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CASE REPORT

Biochemical Monitoring and Management During Pregnancy in Patients with Isovaleric Acidaemia is Helpful to Prevent Metabolic Decompensation

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Abstract The facilities for neonatal screening, early diagnosis, and effective treatment of isovaleric acidaemia (IVA) have improved greatly over the past decades. Accordingly, IVA patients reach adolescence and may consider having children. The maintenance of a stable metabolic condition is a challenge to both the patients and their multidisciplinary team of care providers. This report presents three women with IVA during their five single or twin pregnancies, whose clinical condition were monitored with contrasting approaches. Metabolic profiles were determined and compared in these pregnancies. In one case, two pregnancies were strictly managed and monitored by measuring plasma acylcarnitine and amino acid profiles, together with adjustment of the diet and/or supplementation of L-carnitine and/or glycine. In addition, complications were prevented by intravenous glucose and L-carnitine during labor and postpartum. In two other cases, the metabolic condition of patients was less frequently monitored and additional treatment with intravenous L-carnitine and intravenous glucose/dextrose was only prescribed during periods of hyperemesis gravidarum. With respect to the differences in management and monitoring of maternal IVA all pregnancies were without complications for mother and child. Despite the favorable outcome in uncontrolled pregnancies in IVA, careful monitoring and management during pregnancy is helpful to prevent life-threatening conditions like metabolic decompensation.

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Abbreviations

IVA Isovaleric acidaemia
IVD Isovaleryl-CoA dehydrogenase

Introduction

Isovaleric acidaemia (IVA; OMIM 243500) is an autosomal recessive form of a branched-chain organic aciduria. IVA can present in the neonatal period with an acute episode of severe metabolic acidosis with vomiting, secondary hyperammonemia, and moderate ketosis, potentially resulting in coma/death when left untreated. Patients with IVA can suffer episodes of acute metabolic decompensation precipitated by intercurrent stressing events. IVA is caused by deficiency of isovaleryl-CoA dehydrogenase (IVD; OMIM 607036), the enzyme which catalyzes the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA. This results in

the accumulation of isovaleryl-CoA derivates, which are detected in urine and blood as the conjugation products isovalerylglycine and isovalerylcarnitine (Vockley and Ensenauer 2006). The main goal of treatment is to achieve a state of anabolism, reducing formation of isovaleryl-CoA formation from leucine catabolism. Treatment strategy for patients with IVA may include a leucine-free formula, protein-restricted diet, L-carnitine or glycine supplementation or a combination thereof. The effects of treatment on long-term neurological development in IVA patients have not yet been completely clarified (Martin-Hernandez et al. 2009). By adhering to effective treatment, patients reach adolescence in a healthy condition and may consider having children.

Pregnancies and the fetal outcome have been described in a number of patients with amino acidopathies and disorders of intermediate metabolism. Most pregnancies were successful despite poor biochemical monitoring. Only a small number of maternal inborn errors have been shown to affect fetal health (Lee 2006; Rubio-Gozalbo et al. 2010; van Spronsen et al. 2003). The effects of treatment also need consideration; however, no pregnancy safety profiles are available for the majority of therapeutic drugs (Preece and Green 2002; Walter 2000).

Sharing experiences in this field will lead to improved therapy during pregnancy for patients with an inborn error of metabolism and expands the knowledge of adverse effects of therapy for the fetus. Two previous cases with a favorable outcome of two pregnancies in patients with IVA have been described (Shih et al. 1984; Spinty et al. 2002), to which we now add the clinical history of five more pregnancies with favorable outcomes.

Case Report

First Case

This woman with IVA had two successful pregnancies as described below. She has always been compliant to a combined therapy of protein-restricted diet, a leucine-free formula (30 g/day), and supplementation of L-carnitine (2,970 mg/day) and was reasonably well controlled with a normal development. Biochemical follow-up during the past years was performed in plasma taken randomly during the day. In the preconception period of both pregnancies her treatment was intensified in order to optimize metabolic control. Before her first pregnancy the free carnitine concentration was 8.7 μmol/l (total carnitine: 33.1 μmol/l, isolalerylcarnitine: 20.1 μmol/l), this concentration is below the reference range for healthy individuals (Blau et al. 2008). Increasing L-carnitine supplementation (three doses of 1,980 mg L-carnitine/day) marginally increased the free carnitine concentration (11.3 μmol/l). A combination of three doses of 1,320 mg L-carnitine supplementation with three doses of 6 g glycine/day resulted in 23.6 μmol/l free carnitine. The patient stopped her anticonception and became pregnant quickly thereafter. Also in the pre-conception period of the second pregnancy she was treated with the L-carnitine/glycine combination.

