대한 유전성 대사 질환 : 2018;18(3):69~77

종 설

Defects in Ketone Body Metabolism and Pregnancy

Toshiyuki Fukao, MD, PhD

Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido, Gifu, Japan

Pregnancy and delivery pose a high risk of developing metabolic decompensation in women with defects of ketone body metabolism. In this review, the available reported cases in pregnancy are summarized. It is very important to properly manage women with defects of ketone body metabolism during pregnancy, especially nausea and vomiting in the first trimester of pregnancy, and during labor and delivery. Pregnant women with deficiencies of HMG-CoA lyase or succinyl-CoA:3-ketoacid CoA transferase (SCOT) often experience metabolic decompensations with nausea and vomiting of pregnancy, often requiring hospitalization. For successful delivery and to reduce stresses, vaginal delivery with epidural anesthesia or elective cesarean delivery with epidural or spinal anesthesia are recommended for women with HMG-CoA lyase and SCOT deficiency. In beta-ketothiolase deficiency, four pregnancies in three patients had favorable outcomes without severe metabolic problems.

Key words: Pregnancy, Labor, Delivery, Ketone body metabolism, HMG-CoA lyase, HMG-CoA synthase, Succinyl-CoA:3-ketoacid CoA transferase, Beta-ketothiolase

Introduction

The ketone bodies acetoacetate (AcAc) and 3-hydroxybutyrate (3HB) are short-chain (C4) carboxylic acids produced in the liver, using acetyl-CoA mainly via fatty acid beta-oxidation[1]. Ketone bodies are transported from the liver to other tissues, including the brain, where they are metabolized to acetyl-CoA to produce energy via the tricarboxylic acid cycle[1,2]. Ketone bodies are an important alternative fuel source for extrahepatic tissues, especially during a shortage in the glucose supply. Lypolysis and ketogenesis are induced by catecholamines and glucagon and are suppressed by insulin[3]. Hence, catabolic conditions enhance ketone body synthesis.

책임저자: Toshiyuki Fukao, MD, PhD
Department of Pediatrics, Graduate School of Medicine, Gifu University, 1-1 Yanagido, Gifu, Gifu 501-1194, Japan
Tel: +81-58-230-6380, Fax: +81-58-230-6387
E-mail: toshi-gif@umin.net

Defects in ketone body synthesis (ketogenesis) result in hypoketotic hypoglycemic crises during catabolic conditions such as prolonged fasting or febrile illness; defects in ketone body utilization (ketolysis) result in ketoacidotic crises during similar conditions[2-4]. The former includes deficiencies of mitochondrial HMG-CoA synthase (HMGCS2) and HMG-CoA lyase (HMGCL). The latter includes succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency and beta-ketothiolase (T2) deficiency (Fig. 1). Deficiencies of HMGCL and T2 also affect leucine and isoleucine catabolism, respectively.

In general, the prognosis of ketone body metabolism disorders is favorable if there are no severe neurological sequelae of severe metabolic crises[4]. Most patients develop metabolic crises in their infancy or early childhood and the frequency of metabolic crises decreases with age in these disorders. Hence, women with ketone body metabolism disorders reach reproductive age and can

become pregnant.

Pregnancy and delivery have been reported to be risk factors for women with inherited metabolic diseases. Pregnancy dramatically changes the metabolic condition, especially lipid and amino acid metabolism[5]. Nausea and vomiting of pregnancy (NVP) induces a catabolic state[6]. Delivery is also a very stressful condition for the mother. Hence, it is understandable that pregnancy and delivery pose increased risks for women with defects in ketone body metabolism. Several reports of pregnancies in women with these disorders have been published[7–14].

In this review, I would like to discuss the risk of pregnancy and delivery in women with defects in ketone body metabolism by detailing several such reported cases.

Ketone body metabolism and its regulation

Free fatty acids (FFA) are the source of ketone body synthesis[3]. In adipose tissue, FFA are released into circulation by hormone–sensitive lipase. FFA release is enhanced by catecholamines but suppressed by insulin. Circulating FFA are trapped by the liver and then enter hepatocyte mitochondria. The rate limiting step of mitochondrial free fatty acid uptake is mediated by carnitine palmitoyltransferase 1. This step is enhanced by glucagon and suppressed by insulin. Hepatic mitochondrial beta–oxidation of FFA yields plenty of acetyl–CoA and acetoacetyl–CoA, the latter produced by condensation of acetyl–CoA. HMGCS2 further catalyzes the condensation of acetyl–CoA and acetoacetyl–CoA to form HMG–CoA. Glucagon enhances, but insulin suppresses, HMGCS2 activity. HMG–CoA is then cleaved into AcAc and acetyl–CoA by HMGCL. A portion of the AcAc produced is converted into 3HB by 3–hydroxybutyrate dehydrogenase (3HBD). Hence, ketogenesis is promoted by catecholamines and glucagon and inhibited by insulin[3].

