fetal malformations	Unknown
Pelizzo et al. (11)	RYGB	Folate Vitamin B-12 Severe anemia	Not reported	None	NTD Fetal malformations	Unknown
Pelizzo et al. (12)	RYGB	Vitamin B-12 Vitamin A 1,25$(OH)_2$D Fe Ferritin	201 (243–894) pg/mL 0.24 (0.25–0.86) μg/mL 44.6 (48–110) pmol/L 16 (25–156) μg/dL 2 (18–440) μg/L	22 wk: vitamins, minerals	NTD Ventricular dilatation	Unknown
Pelizzo et al. (12)	RYGB	Vitamin B-12 Vitamin A 1,25$(OH)_2$D Fe Ferritin	<15 (243–894) pg/mL 0.1 (0.25–0.86) pg/mL 40.3 (48–110) pmol/L 73 (25–156) μg/mL 10 (18–440) μg/dL	20 wk: vitamins, minerals	NTD Ventricular dilatation	Unknown Unknown

(*Continued*)

TABLE 1 (*Continued*)

Study (reference)	Procedure	Maternal Nutrient deficiency	Maternal laboratory values[2]	Supplementation	Neonatal complications	Long-term outcome
Pelizzo et al. (12)	BPD	Not confirmed	Unknown	None	NTD Bilateral microphthalmia Sensorineural deafness Skeletal dysplasia Short limbs	Failure to thrive
Smets et al. (27)	BDP	Vitamin A	17 (30–80) μg/dL (16 wk) 14.5 μg/dL (30–80) (22 wk)	Multivitamin i.v. Vitamin B-12 Fe Folic acid	Bilateral microphthalmia	Unknown
Van Mieghem et al. (23)	AGB	Coagulopathy Low vitamin K factors Phylloquinone Vitamin A	PT: 12 s (not reported) aPTT: 29 s (not reported) F II: 56% (not reported) F VII: 40% (not reported) F X: 27% (not reported) 0.2 (0.8–5.3) nmol/L 72 (300–650) μg/L	Water-soluble vitamins TPN	Preterm birth Cerebral hemorrhage	Perinatal death
Wardinsky et al. (31)	RYGB	None	NA	Not reported	Macrocytic anemia Vitamin B-12–deficient breast milk Vitamin B-12 deficiency Folate deficiency	Developmental delay Improvement at 12 mo

[1] AGB, adjustable gastric banding; aPTT, activated partial thromboplastin time; BPD, biliopancreatic diversion; BDP-D, biliopancreatic diversion with duodenal switch; Ca, calcium; F, factor; Fe, iron; incl, including; INR, International Normalized Ratio; NA, not applicable; NTD, neural tube defect; P, phosphorus; PP, postpartum; PT, prothrombin time; RYGB, Roux-en-Y gastric bypass; Se, selenium; T, total parenteral nutrition; Zn, zinc; 1,25$(OH)_2D$, 1,25-dihydroxyvitamin D.

[2] Maternal laboratory values are presented as measured maternal values; reference intervals in parentheses.

TABLE 2 Overview of cohort studies: main findings[1]