During pregnancy, supplementation (Supplementary Table) was adjusted by biochemical monitoring and not by weight gain. In the first months of her first pregnancy the free carnitine concentration decreased from 36.3 μmol/l to 10.5 μmol/l (Table 1A). Increasing the supplementation to three doses of 10 g glycine/day in the fifth month was not effective; increasing supplementation to 15 g glycine in the sixth month resulted in a concentration of 24.5 μmol/l free carnitine (Table 1A). The concentrations of the branched-chain amino acids (Table 1B) and the other amino acids (data not shown) were normal compared to the reference range during the first pregnancy. During the second pregnancy, already in the third month low concentrations of free carnitine levels (13.1 μmol/l; Table 1A) were measured. Glycine and L-carnitine supplementation were ultimately increased to 100 g glycine/day and 10 g L-carnitine/day with only a transient increase of free carnitine (47.3 μmol/l; Table 1A) in the eighth month. The management of the amino acid levels was a challenge in the second pregnancy in which the concentrations of branched-chain amino acids were lower than in the previous pregnancy (Table 1B). The leucine-free formula intake was increased to 80 g/day during the 2 months. The overall increase in maternal weight was normal during both pregnancies and the patient had no periods of hyperemesis gravidarum. Subsequently, growth and development of both fetuses were normal.

At the first signs of labor, intravenous glucose (10%; 2.5 l/day) and intravenous L-carnitine (200 mg/kg per day) were started and oral glycine supplementation (three doses of 15 g glycine/day) was continued during both pregnancies. After additional supplementation during labor of the first pregnancy, free carnitine and total carnitine increased to 435.6 μmol/l and 467.8 μmol/l, respectively (Table 1A). The amino acid profile (Table 1B) and acid–base balance (pH: 7.46, pCO_2: 4.6 kPa, HCO_3^-: 24.9 mmol/l) were normal. During labor of the second pregnancy, free carnitine was 127.7 μmol/l and total carnitine was 175.3 μmol/l (Table 1A) after additional supplementation. Lower levels of glycine and the branched-chain amino acids (leucine and valine; Table 1B) were measured and blood-gas analysis was normal (pH: 7.36, pCO_2: 5.3, HCO_3^-: 21.6 mmol/l). In both pregnancies, intravenous therapy was stopped after 4 h postpartum and acylcarnitine and amino acid profiles normalized within 3 days (Table 1A, B: first day post partum). The acylcarnitine and amino acid

Table 1 Acylcarnitine (A) and amino acid (B) concentrations (μmol/l) in the plasma of a patient with isovaleric acidaemia (case 1) during the first pregnancy, the second pregnancy, labor of both pregnancies, and reference range in healthy individuals (Blau et al. 2008). Free carnitine (C0), total carnitine (Total), isovalerylcarnitine and 2-methylbutyrylcarnitine (C5-iso)

A

Pregnancy(month)	C0		Total		C5-iso	
	First	Second	First	Second	First	Second
1st	36.3	–	52.3	–	11	–
2nd	29.2	28.9	45.2	48.8	10.8	12.2
3rd	–	13.1	–	24.3	–	7.2
4th	20.4	13.9	32.8	26.2	8.1	7.5
5th	10.5	13.1	21.9	20.8	7.7	4.1
6th	24.5	13.5	37.1	21.8	7.2	3
7th	27.7	–	40.6	–	7	–
8th	–	47.3	–	59.1	–	5.8
9th	11.9	12.9	25	26.7	6.7	8.6
Labor	435.6	127.7	467.8	175.3	19.7	30.7
Maternal cord blood	240.9	233.1	276.7	266.3	14	18.3
Post partum	288.4	935.7	334.9	991.6	27.9	37.8
Day 1 after labor	225.9	22.9	279.6	41	36	10.3
Reference	22.3–54.8				0.03–0.23	