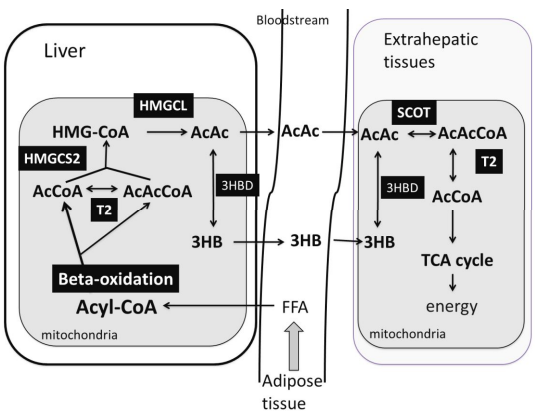

Fig. 1. Summary of ketone body metabolism. Abbreviations: FFA (free fatty acids), T2 (mitochondrial acetoacetyl–CoA thiolase), HMGCS2 (HMG–CoA synthase), HMGCL (HMG–CoAlyase), 3HBD (3–hydroxybutyrate dehydrogenase), SCOT (succinyl–CoA:3–ketoacid CoA transferase), AcCoA (acetyl–CoA), AcAcCoA (acetoacetyl–CoA), AcAc (acetoacetate), 3HB (3–hydroxybutyrate), TCA (tricarboxylic acid cycle).

AcAc and 3HB are then exported into the blood. Extrahepatic tissues, including in the brain, incorporate these ketone bodies into mitochondria. Ketone bodies are converted into acetyl–CoA through the functions of 3HBD, SCOT, and T2 and used as fuel. A rate–limiting enzyme in ketolysis, SCOT, is expressed in extrehepatic tissues and is especially plentiful in heart muscle, the kidneys, and the brain. The SCOT expression level determines the capacity of ketone body utilization[1].

Pregnancy and ketone body metabolism

Ketone body metabolism is important in catabolic conditions. There are two possible catabolic phases during pregnancy. Although the first trimester is generally an anabolic phase in which insulin–dominant lipid deposition occurs, NVP may lead pregnant women to a catabolic state. NVP is

a well-known and common condition, which begins 2-4 weeks after fertilization and peaks between 9 and 16 weeks of gestation; NVP generally resolves by 22 weeks' gestation[6]. If a pregnant woman cannot intake sufficient calories because of nausea and vomiting, the catabolic condition can worsen. Women with defects in ketone body metabolism commonly have metabolic episodes during NVP.

Another catabolic phase occurs in the third trimester of pregnancy. Pregnant women turn from an insulin-dominant anabolic condition to a relatively insulin-resistant lipolytic condition in the third trimester[5]. Under a fed condition, plasma ketone body levels remain low; however, in comparison with nonpregnant conditions, ketone body levels greatly increase under fasting. Ketone bodies can easily cross the placenta to be used as fuel and lipogenic substrates by the fetus. Hence, maternal ketosis is an important adaptive system for development of the fetus[15]. In pregnant women who have a defect in ketogenesis, this adaptive mechanism does not function. Pregnant women with a ketolytic defect may develop ketoacidosis more easily during this period than women with this defect who are not pregnant.

Labor is another ketogenic condition as the physical and psychological stresses that occur during childbirth are ketogenic stresses. Prolonged labor may result in ketoacidosis in pregnant women with a ketolytic defect.

HMGCL deficiency

HMGCL deficiency is a defect in both ketogenesis and the leucine catabolic pathway[16]. About one-third of patients present with hypoglycemic decompensation during the neonatal period. The remaining patients develop a hypoglycemic crisis, which resembles Reye syndrome with severe metabolic acidosis, hyperammonemia, and fatty liver during their late infancy, usually precipitated by infectious diseases[2,4]. Some patients die or develop retardation owing to severe decompensation. Non-episodic treatment involves avoiding fasting and consuming enough calories in a low-fat, high-carbohydrate diet, with carnitine supplementation. HMGCL-deficient patients may have recurrent metabolic crises and may develop hypoglycemia, even in adulthood[4].

