



Case Report

Successful pregnancy and childbirth without metabolic abnormality in a patient with holocarboxylase synthetase deficiency

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ABSTRACT

Holocarboxylase synthetase deficiency (HSD), an autosomal recessive biotin cycle disorder, is caused by *holocarboxylase synthetase (HLCS)* genetic variants, resulting in multiple carboxylase deficiency. Catabolic stress can induce metabolic crises in patients with HSD. Although pharmacological doses of biotin have improved HLCS enzyme activity and HSD prognosis, the prolonged life expectancy has gradually highlighted novel issues in adult patients with HSD. To the best of our knowledge, there is only one report on a case of HSD during pregnancy and childbirth, and the metabolic profile was not well defined. In this report, we present the history and metabolic profile of a woman with HSD who had an uncomplicated pregnancy and childbirth. A high pharmacological dose of biotin, 100 mg/day, had no effect on the fetus. Even during the emergency cesarean section, the detailed metabolic assessments revealed no significant laboratory findings, such as ketolactic acidosis, hyperammonemia, and remarkable acylcarnitine change. This report suggests that a woman with HSD who regularly takes biotin can conceive and give birth safely, and biotin doses of 100 mg/day may not influence the growth and development of the fetus. Further research and case studies on pregnant women with HSD are required to determine an acceptable maximum dosage of biotin for human fetuses.

1. Introduction

Holocarboxylase synthetase deficiency (HSD, MIM# 253270) is caused by biallelic pathogenic variants in the *holocarboxylase synthetase (HLCS)* gene (MIM* 609018) [1]. The HLCS enzyme (EC 6.3.4.11) catalyzes the linkage reaction of biotin, a water-soluble vitamin also known as vitamin H or B7, to inactivate apocarboxylases [2]. Adenosine triphosphate-dependent biotinylation at the lysine residue of the Met-Lys-Met sequence activates propionyl-CoA carboxylase (EC 6.4.1.3), pyruvate carboxylase (EC 6.4.1.1), 3-methylcrotonyl-CoA carboxylase (EC 6.4.1.4), acetyl-CoA carboxylase-alpha (EC 6.4.1.2), and acetyl-CoA carboxylase-beta (EC 6.4.1.2). Carboxylases play an important role in gluconeogenesis, fatty acid metabolism, and branched-chain amino acid catabolism [2]. Patients with HSD may have hypoglycemia, ketolactic acidosis, and hyperammonemia early after birth, resulting in emesis, hypotonia, lethargy, seizures, developmental delay, and death [3]. The metabolic disturbance can be corrected with high-dose biotin supplementation because pharmacological biotin increases carboxylase

activity [4]. To maximize the benefits of biotin and prevent irreversible complications, newborn screening has been performed to identify pre-symptomatic individuals with HSD as biotin supplementation can improve the metabolic state and life expectancy in patients with HSD [5]. The improved prognosis has highlighted the unexpected problems in adulthood, as with other inborn errors of metabolism. For instance, pregnancy is an important life event for women who have inborn errors of metabolism [6–8]. However, to the best of our knowledge, there is only one report on women with HSD during pregnancy and childbirth, and the metabolic profile was not described in detail [9]. Furthermore, while biotin appears to be safe, including prenatal therapy [10], acceptable doses for ensuring fetal safety during pregnancy have not been established.

In this report, we present the case of a pregnant patient with HSD who underwent an emergency cesarean section and received high-dose biotin supplementation.

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2. Clinical case

The patient is a 33-year-old woman with HSD. She was born spontaneously at term and suffered from metabolic acidosis and respiratory failure within 1 day of birth. After the detection of 3-OH propionic acid and 3-OH isovaleric acid in urine, oral biotin (10 mg/day) and L-carnitine were administered, which improved the symptoms. The detailed *in vitro* analysis of this patient (patient #1) been reported previously in a paper [11]. No episode of metabolic attack was found with biotin increasing to 40 mg/day at 2 months of age and. The biotin was increased to 50 mg/day at 16 years of age according to weight gain. Her height and body weight have grown within 0 to -0.5 SD. She showed mild developmental delay (developmental quotient was 100 at the age of 9 months, 59 at 2 years, 66 at 3 years and 5 months, and 69 at 10 years). She graduated from a regular junior high school and has worked. A mild psoriasis-like lesion was observed on her neck which persisted despite the increase in the biotin dose increase to 100 mg/day at 32 years and 2 months of age. Genetic test revealed homozygous pathogenic variants of p.Leu237Pro in the *HLCS* gene (NM_000411), which is known to be one of the most common mutations in Japan [12].