Study (reference)	Procedure	Study population	Main findings
Bebber et al. (13)	RYGB	39 pregnancies (9 miscarriages)	Vitamin B-12: low (<175 pg/mL) in 53% (n = 16/31) of the women in T1 Folic acid: low (4–17 μg/L) in 16% (n = 5/31) of the women in T1
Dao et al. (14)	RYGB	21 early pregnancies (<1 y after surgery) 13 late pregnancies (≥1 y after surgery)	Iron: deficiency in 1 patient of early group
Devlieger et al. (20)	Mixed	49 pregnancies	Vitamin A: deficiency (<300 μ/L) in 19% (T1) and 58% (T3) of the women Vitamin B-12: deficiency (<191 ng/L) in 35% (T1) and 41% (T3) of the women Folic acid: deficiency (<252 μg/L) in 3% (T1) and 0% (T3) of the women Thiamin: deficiency (<70 nmol/L) in 2% (T1) and 17% (T3) of the women 25(OH)D: severe deficiency (<7 μg/L) in 14% (T1) and 6% (T3) of the women 25(OH)D: mild deficiency (7–20 μg/L) in 26% (T1) and 36% (T3) of the women Ferritin: deficiency (<30 μg/L) in 27% (T1) and 42% (T3) of the women No association between supplement intake and deficiencies One women was diagnosed with an NTD
Dixon et al. (17)	AGB	79 consecutive first pregnancies	No specific nutritional deficiencies 84% of the women reported daily intake of multivitamin
Faintuch et al. (18)	RYGB	14 pregnancies	Iron: occasional low values in T2 (78 ± 50 μg/dL; RV: 37–145 μg/dL) Vitamin B-12: occasional low values in T2 (193 ± 102 μg/dL; RV 180–914 μg/dL)
Gadgil et al. (16)	Mixed	456 pregnancies after surgery 338 pregnancies before surgery	Vitamin B-12: deficiency in 12% after surgery vs. 2% before surgery Folate: deficiency in 7% after surgery vs. 1% before surgery Vitamin D: deficiency in 3% after surgery vs. 0% before surgery Iron: deficiency in 9% after surgery vs. 2% before surgery
Jans et al. (19)	Mixed	49 pregnancies 27 pregnancies without surgery	Phylloquinone: lower in surgical (0.44 nmol/L) vs. nonsurgical (0.65 nmol/L) group in T1 For study group higher in T3 (4.7 nmol/L) vs. T1 (0.42 nmol/L)
Nomura et al. (15)	RYGB	17 pregnancies <4 y after RYGB 13 pregnancies ≥4 y after RYGB	Anemia: defined as hemoglobin <11 g/dL More i.v. iron in late (30.8%) vs. early (0%) group (P = 0.026)

[1] AGB, adjustable gastric banding; NTD, neural tube defect; RYGB, Roux-en-Y gastric bypass; RV, reference value; T1, first trimester of pregnancy; T2, second trimester of pregnancy; T3, third trimester of pregnancy; 25(OH)D, 25-hydroxyvitamin D.

sufficient information for a comprehensive understanding. Globally, depleted maternal concentrations and deficiencies of vitamins A and B-12, phylloquinone, and folate, together with low iron concentrations, have been reported. The most common adverse fetal and neonatal outcomes related to these deficiencies include visual complications (vitamin A), intracranial hemorrhage (phylloquinone), neurological and developmental impairment (vitamin B-12), and NTDs (folate).

Our findings are in line with those of Maggard et al. (37), who found minimal evidence of nutritional adverse events in pregnancies after bariatric surgery. The main reasons for this were inappropriate study designs and the fact that most studies monitored supplement adherence rather than nutritional serum concentrations. A study by Johansson et al. (38) measured birth outcomes, including large-for-gestational age, small-for-gestational age, preterm birth, neonatal death, and major congenital malformation, in pregnancy after bariatric surgery. Although nutritional status of the mothers and infants was not measured, because this was not a focus of the study, the outcomes measured could be associated with malnutrition during pregnancy. In fact, the possibility of nutritional deficiency in iron, vitamin B-12, and folate was acknowledged in the article.

TABLE 3 Proposed micronutrient screening in pregnancy after bariatric surgery

Who	All women regardless of type of surgery	
When	Preconception period	Every 6 mo
	Pregnancy	Every trimester of pregnancy Additional screening if low concentrations despite supplement
	Postpartum	At 6–8 wk, especially breastfeeding mothers
What	Weak evidence	Vitamins A, D, and B-12; folate; phylloquinone; iron
	No evidence	Zinc, calcium, magnesium, iodine
Note	Intention of becoming pregnant	Prenatal multivitamin with vitamin B-12 and folate
	Caution with	Hyperemesis gravidarum, gestational weight loss

Important adverse maternal, fetal, and neonatal outcomes were revealed by the search, mainly in the large number of case reports. Publication bias certainly must be taken into account. For a variety of reasons, adverse outcomes are unlikely to be reported and published. It can therefore be anticipated that the published cases represent only a fraction of the clinical practice. On the other hand, the fact that adverse events are highlighted may affect readers' judgment of actual risk. Therefore, these cases should be interpreted with caution. Case-report studies are seen as a research design with the greatest chance of bias in outcomes and are situated low in the hierarchy of level of evidence (39). Cohort studies are also known to have low internal validity and are therefore situated in the middle of the levels of evidence. Moreover, the lack of inclusion and exclusion criteria for the historical cohorts may suggest a certain degree of selection bias, because a cohort could be determined retrospectively with knowledge about a certain outcome or only a part of the initial cohort might have been selected (10). The cohort studies within this systematic review mainly showed nutritional deficiencies. Only the prospective cohort mentioned 1 termination of pregnancy after diagnosis of an NTD in a folate-deficient woman with a history of bariatric surgery (19, 20). It is impossible to know to which extent the deficiency in folic acid was the direct cause of the congenital malformation because NTDs are also more frequent in overweight and obese women than in normal-weight women (40). Most women after bariatric surgery are still obese, as was the woman in this cohort [BMI (in kg/m^2): 36.0].