In 2012, Langendonk reported two cases of HMGCL-deficient women who experienced pregnancy and delivery[9] severe complications were reported. One woman died during a decompensation in week 9 of her second pregnancy (Case 1). Another woman had a miscarriage following a severe decompensation at 10 weeks of pregnancy (Case 2). In a previous review[4], we emphasized that pregnancy and delivery might lead to increased risks for both the woman and fetus. After that, other four pregnancies in three HMGCL-deficient women have been reported[11,12,14]. The outcomes for mother and fetus were favorable in all cases, but these results were obtained by careful management during pregnancy and delivery. Herein, these cases are summarized briefly. Additional details can be found in the original case reports.

Case 1[9,12]: A 22-year-old female with HMGCL deficiency successfully delivered a baby weighing 3,218 g at 40 weeks' gestation with induction of labor, although she had recurrent decompensation during pregnancy. The patient was treated with carnitine, uncooked cornstarch, and prednisolone during pregnancy. No further detailed information is available. However, owing to learning difficulties, this patient did not attend medical follow-up after her first successful pregnancy, and she had se-

veral episodes of metabolic acidosis. During her second pregnancy at age 24 years, coagulopathy resulted in spontaneous abortion at 9 weeks' gestation in this patient. Her condition was further complicated by hyperammonemia, sepsis, and pulmonary and cerebral edema, eventually leading to cardiac arrest.

Case 2[9]: A 20-year-old female with HMG-CoA lyase deficiency also experienced metabolic acidosis with hyperammonemia and respiratory distress during her first pregnancy. She was treated with carnitine and metoclopramide; this resulted in intrauterine death of the fetus at 10 weeks of gestation. At 24 years of age, the patient decided to terminate her second pregnancy at 6 weeks' gestation, although she had been well until that time.

Case 3[11] The patient presented with severe metabolic acidosis and hypoglycemia and was diagnosed with HMG-CoA lyase deficiency at 3 months of age. She had experienced several metabolic decompensations before age 12 but remained relatively stable thereafter. She is cognitively normal. At age 28 years, she presented for prenatal care at 4 weeks' gestation. This patient had no metabolic decompensation during her pregnancy, with strict metabolic control through adequate nutrition and monitoring of maternal and fetal weight gain. At 36 weeks 5 days, she had spontaneous rupture of membranes. During labor, 10% glucose-containing intravenous fluids and levocarnitine at 200 mg/kg/day were supplemented; however, she had two episodes of vomiting and subsequently developed metabolic acidosis. A baby was finally born by cesarean delivery. To minimize catabolism, 10% dextrose-based intravenous fluids were maintained after delivery, until adequate oral intake was achieved.

Case 4[12]: This patient had hypoglycemia in the neonatal period and experienced repeated decompensations with hypoglycemic episodes. At the age of 15 months, she was diagnosed with HMGCL deficiency. She is a homozygote of c.876+1G>C. During childhood and adolescence, treatment consisted of oral carnitine with a regular high-carbohydrate, low-protein, and low-fat diet (3-hourly meals). Various infections, together with hypoglycemia, resulted in inpatient treatment every 2-3 years. At age 19 years, the patient developed nausea and vomiting and was admitted to the hospital, where it was determined that she was pregnant, at 8 weeks of gestation. After metabolic control, she was discharged and had no further episodes of hypoglycemia during the entire pregnancy. Delivery was performed by elective cesarean delivery under spinal anesthesia and total parenteral nutrition at week 37+1 day of gestation. A healthy male infant (3,055 g) was delivered. Two years later, the patient presented to the outpatient clinic with vaginal spotting and nausea and was revealed to be pregnant, at 6 weeks' gestation. She was seen frequently in the metabolic outpatient clinic at 2- to 3-week intervals. She had an uneventful cesarean delivery at week 37 and 6 days under epidural anesthesia and gave birth to a healthy baby girl.

