Mind the B2: Life-Threatening Neonatal Complications of a Strict Vegan Diet during Pregnancy

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Established Facts

- An inborn error of metabolism should be considered in any neonate with lactate acidosis and hypoglycaemia.
- Maternal diet during pregnancy has a profound impact on the health of the offspring.

Novel Insights

- Maternal riboflavin deficiency can result in a clinical and biochemical picture with lactic acidosis and hypoglycaemia in the newborn, resembling multiple-acyl-CoA-dehydrogenase deficiency (MADD), a lethal metabolic disease.
- Rapid treatment with riboflavin and adequate carbohydrate intake result in a very favourable outcome in the short term. Whether or not neurodevelopment is hampered in the long term still needs to be established.
- More awareness of the dangers of an inadequate diet, including riboflavin deficiency, during pregnancy should be raised under health care professionals that are taking care of pregnant women.

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Keywords
Riboflavin · Hypoglycaemia · Lactic acidosis · Vegan diet

Abstract
An increasing number of women of reproductive age follow vegan diets. Because vegan diets are deficient in a number of essential nutrients, guidelines address the necessity of supplementations such as iron, zinc, and vitamin B12. However, the risk of riboflavin (vitamin B2) deficiency is not properly addressed. We report a case of a male neonate with a life-threatening hypoglycaemia and lactic acidosis due to severe riboflavin deficiency. The mother followed a strict vegan diet with intermittent use of supplements (folic acid, vitamin B12, vitamin D, omega 3). This case highlights the importance of adequate counselling of all pregnant women adhering to vegan diets to ensure sufficient intake of essential nutrients and vitamins, including riboflavin.

Introduction

Vegan diets are gaining ground. In a large survey, 6% of US citizens reported following a vegan diet [1]. The majority of vegans is female and of reproductive age [2]. A vegan diet imposes a risk for nutrient deficiencies, especially for pregnant females who have a higher recommended daily intake (RDI). The Academy of Nutrition and Dietetics advises to monitor the intake of iron, zinc, vitamin B12, and essential fatty acids in pregnancy [3]. Recent studies demonstrate the association of a maternal vegan diet with an increased risk of the infant being small for gestational age [4]. Cases of exclusively breastfed children with B12 deficiency and clinical symptoms born to mothers on a vegan diet have been reported [5]. Remarkably, the risk of riboflavin (vitamin B2) deficiency is not considered in the current guidelines for pregnancy [3, 6–8].

Riboflavin is a water-soluble vitamin which is not stored in the body. Dietary riboflavin comes from dairy products, meat, fish, and green vegetables. In some countries, flour (cereals and bread) may be fortified with riboflavin; however, this is not the policy in the Netherlands [9]. Recommended intakes range from 0.3 mg/day in infancy to 2.0 mg/day in lactating women [10–12]. Riboflavin is the precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), cofactors for enzymes called flavoproteins, which play an essential role in fat, carbohydrate, and protein metabolism [10]. Two publications reported clinical symptoms of riboflavin deficiency in newborns of mothers who were carriers of a riboflavin transporter deficiency or had an unexplained riboflavin deficiency [13–16]. Furthermore, newborns without clinical symptoms demonstrated abnormal newborn screening results (suspected very-long-chain acyl-CoA dehydrogenase deficiency) due to riboflavin deficiency secondary to maternal vegan, vegetarian, or lactose-free diets in pregnancy [17]. We describe a life-threatening condition in a neonate caused by riboflavin deficiency resulting from a maternal vegan diet.

Case Report
A 1-day-old male neonate was presented because of poor feeding, tachypnoea, and hypothermia. He was the first child of non-consanguineous Caucasian parents, born after an uncomplicated pregnancy (gestational age 37+2 weeks) and delivery. Birthweight was 3,260 g (p50–80). Apgar scores were 9, 10, and 10. The mother was healthy, but for obesity (29 years, BMI 30.3 kg/m²), she did not use any medication. Supplements, because of a strict vegan diet (folic acid, vitamin B12, vitamin D, omega 3), were used intermittently.

Physical examination showed a non-dysmorphic, unwell, and tachypnoeic neonate. Temperature was 96.4°F (35.8°C). There were no signs of circulatory or respiratory insufficiency. Neurological examination showed hypotonia without encephalopathy. Laboratory results demonstrated a severe hypoglycaemia (0.4 mmol/L, 7 g/dL) and a lactic acidosis (pH 7.21, PCO2 4.1 kPa/31 mm Hg, bicarbonate 12 mmol/L, base excess −15.5, lactate 10.9 mmol/L). Hypoglycaemia was corrected with an intravenous bolus of glucose 10% followed by continuous infusion. The child was admitted under suspicion of neonatal early onset sepsis and treated accordingly. Because of a persistent lactic acidosis, metabolic studies were performed. The plasma acylcarnitine profile demonstrated accumulation of acylcarnitines (C4–C18) and urine organic acids showed high excretion of lactate, ethylmalonic acid, glutaric acid, 2-hydroxyglutaric acid, and (hydroxy)-dicarboxylic acids. This raised the suspicion of multiple acyl-CoA dehydrogenase deficiency (MADD, OMIM 231680), an inborn error of metabolism with a poor prognosis: most affected infants die within a few days after birth. As a differential diagnosis, a severe riboflavin deficiency was considered.

