Case Report Journal of pediatric endocrinology and metabolism

Linnea Äärelä, Pasi I. Nevalainen, Kalle Kurppa* and Pauliina Hiltunen

First Scandinavian case of successful pregnancy during nitisinone treatment for type 1 tyrosinemia

https://doi.org/10.1515/jpem-2019-0540
Received November 18, 2019; accepted February 24, 2020

Abstract

Background: Type 1 tyrosinemia is a hereditary metabolic disease in which tyrosine metabolites damage the liver and kidneys. Nitisinone medication revolutionized the treatment, but the effects of the drug during human pregnancy are unknown.

Case report: A 17-year-old tyrosinemia patient became pregnant. Nitisinone was continued throughout pregnancy with a varying serum concentration and dose ranging from 0.8 to 1.4 mg/kg/day. Blood tyrosine remained stable until it increased in late pregnancy. α-fetoprotein increased to 284 μg/L without new changes in liver. Urine succinylacetone remained undetectable, but there were signs of possibly reoccurring kidney tubulopathy. Fetal ultrasound monitoring was normal throughout the pregnancy and the newborn healthy. After the delivery, α-fetoprotein normalized, but tyrosine continued to rise for up to 1 year. The child is developing normally.

Conclusions: Pregnancy during nitisinone was successful, but tailoring of the drug dose and possibly reappearing complications, as also increasing serum tyrosine concentration after delivery warranted intensified surveillance.

Keywords: complications; nitisinone; pregnancy; tyrosinemia.

***Corresponding author: Kalle Kurppa,** MD, PhD, Tampere Center for Child Health Research, Tampere University and Department of Paediatrics, Tampere University Hospital, Tampere, Finland; and University Consortium of Seinäjoki and Department of Paediatrics, Seinäjoki Central Hospital, Seinäjoki, Finland,
Phone: +358503186255, E-mail: kalle.kurppa@tuni.fi.
https://orcid.org/0000-0003-4757-2164
Linnea Äärelä and Pauliina Hiltunen: Tampere Center for Child Health Research, Tampere University and Department of Paediatrics, Tampere University Hospital, Tampere, Finland
Pasi I. Nevalainen: Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

Learning points

What is new:

- Marked decrease in serum nitisinone concentration during pregnancy necessitated almost doubling the dosage
- Pregnancy during nitisinone treatment was successful even with doses higher than previously reported
- Possibly reoccurring complications of tyrosinemia during pregnancy and long-lasting increase in tyrosine levels after delivery indicate a need for intensified surveillance

Introduction

Type 1 tyrosinemia is caused by an inherited deficiency of fumarylacetoacetate hydrolase (FAH), an enzyme crucial to the phenylalanine and tyrosine catabolic pathway. Inactivity of FAH leads to accumulation of tyrosine and formation of toxic metabolites, which damage hepatocytes and renal tubules leading to liver dysfunction, tubulopathy, and eventually to hepatocellular carcinoma [1]. Estimated prevalence is 1:100,000 in Europe and even 1:2000–20,000 in high prevalence areas [1, 2]. In the early days, the prognosis of tyrosinemia was poor, early liver transplant being the sole effective treatment [3]. The introduction of nitisinone [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione] in the 1990s revolutionized the treatment. Nitisinone prevents the production of toxic downstream metabolites but causes accumulation of tyrosine, which must be controlled with protein restriction [4].

Nitisinone markedly increased long-term survival [5], and consequently, increasing numbers of women with type 1 tyrosinemia are now reaching childbearing age. There is, however, a scarcity of data on the kinetics and effects of the medication during human pregnancy; so far, only a few case reports from limited geographical areas were published [6–8]. Further data would be much needed, particularly as high nitisinone doses were shown to be teratogenic in animal models. Moreover, the few

pregnancy cases published on patients with type 2 tyrosinemia indicated that maternal tyrosine levels may have a major impact on fetal development [9, 10].

We report the first Scandinavian case of successful pregnancy in a patient with type 1 tyrosinemia. Besides careful follow-up of the developing fetus, particular attention was paid on the implementation of the treatment and possibly reoccurring disease complications.

Case description

The mother was born of a non-consanguineous marriage of healthy parents after an uneventful pregnancy. At the age of 2 years, she presented with poor growth, rickets, and liver failure. Investigations showed high concentrations of blood tyrosine and α-fetoprotein (AFP), kidney tubular dysfunction, and dysplastic liver nodules. She was subsequently diagnosed with type 1 tyrosinemia with homozygotic Finnish mutation W262X [2]. Protein restriction and nitisinone treatment (0.8 mg/kg/day) resulted in normalization of the laboratory parameters and hepatic findings. During the following years, the treatment was successful apart from persistent osteopenia. Her growth and development were normal, and there were no signs of other extrahepatic complications.