Case 5[14]: This patient was diagnosed at the age of 10 months during a first hypoglycemic crisis following gastroenteritis. She had homozygous mutation in HMGCL (c.122G>A; p.R41Q), a common pathogenic variant seen in patients from Saudi Arabia. She was on a leucine-restricted diet and L-carnitine supplementation. There was no history of metabolic decompensation in her adult life. At age 20 years, she disclosed that she was 7 months pregnant during a routine follow-up appointment at the metabolic clinic. She had remained metabolically stable with an uneventful pregnancy thus

far. The patient was followed up in the high-risk pregnancy clinic for the remainder of her pregnancy. She was electively induced at 38 weeks and 3 days of gestation. During labor, she received intravenous 10% dextrose with electrolytes and carnitine injections. Elective epidural anesthesia was administered. She delivered a healthy male infant by normal vaginal delivery.

In HMG-CoA lyase-deficient patients, hypoglycemia may develop, even in adulthood[4]. In HMGCL-deficient women, NVP with decreased food intake poses a very high risk for developing hypoglycemia and metabolic decompensation. NVP begins 2-4 weeks after fertilization and peaks between weeks 9 and 16 of gestation[6]. NVP is the first sign of pregnancy in some women. In this disorder, maternal hypoglycemia with hypoketosis may mean a risk of energy shortage in the fetus. Regular metabolic evaluation and dietary control may be necessary, especially during the first trimester. Metabolic control should be individualized. Frequent meals with sufficient caloric intake, glucose polymer intake if glucose levels are low, and cornstarch at night are appropriate treatment measures for HMGCL-deficient pregnant women. In the case of a shortage in caloric intake, inpatient treatment with intravenous glucose infusion is necessary. In the third trimester, pregnant women also have a catabolic phase and tend to develop ketosis in cases of calorie restriction[15]. During this period, it seems important to maintain adequate blood glucose levels to supply enough calories to the fetus, because ketone bodies are not supplied in HMGCL-deficient mothers. For successful labor, to reduce stresses, vaginal delivery with epidural anesthesia or elective cesarean delivery with epidural anesthesia or spinal anesthesia are recommended.

Langendonk's advice to women with HMG-CoA lyase deficiency who are planning a pregnancy is very reasonable[9]. If these women experience any nausea at all (even in the absence of vomiting), they should attend a hospital immediately for monitoring, antiemetic treatment, and to address nutrition or energy requirements. A very low threshold for hospital admission is recommended. Dietetic assessment should be carried out prior to pregnancy, to ensure adequate caloric intake, and this should be regularly reviewed and updated throughout pregnancy.

HMGCS2 deficiency

This disorder only affects ketogenesis. HMGCS2 deficiency is clinically characterized by hypoglycemic crises[17]. Most patients present with symptomatic hypoglycemia with metabolic acidosis and fatty liver, often during a gastroenteritis episode, and patients show an absence of clinical symptoms between acute episodes[4]. Thus far, no pathognomonic markers of urinary organic acids or blood acylcarnitine profiles have been identified, although the presence of urinary 4-hydroxy-6-methylpyrone[18] and elevated acetylcarnitine[19] is a possible marker, but only in decompensated conditions. Most patients do not develop severe hypoglycemic crisis after confirmation of the diagnosis, indicating that preventive measures are effective[4].

There are no reports of pregnancy in this disorder. However, similar considerations as for HMGCL-deficient pregnant women are needed for the safety of women with HMGCS2 deficiency.

SCOT deficiency

SCOT deficiency is an autosomal recessive disorder of a ketolytic defect[20]. This disorder is clinically characterized by intermittent ketoacidotic

episodes and asymptomatic intervals between episodes. About one-half of patients develop their first ketoacidotic crisis in the neonatal period[2,4]. If present, permanent ketosis (i.e., the existence of ketosis at all times), even during asymptomatic periods when the patient is well nourished and not fasting, is pathognomonic for SCOT deficiency but is not present in all SCOT-deficient patients [2,4]. There are two reports of SCOT-deficient patients in pregnancy[10,14]. In Case 1, mutation was not reported and Case 2 is a homozygote of c. 1402C>T(p.R468C) in OXCT1[14].