The scoring systems used for the quality appraisal shed light on the incompleteness of reporting details for both cohort and case-report studies, although specific reporting guidelines do exist [e.g., CARE and STROBE (Strengthening The Reporting of OBservational studies in Epidemiology) guidelines]. The heterogeneity in the findings makes it hard to generate an overall picture of the current literature. This heterogeneity is reflected by the following aspects: *1*) studies used different cutoff values to define micronutrient deficiencies; *2*) studies reported on all types of surgery, including the rarely performed malabsorptive procedures; and *3*) the time between surgery and conception varied markedly between the different studies. The first year after surgery is known to be a period of rapid weight loss and is believed to be harmful for both mother and child (41). For this reason, it is recommended to delay pregnancy until 12–18 mo after surgery (42). Surprisingly, only a limited number of the case studies presented data on micronutrient deficiencies and adverse events in women who became pregnant within 18 mo after surgery (12, 22, 24, 34, 35). In addition, the mean period between surgery and conception in the cohort studies varied between 18 and 36 mo, with no or very limited information on the critical period of the first 18 mo after surgery. From these limited data, however, no indication was found of seriously adverse events from depleted micronutrient concentrations in pregnancies within the first 18 mo after surgery. Stronger evidence is needed before the recommendation of delaying pregnancy 12–18 mo after surgery can be re-evaluated.

The lack of adverse health outcomes due to iron deficiency in this population could be explained by the short follow-up period in the different studies and by missing information on ferritin, hemoglobin, or hepcidin, which are better indicators of iron depletion or iron anemia. Adverse effects due to iron deficiency have a time lag before the developing infant is affected. During pregnancy, different mechanisms evolve that ensure adequate iron status for the developing child, even if this occurs to the detriment of the mother (e.g., an increase in the percentage of iron transfer from mother to developing infant) (43).

To increase the level of knowledge, large cohort studies are needed to obtain prevalence and incidence rates of micronutrient deficiencies in pregnancies after bariatric surgery and to document the effect of supplementation regimens because the optimal regimens and micronutrient requirements are unclear. Comparative studies are needed in obese and lean pregnant women without bariatric surgery, because it has been shown that most micronutrient serum concentrations seem to be lower in obese pregnant women than in their lean counterparts (44). The cause of nutritional deficiencies in obese pregnant women is not completely known but might be related to poorer dietary patterns (45–47) and differences in requirements of and physiologic responses to critical nutrients (47). A poor dietary pattern has been shown in pregnant women with previous bariatric surgery (48), and this combined with their gastrointestinal modifications may theoretically increase the risk of micronutrient deficiencies. Moreover, pregnant women with previous bariatric surgery often still enter pregnancy with overweight or obesity. Therefore, prepregnancy BMI remains an important variable that should be incorporated in these comparative analyses. Studies on breast-milk composition could be of value, because case reports showed vitamin deficiencies and negative outcomes in exclusively breastfed children in postpartum women with previous bariatric surgery. Finally, counseling women who may become pregnant or those who are pregnant needs to be evaluated to increase the adherence to vitamin supplements, because individuals post–bariatric surgery may not be compliant in taking vitamins (49).

Strong recommendations for the clinical field cannot be formulated until more research is performed. On the basis of the weak evidence gained from this systematic review and from our clinical experience with earlier and current research projects in this population (50), we tentatively present some suggestions for the screening and monitoring of micronutrient concentrations in the preconception and pre- and postnatal periods of women with a history of bariatric surgery (**Table 3**).

A limitation of this systematic review is that it relies only on case reports and cohort studies. This review did not capture the complete "1000 day" concept because the search and results were limited to the early postpartum period; however, we reported several severe complications with long-term to permanent health consequences reaching far beyond the second year of life. A strength of this study is that all of the evidence was collected in a systematic manner. In addition, rigorous quality assessment was undertaken by 2 independent reviewers. Until larger prospective cohort studies have been performed, this systematic review can conclude that the evidence on micronutrient deficiencies and related adverse outcomes in pregnancy after bariatric surgery is relatively weak, most probably due to the variable quality of the research published so far.

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