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Maternal vitamin A deficiency and neonatal microphthalmia: complications of biliopancreatic diversion?

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Abstract Biliopancreatic diversion (BPD) for morbid obesity carries a serious risk of nutritional deficiencies that might impair embryogenesis. Consequently, attention should be given to the potential of risk to the fetus of BPD in women of childbearing age. We present the case of a pregnant woman who had undergone BPD 8 years previously, with documented vitamin A deficiency, who gave birth to a child with bilateral microphthalmia. Infectious and genetic causes of microphthalmia were excluded. A search of the literature revealed that vitamin A deficiency may cause a disruption of ocular development. We conclude that nutritional deficiencies may cause a spectrum of fetal malformations. As the effect of BPD relies on malabsorption, fetal risk should be considered before BPD is offered to morbid obese women of childbearing age.

Keywords Biliopancreatic diversion · Foetal risks · Hypovitaminosis A · Microphthalmia · Pregnancy

Introduction

Morbidly obese women of childbearing age are faced with a difficult choice: should they choose for a pregnancy at a high body weight or should they undergo surgical therapy prior to becoming pregnant? Both options carry potential risks to both the pregnant woman and the fetus. In a recent publication biliopancreatic diversion (BPD) is presented as having major beneficial effects for mother and child [9]. However, as the procedure relies on intestinal malabsorption, it inevitably leads to a serious risk of developing micronutrient and other nutritional and metabolic deficiencies. Little is known about the effects of malabsorption

during pregnancy on embryogenesis, fetal nutrition and growth. Cools et al. recently reported nine cases of BPD-related adverse neonatal outcome [2]. We report here a baby born with bilateral microphthalmia, the mother of whom had low vitamin A levels after BPD. The highly probable relationship between eye anomalies and vitamin A deficiency during pregnancy is discussed.

Case report

A 32-year-old woman, gravida 7, para 4, aborta 2, presented to our prenatal clinic for the first time for her seventh pregnancy. The father, who was the same father for all pregnancies, was healthy. At the age of 24, the mother had undergone BPD at another institution for the treatment of morbid obesity. Her weight before surgery was 120 kg, with a body mass index (in kg/m²) of 45. She lost 60 kg during the first year after her surgery, but eventually regained 6 kg.

The patient's obstetric history included two uncomplicated pregnancies that preceded the BPD procedure in which she delivered two healthy boys with birth weight 3550 g and 3530 g, respectively. The first pregnancy after the bypass (G3) was complicated by subjective symptoms such as dizziness, headache, low back pain and nausea. That pregnancy resulted in preterm premature rupture of membranes at 18 weeks of gestation and ended with partus immaturus. During the next pregnancy (G4) she presented with the same subjective complaints. That pregnancy resulted in a full-term healthy boy with a birth weight of 2610 g. Her next pregnancy (G5), again complicated by the same subjective symptoms, ended in a preterm birth at 28 weeks. The baby, a girl, died from chronic lung disease at the age of 5 months. The fourth pregnancy after bypass surgery (G6) led to a miscarriage at 8 weeks. Genetic or thrombophilia work-up for the mother had not been performed.

During the index pregnancy fetal growth was at the 5th centile; foetal malformations were not noted. From the 11th week of gestation onwards the vitamin status of the

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mother was monitored along with other nutritional parameters (Table 1). She was hospitalized at 12 weeks' gestation for intravenous administration of a multivitamin preparation, extra vitamin B12 and iron, together with oral supplementation of folic acid and multivitamins. Despite that supplementation there was a documented hypovitaminosis A at least from week 16 until the 24th week of gestation. From week 28 of gestation she was hospitalized 5 days weekly for parenteral nutrition. From then on her subjective complaints disappeared and she felt fine. Weight gain during this pregnancy was 9.6 kg. At 37 weeks' gestation, the mother had a spontaneous vaginal delivery of a 2170 g (10th centile) female infant with Apgar scores of 10 at both 1 and 5 min. Birth length was 45 cm (25th centile) and head circumference was 33 cm (50th centile).

Clinical examination of the newborn infant revealed bilateral microphthalmia and simian crease in both palms. Cerebral ultrasound showed ventricular asymmetry, with the left ventricle being larger than the right. Echographic evaluation of the kidneys was normal. Magnetic resonance imaging showed bilateral microphthalmia with cystic colobomata. Multifocal nodular signal intensity deviations in the wall of the lateral ventricles were suggestive of subependymal heterotopias. Hearing screening by brain-stem-evoked response audiometry was normal.