The patient became pregnant at the age of 17 years. She started monthly visits for evaluation after gestational week 8. Week 15 fetal ultrasound was normal. During the pregnancy, natural protein intake was raised from 22 to 26 g/day, and phenylalanine and tyrosine-free supplement from 38 to 60 g/day to meet the increased nutrient demands and weight gain (from 43 to 54 kg). Blood nitisinone concentration decreased, and the dose had to be increased from 0.8 mg/kg to 1.4 mg/kg/day (Figure 1). The dosage was adjusted aiming to keep urine succinyl acetone undetectable and plasma nitisinone within target range (40–60 μmol/L) [11]. The blood samples were drawn in standardized manner in the morning. Tyrosine remained relatively stable until late pregnancy, when it rapidly increased and remained elevated several months after the delivery (Figure 1). AFP rose from prior <5 μg/L to 284 μg/L without new changes in liver function or imaging, while urine succinyl acetone remained undetectable. Ultrasound monitoring (at 19, 27, 31, 36, 38, and 40 weeks) showed normal fetal development. Compensated metabolic acidosis and fluctuating α-1-microglobulin levels were observed throughout the pregnancy, possibly due to reoccurring tubular dysfunction.

After 40 weeks of gestation, the patient gave birth to a non-affected healthy boy. The newborn was clinically normal and average sized (3660 g, 0 SD; 50 cm, −0.7 SD; head circumference 35.0 cm, −0.3 SD). The mother did not breastfeed as it was not recommended during nitisinone treatment given previously observed adverse effects in animal models. Mother's protein intake and nitisinone dosage were gradually reduced to pre-pregnancy levels. Metabolic acidosis and elevated AFP normalized rapidly, but tyrosine increased to 900 μmol/L, even with strict dietary compliance and remained elevated after the delivery. The mother lost approximately 10 kg of weight within 4 months after delivery, including normal weight loss after childbirth.

The newborn was clinically healthy and had no abnormalities in abdominal, cardiac, and brain imaging studies.

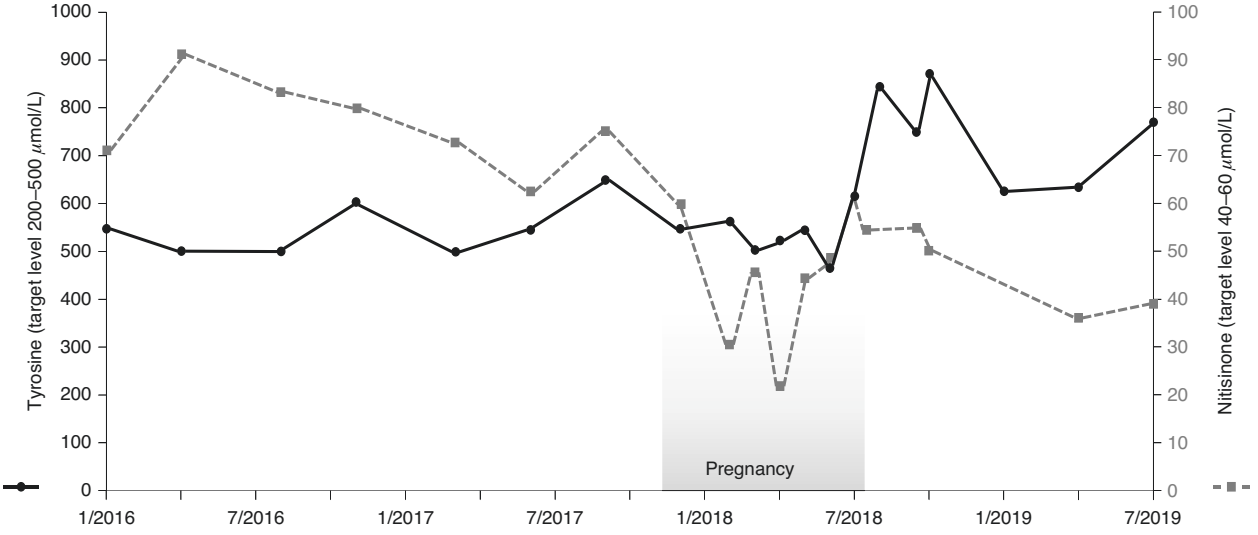

Figure 1: Plasma tyrosine and nitisinone concentration of the mother with type 1 tyrosinemia before, during, and after the pregnancy.