She had non-consanguineous marriage and became pregnant unexpectedly at the age of 32 years and 10 months. Oral supplementation of biotin (100 mg/day) and L-carnitine (750 mg/day) were continued, and no complications during pregnancy, including hyperemesis gravidarum, were observed. There was no evidence of a metabolic crisis, such as an abnormal acylcarnitine profile in dried blood spots, metabolic acidosis, or hyperammonemia (Table 1). Fetal echocardiography revealed normal fetal growth with no fetal edema or malformation (Fig. 1). Since fetal body weight increased rapidly after 31 gestational weeks, the L-carnitine dose was increased from 750 to 1500 mg/day. Although she was induced to deliver at 41 gestational weeks, vaginal delivery was impossible due to cephalopelvic disproportion. The water breaking and meconium-stained amniotic fluid were found, prompting an emergency cesarean section. Preoperatively, sugar-free Ringer's lactate solution was infused for 2 h, and then postoperatively, maintenance fluid therapy was administered at glucose infusion rate of 2 mg/kg/min. Fasting was limited to skipping lunch on the day of the surgery. She did not have a metabolic crisis during or after the cesarean section. There were no congenital malformations or metabolic abnormalities in her baby. Her baby's 3-hydroxyisovalerylcarnitine level in dried blood spots was 1.09 at 7 days and normalized at 1 month.

3. Discussion

This report detailed the metabolic profile of a woman with HSD who had an uncomplicated pregnancy and cesarean section. She became pregnant at a time when her condition was stable, and she was able to continue taking biotin throughout her pregnancy. An emergency

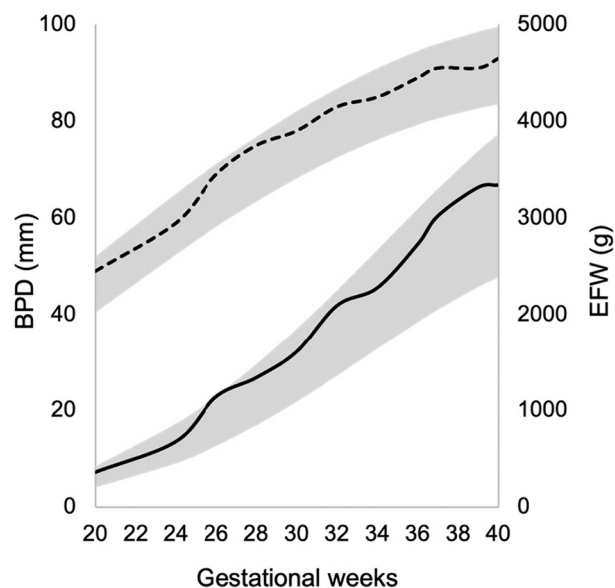


Fig. 1. The growth of the fetus of the patient with HSD. The solid and dotted lines represent estimated fetal weight (EFW) and biparietal diameter (BPD), respectively. The upper and lower gray bands represent the two standard deviation ranges of BPD and EFW, respectively [13]. Abbreviations: BPD, biparietal diameter; EFW, estimated fetal weight.

cesarean section did not result in any metabolic abnormalities. Despite receiving 100 mg of biotin per day, which is the highest dose based on previous reports [9], the fetus grew normally and had no apparent malformations.

Our patient with HSD showed neither symptoms nor significant laboratory changes due to *HLCS* disturbances, suggesting that a pregnant patient with HSD who shows biotin responsiveness would be fertile and be able to safely deliver while receiving biotin treatment as mentioned in a previous report [9]. In addition, sequential blood acylcarnitine analysis of our patient revealed the stability of carboxylases' activity *in vivo* throughout her pregnancy. The acid-base balance, ammonia levels, and metabolic status of the patient were normal. The stable profile of blood acylcarnitine may be associated with the maternal-fetal transfer of acylcarnitine, although transplacental C5-OH resulted in false-positive newborn screening of babies not only in a previous report but also in this report. In fact, C5-OH and C3/C2 levels during pregnancy seem to be lower than those before pregnancy, even considering the maternal physiological change that free carnitine levels decrease to approximately half their prepregnant levels [14]. Pregnancy might improve the acylcarnitine profile of mothers with inborn errors of metabolism; however, more attention should be paid to low free

Table 1
Sequential metabolic profile in a patient with HSD during pregnancy and after delivery.