Course
The patient started a low protein/fat and high carbohydrate feeding regimen. Oral L-carnitine (50 mg/kg/day) and riboflavin (45 mg/kg/day) were started awaiting the results of genetic tests. The patient demonstrated rapid clinical improvement. With genetic studies (Sanger sequencing of the coding regions plus flanking intronic sequences using genomic DNA) of the electron transfer flavoprotein subunit A and B and electron transfer flavoprotein dehydrogenase genes, the diagnosis of MADD was ruled out. The patient was switched to regular infant formula.

Jaeger et al.
The mother was evaluated for riboflavin deficiency. She had an abnormal acylcarnitine profile, with accumulation of C4 and medium chain acylcarnitines. Plasma riboflavin was very low (0.6 nmol/L, ref 3.9–49 nmol/L) with a low FMN (2.3 nmol/L, ref 2.8–21.4 nmol/L) and a normal FAD (77.6 nmol/L, ref: 46–114 nmol/L). Riboflavin, FMN, and FAD concentrations were measured by high-performance liquid chromatography using fluorescence detection of the analytes according to the method of Capo-chichi et al. (2000) with minor modifications [10]. The mother had no clinical signs of riboflavin deficiency. Dietary assessment using a 3-day food record showed an average caloric intake of 2,148 kcal/day and revealed a daily riboflavin intake of 0.46 mg/day (RDI 2.0 mg/day in lactating women) [12]. Her diet was also deficient in the vitamins A, D, and B12 (20% vs. 16% vs. 40% of RDI, respectively). Laboratory nutrient assessment demonstrated normal levels of vitamin A, B1, B6, B12, E, and albumin. Vitamin D was low (35 nmol/L) and there was an iron deficiency (ferritin 12 [ref 15–150 µg/L]; serum iron 5.6 [ref 11–27 µmol/L]).

All known genetic diseases affecting riboflavin uptake and metabolism (FLAD1 in child; SLC52A1, SLC52A2, SLC52A3 in mother and child) were ruled out by Sanger sequencing of respective genes as well. On day 12 of life, the patient was discharged in good clinical condition and was fed formula throughout. Acylcarnitine profile analysis on day 24 showed complete normalization. After excluding inborn errors of riboflavin metabolism, oral riboflavin supplementation was discontinued.

Discussion/Conclusion

We present a newborn with life-threatening hypoglycaemia and lactic acidosis due to riboflavin deficiency caused by an insufficiently supplemented maternal vegan diet. Since riboflavin and especially its derivatives, FMN and FAD, are important cofactors for fat, carbohydrate, and protein metabolism, a riboflavin deficiency may cause severe clinical illness with a biochemical profile comparable to MADD [10]. The distinction between these two conditions can only be made by genetic studies.

The interest in vegan diets in developed countries has surged over the last years [1]. Professionals involved in the care of pregnant women reported awareness of the risks for nutrient deficiencies of a vegan diet during pregnancy as well as a lack of knowledge for adequate counselling. Only 25% of midwives and 14.5% of obstetricians reported referring pregnant women on a vegan diet to a dietician and only 40% of dieticians felt capable to advise pregnant women on a vegan diet [2].

Both studies and guidelines discuss potential insufficient content of essential nutrients (vitamin B12, vitamin D, calcium, zinc, iron, proteins, essential fatty acids, iodine) in vegan diets [3, 7]. However, there are no reports of the need for monitoring of riboflavin intake.

Our case illustrates that a maternal vegan diet without adequate riboflavin intake can result in a life-threatening condition in the newborn. Riboflavin deficiency should be considered in a newborn with an unexplained hypoglycaemia and lactic acidosis, especially when born to a mother on a vegan diet.

More awareness of the dangers of an inadequate diet, including riboflavin deficiency, during pregnancy should be raised under health care professionals that are taking care of pregnant women. This case highlights the importance of adequate counselling of all pregnant women adhering to a vegan diet.

Statement of Ethics

Written informed consent was obtained from the parents of the subject described in this case report for publication of the details of his medical case. Ethics approval was not required, based on national guidelines. This is not a study; therefore, consent was not required.

Conflict of Interest Statement

Mirjam Langeveld is involved in premarketing studies with Sanofi-Genzyme, Protalix, and Idorsia. Financial arrangements were made through AMC Research BV. No fees, travel support, or grants were obtained from Pharmaceutical Industry. The rest of the authors have no conflicts of interest to declare.

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Author Contributions

Bregje Jaeger, Willemijn Corpeleijn, and Annet M Bosch were involved in data collection and drafted the article. Susan Goorden and Hans Waterham performed the laboratory and genetic tests and revised the manuscript. Monique Dijsselhof, Jorien Haverkamp, Mirjam Langeveld, and Elisabeth Westerbeek were involved in data collection and revised the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.
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