The child is currently 1.25 years old and showing normal neuromotor development. He is also able to speak a few words and is growing within acceptable limits (height –1.5 SD, weight +1.5 SD) [12].

Discussion

Pregnancy during nitisinone treatment was successful, and no adverse effects were observed on the fetus. The infant has been healthy in all clinical and laboratory evaluations during the first year of life. To date, only three cases (in Belgium, France, and the United States) of pregnancy carried to term during nitisinone treatment for tyrosinemia type 1 were reported [6–8]. Further studies are of utmost importance, as nitisinone is still not recommended in pregnancy (https://www.ema.europa.eu/en/medicines/human/EPAR/orfadin#product-information-section). Together with earlier reports, our study demonstrates the fetal safety of the drug. This is good news, as discontinuation of the medication predisposes the affected mother to a serious risk of acute liver failure and malignancy.

However, caution is still needed until more evidence accumulates, since nitisinone was shown to be teratogenic in animal models. For example, in rabbits, nitisinone increased the risk of umbilical hernia and gastroschisis, while in mice, it reduced pup growth and survival during the weaning period. The adverse effect started from a 2.5-fold higher dose than the maximum recommended human dose (2 mg/kg/day). Here, nitisinone had to be raised to 1.4 mg/kg/day during pregnancy, which was higher than previously reported (Table 1), but still below the maximum dose and harmful quantities in animal models. In the reports by Garcia Segarra et al. [6] and Vanclooster et al. [7], the dosages during pregnancy were the same as the previous, while Kassel et al. [8] did not report the dose. Our case provides evidence that nitisinone can be used safely with somewhat higher dose, which is important as the aforesaid adverse effects in animal studies were dose related. Moreover, the increase was due to low plasma drug concentration, and arguably, the actual quantity reaching the fetus was not increased. A similar, but less marked, tendency for decreasing nitisinone concentration was also reported in the two aforesaid studies [6, 8].

Besides nitisinone, high tyrosine concentration may also be harmful in pregnancy. Cerone et al. [10] described two babies with microcephaly, developmental delay, and low birth weight born to a mother with type 2 tyrosinemia whose tyrosine levels exceeded 1000 μmol/L during pregnancy, while Francis et al. [9] described a similar case in which adverse outcome was avoided by controlled tyrosine levels. Although nitisinone is not used to treat tyrosinemia type 2, similar risks associated with elevated tyrosine levels could also be present in type 1 tyrosinemia. Further emphasizing the importance of controlling the mother's tyrosine level, there seems to be active transplacental transport, and the levels in the fetus may be higher than those in the mother [6, 7].

Treatment of tyrosinemia during pregnancy is, therefore, a matter of balancing between maintaining tyrosine and nitisinone concentrations safely low, while simultaneously ensuring the needed protein supply to mother and fetus. In the report by Garcia Segarra et al. [6], the baby's weight and head circumference were quite small, possibly

Table 1: Comparison between the present case of pregnancy in a mother with type 1 tyrosinemia and the three previous cases described in the literature.

	Vanclooster et al. [7]	Garcia Segarra et al. [6]	Kassel et al. [8]	The present case
Mother's age at diagnosis, year	3.0	0.9	2.0	2.7
Pregnancy				
Age at conception, years	19	21	16	17
Total protein intake, median or range, g/day	56–76	70	ND	72
T/P[a] free formula, median, g/day	76	ND	ND	60
Nitisinone, mg/kg/d[b]	0.5	0.6	<1.0	1.4
Nitisinone concentration, range, μmol/L	68–96	41–57	10–70	22–63
Tyrosine concentration, range, μmol/L	500–693	375–838	400–750	430–603
Pregnancy outcome	Normal	Normal	Normal	Normal
Gestational age at delivery, weeks	41	41	37	40
Infants weight, kg	2.950	2.615	2.900	3.660
Child also affected with tyrosinemia	No	Yes	No	No

[a]Tyrosine/phenylalanine. [b]Maximum dose used during pregnancy. ND, no data.

due to poor dietary compliance and widely varying tyrosine concentration during pregnancy. Similarly, Vanclooster et al. [7] and Kassel et al. [8] reported smaller newborns and higher tyrosine fluctuations than the present case (Table 1). This suggests that steady concentration of tyrosine could be beneficial to the fetus, but firm conclusions cannot be drawn based on these few cases.

