Gastric bypass: a risk factor for neural tube defects?

Case report

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Gastric bypass surgery has become a safe and acceptable surgical weight loss treatment for individuals who suffer from refractory morbid obesity.1 However, in rare cases, patients who have undergone gastric bypass surgery can have difficulties absorbing certain vitamins and nutrients postoperatively.12,17 Among the possible deficiencies, folate malabsorption is often described as a transient problem that is easily corrected with daily consumption of a multivitamin.3,17 Adequate folate consumption, either through diet or supplementation, has clearly been shown to be effective in the prevention of NTDs in newborns.1 As such, young women who have previously undergone gastric bypass surgery for weight reduction may be at a relatively higher risk of giving birth to babies with NTDs due to their impaired ability to absorb folate, if they do not receive adequate supplementation.8,13,17

The link between gastric bypass surgery, folate deficiency, and NTDs has been supported by a small number of case illustrations, the last of which was reported nearly 20 years ago.5,11,17 We describe a similar case of a woman who failed to adhere to a daily multivitamin supplementation regimen after gastric bypass and subsequently delivered a baby with a myelomeningocele. This case presentation after so many years suggests that we as physicians need to revisit this problem and ensure that young women who undergo surgery for gastric bypass understand that the procedure can render them at risk for having a child with an NTD. Furthermore, the importance of compliance with daily multivitamin supplementation must be stressed. Through our case discussion and review of the literature, we aim to raise awareness so that this devastating outcome can be prevented. We believe aggressive vitamin supplementation, along with patient counseling with a clear explanation that NTDs can be associated with multivitamin noncompliance, may help prevent their occurrence following gastric bypass surgery.

Case Report

History. In 2005, this 38-year-old woman lost 125 pounds after undergoing laparoscopic gastric bypass surgery with creation of a Roux-en-Y anastomosis. At the time, she was the mother of an otherwise healthy 21-year-old daughter who was born with an asymptomatic heart murmur. Her family history was significant for a cousin with spina bifida occulta. She unexpectedly conceived ~ 1 year after her gastric bypass. Prenatal ultrasonography was initially performed for cardiac evaluation, given her other child’s heart murmur and revealed an open neural tube defect and myelomeningo-
Gastric bypass and neural tube defects

celate at approximately L-5 to S-1. The banana sign and lemon sign were also noted along with clubbing of the right foot.

Alpha-fetal protein measurement was not performed because the patient declined amniocentesis. Baseline folate and B_{12} levels were obtained only after the diagnosis was made on ultrasonography. The levels were normal, but prenatal vitamins, including folate and B_{12} supplementation, had already been initiated.

At 29 weeks’ gestation, the woman exhibited a clinically acute abdomen with signs of peritonitis and a white blood cell count of 18000/mm^3. Exploratory laparotomy revealed an internal hernia and 10-cm area of necrotic biliary limb and small segment of the distal jejunum trapped within the mesenteric defect between the biliary and the Roux limb. In an open procedure, the gangrenous small bowel segment including the anastomosis was completely resected. A new Roux-en-Y anastomosis was performed and the mesenteric defect closed. Nine weeks later the patient delivered an otherwise healthy baby girl with a large myelomenigocele via cesarian section.

**Discussion**

Although the exact mechanism remains unclear, the importance of folic acid and its potential effect on NTD development was first postulated in 1964. Folic acid, a water-soluble B vitamin that is abundant in green leafy vegetables, is composed of pteridine, p-aminobenzoic acid, and glutamate. In its most active form as tetrahydrofolate, it transfers formyl and hydroxymethyl groups during the breakdown of homocysteine, histidine, tryptophan, and serine. Thus, folate is essential for the transfer of R-groups during purine and DNA synthesis.

Years after the association of folate with NTD was first described, 2 randomized clinical trials offered convincing support for the role of folic acid in reducing the occurrence of NTDs both in children born to women who had previously delivered a baby with an NTD and in children born to women who had not. Compared to a multivitamin regimen alone, daily consumption of 4.0 mg of folic acid at least 1 month prior to conception through the first trimester prevented recurrent NTDs by greater than 70%. Among women who had not previously delivered babies with NTDs, those taking daily vitamin supplements containing 0.8 mg of folic acid 1 month prior to conception until the date of their second missed menstrual period reported no NTDs. In an effort to capture the effect of periconceptual folate intake on the incidence of first-occurrence NTDs, nearly 5000 women were randomized to either receive vitamin supplementation with or without folic acid. Six cases of NTDs occurred in infants born to 2391 women who received a trace-element supplement without folic acid. Interestingly, no NTDs were observed in the infants of the 2471 women who took a multivitamin containing folic acid.