Laboratory Measure	Non-pregnant	Gestational weeks								Emergency cesarean section			
		12	20	30	32	36	38	40	Before	After	POD 1	POD 2	
C0, μM	44.27	19.2	18.2	21.89	21.91	21.89	27.71	21.59	22.63	17.42	22.74	34.06	
C3, μM	3.88	2.14	1.39	1.47	1.47	1.54	1.78	1.96	1.94	1.22	1.6	2.54	
C5-OH, μM	10.59	4.38	2.67	2.58	2.58	2.46	2.31	2.08	2.13	1.88	2.49	1.92	
C3/C2, μM	0.123	0.169	0.1	0.063	0.063	0.075	0.078	0.086	0.075	0.058	0.062	0.126	
pH	7.381	NA	NA	NA	NA	7.424	7.41	7.408	7.41	7.37	7.442	7.429	
PvCO ₂ , mm Hg	48.2	NA	NA	NA	NA	34.5	36.9	37.6	36.7	39.1	37	38	
HCO ₃ ⁻ , mM	28	NA	NA	NA	NA	22.2	22.9	23.2	22.8	22.1	24.9	24.7	
Anion Gap, mEq/L	6.7	NA	NA	NA	NA	5.6	4.2	2.7	0.3	1.3	-0.3	1	
Glucose, mg/dL	101	NA	NA	NA	NA	99	79	100	86	105	116	160	
Lactate, mM	2.6	NA	NA	NA	NA	1.2	1.3	1.3	1.6	2.4	1.7	1.6	
NH ₃ , $\mu\text{g/dL}$	44	NA	NA	NA	NA	34	17	18	20	<10	16	18	

POD, post-operative day; NA, not available; C0, free carnitine; C2, acetylcarnitine; C3, propionylcarnitine; C5-OH, 3-hydroxyisovalerylcarnitine.

carnitine levels generally found in pregnant women as mentioned above.

A pharmacological dose of biotin or higher did not appear to influence fetal development. Our patient has been taking 100 mg of biotin per day, which is 2000 times the normal intake amount for non-affected individuals. In a previous report, no adverse effects were observed when biotin was administered orally or intravenously at >600 times the amount that a healthy person gets from their diet [15]. Pregnancy in patients with biotinidase deficiency was successful with 5–15 mg of biotin supplementation [10,16]. An experiment with pregnant mice revealed that biotin at 2000 times the normal intake had no effect on the fetus [17]. However, a higher dose of biotin, up to 25,000 times, resulted in short legs (53.3%), micrognathia (34.8%), and edema (31.5%) of the fetus. A similar amount of biotin may be required for refractory eczema in patients with HSD [18]. Thus, attention should be paid to the fetus of a pregnant woman with HSD who requires biotin in excess of pharmacological doses. The accumulation of cases of pregnant patients with HSD and their fetuses would help identify the maximum tolerable amount of biotin in the future.

Our patient with HSD was able to successfully complete pregnancy and childbirth without any metabolic abnormalities. In contrast to biotinidase deficiency, for which pharmacological biotin is prescribed, HSD may result in metabolic decompensation, such as hypoglycemia, ketolactic acidosis, and hyperammonemia, particularly when exposed to a catabolic state [3]. The metabolic state changes from anabolism to catabolism during the third trimester of pregnancy [19]. Previously, a mother with methylmalonic acidemia was reported to have hyperammonemia [20]. In addition, our patient underwent an emergency cesarean section, which may have increased catabolism. These findings indicate that the patient may have been at risk of metabolic decompensation, although the laboratory profile did not reveal any evidence of metabolic crisis. The enzymatic functions of carboxylases would improve with continued biotin administration. Negligible anorexia not affecting food intake during pregnancy may help to stabilize the metabolic state. In addition, her metabolic state can be stabilized with a preemptive glucose transfusion. Women with propionic acidemia, whose pathophysiology is similar to that of HSD, may be able to have pregnancy and childbirth with disease-specific care [21]. Close collaboration between obstetricians and metabolic specialists is required to assist pregnant women and fetuses with inborn errors of metabolism.

4. Conclusions

A patient with HSD was able to complete her pregnancy and have an emergency cesarean section with no metabolic disturbance thanks to pharmacological doses of biotin. The biotin dose of 100 mg/day in the present case did not influence the fetal growth and development. However, further research is required to determine the acceptable biotin dose for the fetuses.

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Ethics statement

This study was approved by the Ethics Committee of Tohoku University Hospital (approval number: 26541). The patient provided written informed consent.

Authors' contributions

MM and YW conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised it. YK, CS, YA, and SK collected data, and reviewed and revised the manuscript. All

authors agreed to be accountable for all aspects of the work and approved the final manuscript as submitted.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Data availability

Data will be made available on request.

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