Case 1[10]: A case report of an 18-year-old SCOT-deficient woman was written from the viewpoint of anesthesiologists. The patient developed the first ketoacidotic crisis at 22 months of age and had several similar episodes until age 5 years. She was given regular oral sodium bicarbonate. With this treatment, she remained essentially well from then on. She had severe NVP causing ketoacidosis during the first trimester of pregnancy and needed hospitalization twice to treat this condition and control her diet. However, the patient was stable during the second and third trimesters. She was admitted at 38 weeks of gestation for induction of labor. The anesthetist successfully managed labor with advice from a consultant in metabolic diseases. To avoid physiological stresses of labor, epidural anesthesia was administered, with careful monitoring, regular urinalysis, sufficient glucose infusion, and oxytocin infusion because of slow progression. A healthy girl weighing 2,810 g was delivered spontaneously, after labor was established.

Case 2[14]: A 19-year-old female with SCOT deficiency presented with severe nausea and vomiting at 6 weeks of gestation. She had recurrent episodes of ketoacidosis since the age of 2 years. She had been on a protein-restricted, low-fat diet and L-carnitine supplementation. She experienced nausea and vomiting resulting in ketoacidosis throughout her pregnancy and needed multiple admissions to her local hospital. She could not intake adequate amounts of calories and proteins owing to intractable nausea and vomiting during most of her pregnancy. This led to a 4-kg weight loss during the first trimester and intrauterine fetal growth restriction. She had elective induction of labor at 38 weeks gestation and delivered a female infant by normal vaginal delivery. During labor and delivery, she was given epidural anesthesia to avoid physiological stress of pain and received 10% glucose in 0.45% saline with 20 mmoL of bicarbonate per each liter of infusion. Carnitine (100 mg/kg/day) was administered intravenously. Glucose infusion with sodium bicarbonate was continued for 24 hours after delivery.

For SCOT-deficient pregnant women, nutritional management during pregnancy is important, to avoid ketoacidotic episodes. However, the NVP period is a high-risk period for ketoacidosis development. Nausea and vomiting in gastroenteritis is a strong catabolic condition and the commonest trigger of ketoacidosis in SCOT-deficient patients. It is easy to understand that NVP reduces calorie intake and enhances stress, inducing ketogenesis and resulting in ketoacidosis in SCOT-deficient patients. It is important to suppress ketogenesis in such conditions; providing sufficient and continuous glucose infusion is effective for this purpose. A low threshold for hospital admission is recommended if the patient cannot intake sufficient calories.

During labor, both of the above patients had epidural anesthesia to reduce physiological stresses and had sufficient glucose infusion to suppress ketogenesis; these measures were effective in these patients.

T2 deficiency

T2 deficiency is an autosomal recessive disorder of a ketolytic defect and isoleucine catabolism[21]. This disorder is clinically characterized by intermittent ketoacidotic episodes but patients are generally asymptomatic between episodes. Neonatal onset is rare in T2 deficiency. In most T2-deficient patients, the frequency of ketoacidotic crises decreases with age and ketoacidotic crises are very rare after age 12 years in reported cases[2,4,22]. The cases of three T2-deficient patients who experienced pregnancy are described[7,8,13].

Case 1[13]: A 25-year-old T2-deficient German woman presented in the 32nd week of gestation. She was diagnosed with T2 deficiency at 8 years of age. She is a compound heterozygote of c.1033_1035delGAA (p.345Edel) and c.1084delA; both mutations are null mutations. Since her pregnancy was first confirmed at 6 weeks of gestation, she had no complications and had taken no specific medications. At 32 weeks' gestation, urinary organic acid analysis showed increased excretion of 2-methyl-3-hydroxybutyrate and tiglylglycine. Thereafter, she received oral L-carnitine supplementation (100 mg/kg/day). This patient delivered a male infant by cesarean delivery because of cephalopelvic disproportion.

Case 2[7]: A T2-deficient Japanese woman experienced two uncomplicated pregnancies and deliveries before she was diagnosed with T2 deficiency. She developed severe metabolic acidosis and was treated with peritoneal dialysis at age 9 months. She had a similar but milder episode at age 3 years. She had no further episodes and received a possible diagnosis of SCOT deficiency. The patient was diagnosed with T2 deficiency at 25 years of age. She is a compound heterozygote of c.431A>C (p.H144P) and c.1168T>C (p.S390P); c.431A>C (p.H144P) is a mutation that retains significant residual activity. This woman was a typical T2-deficient patient with "mild mutation" with subtle urinary metabolites specific to T2 deficiency (2-methyl-3-hydroxybutyrate, tiglylglycine).