Interestingly, we observed a sustained increase in the mother's tyrosine concentration after delivery, even though protein intake was normalized, and strict treatment compliance was confirmed (Figure 1). Vanclooster et al. [7] likewise reported an increase in tyrosine concentration up to 900 μmol/L during the first 2 months postpartum, and Kassel et al. [8] observed a similar tendency. Here, the tyrosine concentration started to decrease five months postpartum but subsequently increased, while Vancloster et al. reported a decrease after three months. These fluctuations may be explained at least partly by the rapid changes in weight and body composition during the catabolic period after giving birth. Dietary indiscretions are likewise possible, underlining the importance of support from the medical team for the patient to achieve strict adherence to low-protein diet. As a possible previously unreported complication, we also observed that the mother had compensated metabolic acidosis throughout the pregnancy, possibly due to reoccurring kidney tubular dysfunction, although this may also be a normal physiological adaptation during pregnancy. The situation, however, normalized soon after delivery, and there were no other signs of renal problems. In fact, this was an additional reason to carefully monitor not only urine succinyl acetone but also blood nitisinone level. Yet, more evidence is needed. A similar decrease in nitisinone levels and a need to increase nitisinone dosage were reported by Kassel et al. [8].

In conclusion, our observations and the few existing reports suggest that nitisinone can be continued safely during pregnancy. However, the required tailoring of the nitisinone dose, prolonged increase in tyrosine concentration, and possible reappearance of complications demonstrated the need for intensified surveillance during pregnancy and even some time after the delivery.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: Äärelä received study grants from the Orion Research Foundation and the Päivikki and Sakari Sohlberg Foundation and Kurppa received grants also from the Sohlberg Foundation and the Foundation of Pediatric Research, otherwise none declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: None declared.
Ethics statements: The study was conducted in accordance with the Helsinki Declaration of 1975 (revised in 2000). Data collection was approved by the Departments of Paediatrics and Internal Medicine in Tampere University Hospital. Patient's written informed consent for data collection and case publication was obtained. According to our national guidelines, no further ethical approval was needed for this retrospective case report.

References

1. Mayorandan S, Meyer U, Gokcay G, Segarra NG, De Baulny HO, et al. Cross-sectional study of 168 patients with hepatorenal tyrosinaemia and implications for clinical practice. Orphanet J Rare Dis 2014;9:107.
2. St-Louis M, Leclerc B, Laine J, Salo MK, Holmberg C, et al. Identification of a stop mutation in five Finnish patients suffering from hereditary tyrosinemia type I. Hum Mol Genet. 1994;3:69–72.
3. Larochelle J, Mortezai A, Belanger M, Tremblay M, Claveau JC, et al. Experience with 37 infants with tyrosinemia. Can Med Assoc J 1967;97:1051–4.
4. de Laet C, Dionisi-Vici C, Leonard JV, McKiernan P, Mitchell G, et al. Recommendations for the management of tyrosinaemia type 1. Orphanet J Rare Dis 2013;8:8.
5. Larochelle J, Alvarez F, Bussieres JF, Chevalier I, Dallaire L, et al. Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec. Mol Genet Metab 2012;107:49–54.
6. Segarra NG, Roche S, Imbard A, Benoist JF, Greneche MO, et al. Maternal and fetal tyrosinemia type I. J Inherit Metab Dis 2010;33(Suppl 3):S507–10.
7. Vanclooster A, Devlieger R, Meersseman W, Spraul A, Kerckhove KV, et al. Pregnancy during nitisinone treatment for tyrosinaemia type I: first human experience. JIMD Rep. 2012;5:27–33.
8. Kassel R, Sprietsma L, Rudnick DA. Pregnancy in an NTBC-treated patient with hereditary tyrosinemia type I. J Pediatr Gastroenterol Nutr 2015;60:e5–7.
9. Francis DE, Kirby DM, Thompson GN. Maternal tyrosinaemia II: management and successful outcome. Eur J Pediatr 1992;51:196–9.
10. Cerone R, Fantasia AR, Castellano E, Moresco L, Schiaffino MC, et al. Pregnancy and tyrosinaemia type II. J Inherit Metab Dis 2002;25:317–8.
11. Chinsky JM, Singh R, Ficicioglu C, van Karnebeek CD, Grompe M, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19.
12. Kayemba-Kay's, Maillet O, Hindmarsh P, Heron A. Growth screening in children aged 3–5 years: a useful tool for public health programs in community pediatrics. J Pediatr Endocrinol Metab 2019;32:727–32.