Maternal and neonatal infection screening, including rubella, toxoplasmosis, varicella, cytomegalovirus, influenza and parvovirus, excluded congenital infections as the cause of microphthalmia. G-banding analysis revealed a normal female karyotype. The patient was screened for SOX2 and PAX 6 genes that are involved in developmental eye pathology. They were both wild type.

Discussion

In BPD, which is a surgical procedure to treat morbid obesity, a distal gastrectomy is performed in which the

ileum is divided 200 cm proximal to the ileocecal valve and anastomosed to the gastric pouch [11]. The distal end of the proximal bowel is anastomosed to the ileum 50 cm proximal to the ileocecal valve, leaving only the last 50 cm of the small intestine available for digestion and absorption. Of the patients who undergo BPD, 6% develop deficiencies of fat-soluble vitamins (ADEK). With the prevalence of obesity rising and the concomitant increasing application of this surgical procedure, special attention needs to be given to women of childbearing age. Friedman et al. studied 1136 BPD patients over an 18-year period and reported a high rate of prematurity births (15.3%) and small for dates (27.8%) among the 239 women who became pregnant subsequent to the operation [4].

In this discussion we focus on the consequences of vitamin A deficiency after biliopancreatic surgery on embryonic development.

Animal studies of vitamin A deficiency during pregnancy have found that this condition can lead to an excess of fetal malformations [3, 8]. The results from early animal experiments pointed to vitamin A deficiency as the main causal factor of abnormal eye development [5]. Vitamin A deficiency in the offspring of a mother with hypovitaminosis A after BPD has been documented [7]. Recent epidemiological and laboratory evidence supports the hypothesis that there may be a genetic recessive predisposition to the teratogenic effects of mild-to-moderate vitamin A deficiency during pregnancy [6]. As seen with other teratogens, there is likely to be a quantitative effect, with varying degrees of vitamin A deficiency giving rise to a mild, moderate or severe phenotype, respectively.

Microphthalmia may be a feature of congenital infection syndromes [1]. It is difficult to assemble infection data retrospectively at an individual level, but based on maternal interrogation for infection during the embryologic window for the induction of microphthalmos and based on maternal and neonatal serology and screening for cytomegalovirus in the baby's urine, we estimate an infectious etiology to be

Table 1 The mother's vitamin status during the index pregnancy

Weeks of gestation	Vitamin A (µg/dL) ^a	Vitamin B12 (pg/mL) ^b	Vitamin E (mg/dL) ^c	Carotene (µg/dL) ^d
11	— ^e	262	—	—
12	—	1,920	—	—
13	—	651	—	—
16	17^f	158	0.6	—
17	—	179	—	—
20	—	272	—	—
22	14.5	159	—	—
24	34.6	>2,000	0.7	8.5
25	70	1,170	—	—
28	—	1,850	—	—
29	—	1,740	—	—

^aNormal reference range: 30–80 µg/dL

^bNormal reference range: 197–866 pg/dL

^cNormal reference range: 0.5–1.8 mg/dL

^dNormal reference range: 40–300 µg/dL

^e—, Not done

^fAbnormal values are given in bold

very unlikely. Amniotic fluid for infectious work-up was not available.

In a series of nine cases of BPD-related adverse neonatal outcome, severe bilateral congenital microphthalmia was present in two neonates [2]. In one of them the mother had vitamin A deficiency during pregnancy. Although in the patient reported here the vitamin A status was documented for the first time at 16 weeks' gestation, it is very unlikely that it would have been normal during the first weeks of pregnancy as under normal physiological conditions the plasma vitamin A level does not decrease during pregnancy [10]. From the 12th week of gestation onwards, the mother was supplemented with vitamins, but it took until 24 weeks' gestation for vitamin A levels to reach normal values.

We admit that the studies cited lack the power to identify a proven causal relationship between vitamin A deficiency and microphthalmia in the particular patient reported here. However, this case underscores the utmost importance of medical care and preconceptional nutritional evaluation and correction for women of childbearing age who have severe malabsorption due to bypass surgery. Preconceptional treatment with parenteral nutrition may sufficiently replete nutrient stores.

In conclusion, the adverse effects of malabsorption on an ongoing pregnancy and the risk of a dismal fetal outcome should be considered before gastric bypass is offered to women of childbearing age. Caregivers should at least inform their patients of the potential perinatal risks.

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