The findings of these studies in addition to others prompted changes in the United States in the 1990s, including fortification of foods with folic acid. In 1991, the US Public Health Service officially recommended that all women with a prior NTD-affected pregnancy should consume 4 mg of folic acid daily, which has since been expanded to all women whose fetuses are at high risk of developing NTDs. Included are women with a partner born with an NTD, a close relative with an NTD, diabetes mellitus Type I, and seizures treated with carbamazepine and valproic acid. Obese women were not included in this category, but appear to have an independent increased risk of NTDs. It has been reported that the odds ratio of having a pregnancy complicated by an NTD among obese women, compared to those who are not obese, is 1.9 and 2.6 for women with body mass indices >29 kg/m\(^2\) and >38 kg/m\(^2\), respectively. It has been hypothesized that this heightened risk is perhaps related to hyperinsulinemia, and similar to diabetic patients, obese women are encouraged to take 4 mg of folate daily prior to conception. For the remaining women of child-bearing age, consumption of 0.4 mg of folic acid daily prior to conception was recommended in 1992. Folate deficiency is well-documented after gastric bypass surgery, with an incidence of 0–38%. The Roux-en-Y gastric bypass is the gold standard bariatric procedure in the United States. This restrictive–malabsorptive procedure is most commonly performed laparoscopically with a restrictive component characterized by the creation of a pouch, consisting of ~30–60 ml of the upper stomach, thus restricting the amount of food the patient is able to eat. The malabsorptive component is due to the bypassing of the first 50–100 cm of the small intestine, which leads to decreased caloric uptake. Although folate absorption occurs predominantly in the upper third of the small intestine, it relies on HCl produced by the stomach. The Roux-en-Y procedure excludes the distal part of the stomach, which is the area primarily responsible for HCl production, thus providing an explanation for postoperative folate deficiency.

Significant weight loss, good patient tolerance of the procedure, and the potential to decrease lifetime disability due to obesity, especially with early intervention, have endorsed the popularity of gastric bypass surgery among patients, including adolescents. Furthermore, postoperative folate deficiency has been reported as mild, and patients are typically asymptomatic. Retrospective studies have shown that folate deficiencies can easily be prevented and corrected in 80% of individuals with a multivitamin alone. The majority of bariatric surgeons, including those at our institution, recommend daily multivitamin supplementation and monthly B\(_12\) injections to all patients after surgery. Patient noncompliance, however, seems to be the most important factor in predicting persistent deficiencies.

It has been suggested that the majority of women undergoing gastric bypass surgery go on to have uncomplicated pregnancies and perhaps even better outcomes due to a relatively lower incidence of hypertension, preeclampsia, and fetal macrosomia. As alluded to earlier, obese women...
are at a higher risk of having an NTD-affected pregnancy compared with nonobese patients.\textsuperscript{14} However, as evidenced by the patient in this case, small bowel ischemia and folate deficiency are potential complications of this procedure. Other authors have reported small bowel obstruction and ischemia in women during their first postgastric bypass pregnancy, and have suggested that the enlargement of the uterus, particularly during the second trimester, facilitates obstruction through an alteration in the intraabdominal pressure.\textsuperscript{4} Bowel obstruction during pregnancy is associated with significant risk of death and complications for both the mother and fetus.\textsuperscript{5} Likewise, folate deficiency as a consequence of gastric bypass surgery may even place these women at risk of giving birth to infants with NTDs. Thus, as gastric bypass surgery continues to gain popularity, these serious complications must be recognized by care providers and appropriately relayed to patients in an effort to maximize its benefits and minimize the risks.

In 1986, Haddow and associates\textsuperscript{6} reported on 3 cases of infants with NTDs born to mothers who had undergone gastric bypass surgery 6–8 years prior in Maine. At the time, only 35 gastric bypass surgeries were performed annually, on average, in women younger than 35 years of age in Maine. The 3 cases suggested a relatively high incidence of NTDs. Although the defects varied, the commonality among the 3 cases was the mother’s failure to take vitamin supplementation after bypass surgery.