B

Pregnancy(month)	Glycine		Leucine		Isoleucine		Valine	
	First	Second	First	Second	First	Second	First	Second
1st	541	–	45	–	67	–	214	–
2nd	570	317	64	131	95	68	253	193
3rd	–	223	–	198	–	65	–	202
4th	320	225	61	85	70	49	202	160
5th	313	221	78	105	48	55	182	151
6th	815	377	39	65	71	38	214	122
7th	614	–	47	–	87	–	249	–
8th	–	1,446	–	24	–	83	–	220
9th	338	345	130	66	67	38	234	106
Labor	391	110	74	54	68	72	226	87
Maternal cord blood	389	248	102	85	72	45	300	144
Post partum	887	154	66	69	87	46	253	154
Day 1 after labor	410	320	100	113	59	68	208	205
Reference	147–321		73–160		34–84		145–283	

profiles in cord blood reflected the maternal metabolic status (Table 1A, B).

From both pregnancies, healthy infants were born at term with a normal weight (3,980 g and 4,200 g, respectively) and Apgar score. Isovalerylcarnitine levels (first child: 0.3 μmol/l, second child: 0.2 μmol/l; Table 2A; the cut-off value is 1.0 μmol/l for isovalerylcarnitine in the newborn screening in The Netherlands) and the concentrations of the branched-chain amino acids (Table 2B) were normal in plasma taken in the first hour after birth of both infants. The free- and total carnitine concentrations (Table 2A) were increased due to maternal supplementation but these levels resolved within a few days without treatment or complications.

Second Case

This woman was diagnosed with IVA immediately after birth. At 25 years of age, she had a normal development and had a twin pregnancy. She was treated with a protein-

Table 2 Acylcarnitine (A) and amino acid (B) concentrations (μmol/l) in plasma of two children immediately after birth from a mother with isovaleric acidaemia (case 1), and reference range in healthy individuals (Blau et al. 2008). Free carnitine (C0), total carnitine (Total), isovalerylcarnitine and 2-methylbutyrylcarnitine (C5-iso)

A

Carnitine	First child	Second child	Reference
C0	79.9	58.9	6.1–22.2
Total	113.4	85.9	
C5-iso	0.3	0.2	0.06–0.37

B

Amino acid	First child	Second child	Reference
Glycine	524	238	101–317
Leucine	88	54	47–175
Isoleucine	38	35	22–82
Valine	135	90	65–201

restricted diet, a leucine-free formula, and L-carnitine (9 g/day). Prior to pregnancy, the plasma concentrations of free carnitine (5 μmol/l) and total carnitine (12 μmol/l) were in the low range compared to the reference range of healthy individuals, and plasma isovalerylcarnitine was 5.7 μmol/l. No additional therapy was prescribed to increase the free carnitine levels. During twin pregnancy, the free and total carnitine concentrations in plasma were 7 μmol/l and 14 μmol/l in the first month and 5 μmol/l and 8 μmol/l in the eighth month, respectively. The amino acid profile was determined in the eighth month of pregnancy: glycine (153 μmol/l), valine (100 μmol/l), isoleucine (35 μmol/l), and leucine (61 μmol/l). She solely received additional treatment (intravenous 10% glucose and 100 mg/kg per day L-carnitine) during periods of hyperemesis gravidarum in the fourth and fifth month of the pregnancy. Blood-gas analyses revealed no metabolic acidosis during these periods (pH: 7.45 and 7.39, pCO_2: 4.1 and 5.2 and HCO_3^-: 21 and 23 mmol/l, respectively), and glucose was within the normal range. A low-to-normal growth of the fetuses was observed when compared to single pregnancies, and protein intake was monitored and controlled during the last trimester of the pregnancy. Without additional medical care during labor and the postpartum period, there was a favorable outcome for mother and twins.

Third Case

This woman with IVA has been very stable with a normal development in spite of minimal therapy compliancy for many years. She has had three pregnancies, the details on the first pregnancy were published previously (Spinty et al. 2002). In this pregnancy, the monitoring and management was carefully planned, with additional treatment of intravenous L-carnitine (100 mg/kg per day), sodium benzoate (250 mg/kg per day), and a standard electrolyte/glucose solution during labor. There were no maternal complications and a healthy child was born.