Case 3[8]: A 32-year-old T2 deficient women at 40 weeks' gestation delivered a baby by emergency cesarean delivery for fetal bradycardia. No clinical history before pregnancy and mutational information is available. This case report was written from the standpoint of anesthesiologists. A multidisciplinary team developed a delivery plan for her management in advance. Spinal anesthesia with invasive blood pressure and temperature monitoring was used, with successful outcome for both mother and baby.

Although SCOT deficiency and T2 deficiency are both ketolytic defects and the above described women with SCOT deficiency were symptomatic during their first trimester, these three T2-deficient women had no significant problems during pregnancy, even though Case 1 had two null mutations. As T2 is involved not only in ketolysis but also in ketogenesis and another medium-chain mitochondrial 3-ketoacyl-CoA thiolase may compensate for the ketolytic pathway in T2 deficiency[22], women with SCOT deficiency may be more vulnerable to NVP than those with T2 deficiency.

Conclusion and Outlook

In general, an increasing number of individuals with inherited metabolic diseases reach adulthood. In defects of ketone body metabolism, the clinical course during childhood is usually well described; however, most clinical reports lack clinical information about these individuals in adulthood.

Pregnancy and labor are the most metabolically stressful events in women. Several reports of pregnancy have been published with respect to three disorders of ketone body metabolism. In general, pregnancy is a high-risk condition for women with ketone body metabolism disorders, especially those with HMG-CoA lyase deficiency as well as SCOT deficiency. Physicians can attempt to manage pregnant women metabolically in pregnancy, but it is too early to detail the best way to manage these patients. Minimum recommendations for the management of pregnant women according to the literature are summarized in Fig. 2. However, patient management should be individualized. Further accumulated information on pregnant women with defects of ketone body metabolism is needed, to develop more precise recommendations.

Acknowledgements

I thank Professor emeritus Tadao Orii (Gifu University) and Professor emeritus Seiji Yamaguchi (Shimane University) for their mentorship. I also thank Ms Naomi Sakaguchi for her dedicated assistance with laboratory work regarding defects in ketone body metabolism. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan grant number 16K09962), by AMED under grant number JP17ek0109276, and by Health and Labor Sciences Research Grants (H29-nanchitou(nan)-ippan-051) for research on rare and intractable diseases. Finally, the author thanks Analisa Avila, ELS, of Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Conflict of interest

Toshiyuki Fukao declares that he has no conflict of interest.

References

1) Mitchell GA, Fukao T. Inborn errors of ketone body metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic & molecular basis of inherited disease McGraw-Hill, New York. NewYork: McGraw-Hill; 2001. p. 2327-56.
2) Fukao T, Harding C. Ketone synthesis and utilization

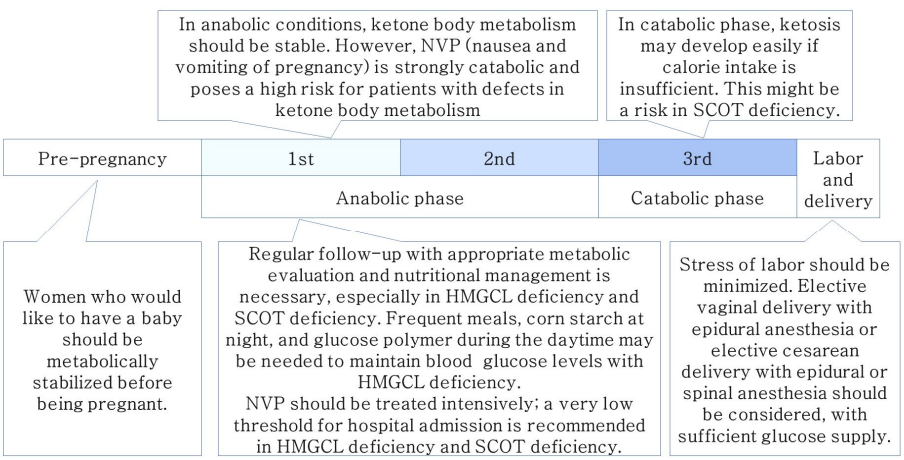

Fig. 2. Minimum recommendations to manage pregnant women with defects in ketone body metabolism.