In 1988, Martin et al.\textsuperscript{15} investigated 3 cases of infants born with NTDs to mothers who had undergone gastric bypass surgery in Iowa. Of 908 women with a history of gastric bypass, 57\% responded to a questionnaire, which identified 73 pregnancies before and 110 pregnancies after surgery. Although no NTDs were reported in the pregnancies preceding gastric bypass, 2 infants with NTDs were born after gastric bypass surgery. A third case of NTD was subsequently identified in a child born to a woman who had not been included in the initial survey. The authors estimated a 12-fold increase in risk of NTDs in infants born to women who had undergone gastric bypass surgery compared with the general population. All 3 women were also noncompliant with daily multivitamin consumption after gastric bypass (Table 1).

In contrast, Knudsen and Källén\textsuperscript{16} failed to identify any NTDs among 77 infants reported through the Swedish Birth Registry as having been born to mothers who had previously undergone bypass surgery. Unlike the aforementioned reports, however, all mothers in the Swedish report had undergone intestinal, not gastric bypass. Intestinal bypass leaves the distal stomach intact, and therefore HCl secretion and folate absorption would not be affected as it is after gastric bypass. Interestingly, the authors postulated the lower birth weights and growth retardation may be secondary to associated metabolic deficiencies.

To our knowledge, this is the seventh case and third report of an infant with an NTD born to a mother who had undergone recent gastric bypass surgery and had failed to take a daily multivitamin postoperatively. This is the first such case reported in nearly 20 years, and we believe it is important to revisit this issue in an effort to prevent such a devastating outcome by raising awareness in the medical community.

There are a few caveats to our findings in this report. First, the mother presented in this case may have already been at an increased risk for developing a baby with an NTD, specifically due to her family history of spina bifida. As stated earlier, high-risk individuals are those who have a “close relative with NTD.” One could argue that it is difficult to decipher the magnitude of the significance of a cousin with the most benign form of the disease. Although the mother delivered a child without spina bifida many years prior to undergoing gastric bypass surgery, each pregnancy is independent, and thus any risk secondary to family history would apply to each pregnancy. The other case reports of NTDs associated with gastric bypass surgery have failed to address whether those women also had other risk factors. Second, we do not have confirmation that the woman in this case was in fact folate deficient, as she unwittingly became pregnant and unfortunately did not have a folate level drawn prior to the start of supplementation. Hence, we cannot conclude that the gastric bypass surgery she underwent and her presumed folate malabsorption caused her baby to develop with an NTD. However, it seems fair to deduce she was relatively folate deficient given the procedure she underwent, and that this probably contributed in some way to the development of a fetus with an NTD.

This additional risk factor, posed by the postoperative malabsorptive state, could easily have been abolished if the patient understood that certain vitamin deficiencies resulting from gastric bypass surgery could be associated with NTDs, and easily corrected with the daily consumption of a multivitamin. Interestingly this notion was validated by the mother during discussion following diagnosis. Although she was aware that folate has a role in preventing NTDs, she failed to appreciate the connection between gastric bypass surgery, folate deficiency, and NTDs. She believed

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<td>Summary of the literature on children with NTDs born to mothers who have undergone gastric bypass surgery*</td>
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<td>Authors &amp; Year</td>
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<td>Martin et al., 1988</td>
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* None of the patients in any study were taking additional vitamin supplementation. Abbreviations: AFP = alpha-fetal protein; MMC = myelomeningocele.
† Diagnosed years after pregnancy.
daily multivitamin supplementation was unnecessary because she was asymptomatic. Thus a clear discussion citing such a devastating complication could positively influence women of child-bearing years to adhere to daily multivitamin supplementation after gastric bypass.

**Conclusions**

Although all women of child-bearing age and especially those who are planning to become pregnant should consume adequate folic acid, we must recognize that women who have undergone gastric bypass may be at an even greater risk of folate deficiency than the general population. Therefore, we suggest they may be at a relatively higher risk of giving birth to fetuses with NTDs. Although the patients themselves may not be symptomatic from the mildly decreased folate levels reported after gastric bypass surgery, their future children are certainly at risk of having devastating outcomes.

Gastric bypass surgery has many positive effects on the overall health of young women and the development and well-being of their future children. Thorough follow-up and counseling of patients, with emphasis on informing them about the potential for NTD development if they fail to strictly adhere to daily multivitamin supplementation must be instituted by all physicians caring for these women. Compliance with daily consumption of a multivitamin is ultimately determined by the patient, but close postoperative follow-up with appropriate folate repletion and supplementation in this population may help to prevent the incidence of NTDs in babies born to women after gastric bypass surgery.

**References**