The prescribed therapy was a protein-restricted diet combined with L-carnitine supplementation (2 doses of 3 g L-carnitine/day). In general, the patient's compliance to therapy was limited with metabolic decompensation during the second and third pregnancy. In the second month of both pregnancies, periods of hyperemesis gravidarum were treated with intravenous 10% dextrose and antiemetics. In addition, intravenous L-carnitine (100 mg/kg) was started because oral L-carnitine was refused. During the second pregnancy, amino acids (branched-chain amino acids: low, glycine: 210 μmol/l) and acylcarnitine profiles (free carnitine: 5.5 μmol/l) in plasma were measured once in the fourth month. During the third pregnancy, the metabolic condition of the patient was checked four times (branched-chain amino acids: low-to-normal, glycine: between 175 and 305 μmol/l plasma). Free carnitine concentrations in plasma were found to be in the range of 6.8–12.1 μmol/l with the isovalerylcarnitine concentration ranging from 3.6 to 7.6 μmol/l. Labor and the postpartum period of the second and third pregnancy were without complications and no additional therapy was given. The second pregnancy and third pregnancy resulted in healthy children with a normal birth weight (2,920 g and 3,940 g, respectively).

Discussion

With neonatal screening, early diagnosis, and effective treatment life expectancy of patients with IVA has considerately improved (van Spronsen et al. 2003). When these patients become pregnant, it is a challenge to both the patients and the multidisciplinary team to maintain metabolic stability. Regarding the changes in maternal metabolism, a planned monitoring and management needs to be considered preconceptionally, as well as during pregnancy, labor, and the postpartum period (Lee 2006). There is limited information about reference ranges for metabolite concentrations in pregnancy (Ghadimi and Pecora 1964; Talian et al. 2007; Winter et al. 1995) and no information about target values for pregnant patients with IVA or other inborn errors of metabolism. By sharing our experience, we hope to improve the management of pregnant patient with IVA and their infants.

It is recommended to monitor the metabolic state of a woman with an inborn error of metabolism before conception (Lee 2006). The metabolic profile of the patient presented in case 1 was strictly managed with different supplements and dosages during preconception. L-carnitine

and glycine supplementation shunts isovaleryl-CoA towards the nontoxic metabolites isovalerylcarnitine and isovalerylglycine, respectively. This combination is especially effective during metabolic stress (Fries et al. 1996). With the addition of glycine supplementation L-carnitine is spared, resulting in higher free carnitine levels. Therefore, a combined L-carnitine and glycine supplementation was prescribed in the patient of case 1. In contrast, in case 2 and 3, the metabolic profile of the patients was not monitored nor intensively managed in the period preceding conception.

The main goals of therapy in IVA are to prevent metabolic decompensation and to prevent accumulation of isovaleryl-CoA. Regarding the first goal, awareness of the anabolic and catabolic periods is required in maternal IVA. The effects of endocrine changes (increased circulation hormones and growth factors) are anabolic and can be beneficial in maternal IVA. In addition, growth development during pregnancy enhances the maternal protein requirements resulting in increased protein tolerance. Therefore, the metabolic condition of the patient needs to be monitored and can be managed by adequate leucine and/or caloric intake. There is a risk of catabolism during periods of hyperemesis gravidarum, during the labor/delivery and the postpartum period in healthy woman but especially in a pregnant woman with IVA. Metabolic decompensation during these periods can be prevented by intravenous glucose/dextrose. The second goal was to enhance the conjugation of isovaleryl-CoA to less toxic compounds; therefore, optimal dosages of L-carnitine and glycine supplementation are required. It is known that free carnitine concentrations reduce during pregnancy in healthy controls (Talian et al. 2007). However, in all three cases there was a difference in the free carnitine levels and reductions (Table 3). In the first pregnancy of case 1, treatment of the patient with L-carnitine and glycine supplementation resulted in a free carnitine level comparable to the reference range of healthy controls. In the second pregnancy of this patient, the same supplementation resulted in lower free carnitine concentrations compared to the first pregnancy. Even a higher L-carnitine supplementation (10 g/day) did not result in a normal concentration of free carnitine. This can be explained by the fact that efficacy of L-carnitine supplementation is limited since there is a maximal dose absorbance of 2 g L-carnitine per administration (Harper et al. 1988). In the case that L-carnitine supplementation is maximal, it is advised to prescribe a combined supplementation of L-carnitine and glycine. Although this combined therapy increased the free carnitine concentration in plasma during the preconception period and the first pregnancy, it was not effective during the second pregnancy. The difference between patients and pregnancies should be evaluated and treated in its own right. In cases 2 and 3 there was no adjustment of therapy, resulting in low carnitine and amino acid concentrations together with periods of hyperemesis gravidarum. The question remains whether a more strict management would have prevented this complication during the pregnancy. The labor and postpartum period has an enormous catabolic effect and it is a time of considerable risk of metabolic decompensation. In two previously published cases (Shih et al. 1984; Spinty et al. 2002) and in case 1 of this report, catabolism was prevented by intravenous glucose and L-carnitine during these periods. In the twin pregnancy of case 2 without additional care, in which the risk for complications is expected to be higher, and in the two pregnancies of case 3 without additional care, however, no complications were observed. Although the postpartum period is mainly recognized as a catabolic event, all patients were metabolically stable within the first days after delivery.