defects. In: Sarafoglou K HG, Roth KS, editor. Pediatric Endocrinology and Inborn Errors of Metabolism 2nd edition. NewYork: Mc Graw Hill Education; 2017. p. 145–59.
3) Fukao T, Lopaschuk GD, Mitchell GA. Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry. Prostaglandins Leukot Essent Fatty Acids 2004;70:243–51.
4) Fukao T, Mitchell G, Sass JO, Hori T, Orii K, Aoyama Y. Ketone body metabolism and its defects. J Inherit Metab Dis 2014;37:541–51.
5) Zeng Z, Liu F, Li S. Metabolic Adaptations in Pregnancy: A Review. Annals of nutrition & metabolism 2017;70:59–65.
6) Bustos M, Venkataramanan R, Caritis S. Nausea and vomiting of pregnancy – What's new? Autonomic neuroscience : basic & clinical 2017;202:62–72.
7) Fukao T, Maruyama S, Ohura T, Hasegawa Y, Toyoshima M, Haapalainen AM, et al. Three Japanese Patients with Beta-Ketothiolase Deficiency Who Share a Mutation, c.431A>C (H144P) in ACAT1 : Subtle Abnormality in Urinary Organic Acid Analysis and Blood Acylcarnitine Analysis Using Tandem Mass Spectrometry. JIMD Rep 2012;3:107–15.
8) Kayani R, Botros S, Moore P. Beta-ketothiolase deficiency and pregnancy. Int J Obstet Anesth 2013;22:260–1.
9) Langendonk JG, Roos JC, Angus L, Williams M, Karstens FP, de Klerk JB, et al. A series of pregnancies in women with inherited metabolic disease. J Inherit Metab Dis 2012;35:419–24.
10) Merron S, Akhtar R. Management and communication problems in a patient with succinyl-CoA transferase deficiency in pregnancy and labour. Int J Obstet Anesth 2009;18:280–3.
11) Pipitone A, Raval DB, Duis J, Vernon H, Martin R, Hamosh A, et al. The management of pregnancy and delivery in 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. American journal of medical genetics Part A 2016;170:1600–2.
12) Santosa D, Donner MG, Vom Dahl S, Fleisch M, Hoehn T, Mayatepek E, et al. Favourable Outcome in Two Pregnancies in a Patient with 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency. JIMD Rep 2017;37:1–5.
13) Sewell AC, Herwig J, Wiegratz I, Lehnert W, Niederhoff H, Song XQ, et al. Mitochondrial acetoacetyl-CoA thiolase (beta-ketothiolase) deficiency and pregnancy. J Inherit Metab Dis 1998;21:441–2.
14) Sulaiman RA, Al-Nemer M, Khan R, Almasned M, Handoum BS, Al-Hassnan ZN. Successful Management of Pregnancies in Patients with Inherited Disorders of Ketone Body Metabolism. JIMD Rep 2017.
15) Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine 2002;19:43–55.
16) Faull K, Bolton P, Halpern B, Hammond J, Danks DM, Hahnel R, et al. Letter: Patient with defect in leucine metabolism. N Engl J Med 1976;294:1013.
17) Thompson GN, Hsu BY, Pitt JJ, Treacy E, Stanley CA. Fasting hypoketotic coma in a child with deficiency of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase. N Engl J Med 1997;337:1203–7.
18) Pitt JJ, Peters H, Boneh A, Yaplito-Lee J, Wieser S, Hinderhofer K, et al. Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency: urinary organic acid profiles and expanded spectrum of mutations. J Inherit Metab Dis 2015;38:459–66.
19) Aledo R, Mir C, Dalton RN, Turner C, Pie J, Hegardt FG, et al. Refining the diagnosis of mitochondrial HMG-CoA synthase deficiency. J Inherit Metab Dis 2006;29:207–11.
20) Tildon JT, Cornblath M. Succinyl-CoA: 3-ketoacid CoA-transferase deficiency. A cause for ketoacidosis in infancy. J Clin Invest 1972;51:493–8.
21) Daum RS, Scriver CR, Mamer OA, Delvin E, Lamm P, Goldman H. An inherited disorder of isoleucine catabolism causing accumulation of alpha-methylacetoacetate and alpha-methyl-beta-hydroxybutyrate, and intermittent metabolic acidosis. Pediatr Res 1973;7:149–60.
22) Fukao T, Sasai H, Aoyama Y, Otsuka H, Ago Y, Matsumoto H, et al. Recent advances in understanding beta-ketothiolase (mitochondrial acetoacetyl-CoA thiolase, T2) deficiency. J Hum Genet. In press 2018.