Table 3 Overview of the monitoring and management of three patients with isovaleric acidaemia during five pregnancies

	Case 1	Case 2	Case 3
Total pregnancies	2	1	3(First pregnancy Spinty et al. 2002)
Biochemical follow-up during the pregnancy	Intense	Limited	Limited
Therapy during pregnancy	First pregnancy: increased glycine supplementation	During hyperemesis gravidarum: intravenous glucose and L-carnitine	During hyperemesis gravidarum: intravenous
	Second pregnancy: increased glycine, L-carnitine supplementation and increased protein intake	In the last part of the pregnancy: increased protein intake	Dextrose, L-carnitine, and antimetics
Complications during pregnancy	Both pregnancies: none	Hyperemesis gravidarum	Hyperemesis gravidarum
Therapy during labor	Both pregnancies: glucose and L-carnitine intravenous and glycine per os	None	None
Outcome	Two healthy infants	Healthy twin	Two healthy infants

Another aspect of pregnancies, is the possible effect of maternal IVA on the fetus and safety of medication used during pregnancy. Fetal carnitine is derived from two sources; from the mother via transplacental transfer (El-Hattab et al. 2010) and to a lesser extent from in utero synthesis (Oey et al. 2006). Therefore, immediately after birth the plasma-free carnitine level of the neonate reflects that of the mother. Carnitine in the fetus and placenta is biosynthesized from lysine and methionine involving four enzymatic steps and may be highly relevant in situations where the maternal carnitine supply is limited, like in maternal IVA (Oey et al. 2006). The safety of medications during pregnancy is known for some drugs, but the list of agents without safety information is still long (Preece and Green 2002; Walter 2000). The effects of L-carnitine during pregnancy have been studied in sows, but unfortunately no information is available in humans. In pregnant sows, it has been shown that L-carnitine has limited influence on lipid metabolism and utilization of nitrogen, but increases the plasma concentrations of insulin-like growth factors. This in turn may stimulate placental development and intrauterine nutrition, resulting in increased birth weight (Doberenz et al. 2006). However, L-carnitine supplementation during the pregnancies of the reported cases did not result in an increased birth weight of the infants. The safety of glycine and L-carnitine supplementation in pregnancies is unknown. Transplacental transfer of amino acids is an active process, with fetal plasma amino acids being higher than maternal plasma levels (Cleal et al. 2007). The concentrations of glycine in the fetus and their effects during maternal glycine supplementation are unknown and need further investigation. The previously described cases (Shih et al. 1984; Spinty et al. 2002) and the patients described in this report suggest that L-carnitine and glycine supplements were not harmful for the developing fetus although the long-term outcomes are not known. If this supplementation could have potentially beneficial effects for the fetus, e.g., by preventing maternally L-carnitine deficiency, remains to be proven. Finally, it is recommended to screen the offspring for IVA. In parents with an autosomal recessive inherited metabolic disorder, the risk of having an affected offspring is low, but is nevertheless considerably higher depending on the allele frequency of carrier in the population.

There is very limited knowledge about metabolic changes in pregnancies. Reference values for acylcarnitine and amino acid concentrations in pregnant patients with IVA are lacking and cannot be extracted from the results of the three cases presented in this report. This suggests that a carefully planned biochemical follow-up and additional management during the pregnancy period can be helpful. We conclude that patients with IVA may have uncomplicated pregnancies, regardless of their metabolic condition or differences in therapeutic strategies (Table 3). The pregnancy, the labor, and the postpartum period were successful in all reported IVA patients with or without additional monitoring and management. A well-established protocol for pregnant patients with IVA has not been established, but managing a well-controlled metabolic condition of the patient with IVA is the main goal in general and should be especially so during pregnancy.

Synopsis

Managing a well-controlled metabolic condition of the patient with IVA is the main goal in general and should be especially so during pregnancy.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Author's Contribution

All authors have contributed to the work presented in this manuscript.

References

Blau N, Duran M, Gibson KM (2008) Laboratory guide of the methods in biochemical genetics. Springer, Berlin

Cleal JK, Brownbill P, Godfrey KM, Jackson JM, Jackson AA, Sibley CP, Hanson MA, Lewis RM (2007) Modification of fetal plasma amino acid composition by placental amino acid exchangers in vitro. J Physiol 582:871–882

Doberenz J, Birkenfeld C, Kluge H, Eder K (2006) Effects of L-carnitine supplementation in pregnant sows on plasma concentrations of insulin-like growth factors, various hormones and metabolites and chorion characteristics. J Anim Physiol Anim Nutr (Berl) 90:487–499

El-Hattab AW, Li FY, Shen J, Powell BR, Bawle EV, Adams DJ, Wahl E, Kobori JA, Graham B, Scaglia F, Wong LJ (2010) Maternal systemic primary carnitine deficiency uncovered by newborn screening: clinical, biochemical, and molecular aspects. Genet Med 12:19–24

Fries MH, Rinaldo P, Schmidt-Sommerfeld E, Jurecki E, Packman S (1996) Isovaleric acidemia: response to a leucine load after three weeks of supplementation with glycine, L-carnitine, and combined glycine-carnitine therapy. J Pediatr 129:449–452

Ghadimi H, Pecora P (1964) Free amino acids of cord plasma as compared with maternal plasma during pregnancy. Pediatrics 33:500–506

Harper P, Elwin CE, Cederblad G (1988) Pharmacokinetics of bolus intravenous and oral doses of L-carnitine in healthy subjects. Eur J Clin Pharmacol 35:69–75

Lee PJ (2006) Pregnancy issues in inherited metabolic disorders. J Inherit Metab Dis 29:311–316

Martin-Hernandez E, Lee PJ, Micciche A, Grunewald S, Lachmann RH (2009) Long-term needs of adult patients with organic acidaemias: outcome and prognostic factors. J Inherit Metab Dis 32:523–533

Oey NA, van Vlies N, Wijburg FA, Wanders RJ, Attie-Bitach T, Vaz FM (2006) L-carnitine is synthesized in the human fetal-placental unit: potential roles in placental and fetal metabolism. Placenta 27:841–846

Preece MA, Green A (2002) Pregnancy and inherited metabolic disorders: maternal and fetal complications. Ann Clin Biochem 39:444–455

Rubio-Gozalbo ME, Gubbels CS, Bakker JA, Menheere PP, Wodzig WK, Land JA (2010) Gonadal function in male and female patients with classic galactosemia. Hum Reprod Update 16:177–188

Shih VE, Aubry RH, DeGrande G, Gursky SF, Tanaka K (1984) Maternal isovaleric acidemia. J Pediatr 105:77–78

Spinty S, Rogozinski H, Lealman GT, Wraith JE (2002) Second case of a successful pregnancy in maternal isovaleric acidaemia. J Inherit Metab Dis 25:697–698

Talian GC, Komlosi K, Decsi T, Koletzko B, Melegh B (2007) Determination of carnitine ester patterns during the second half of pregnancy, at delivery, and in neonatal cord blood by tandem mass spectrometry: complex and dynamic involvement of carnitine in the intermediary metabolism. Pediatr Res 62:88–92

van Spronsen FJ, Molendijk H, Erwich JJ, Smit GP (2003) Inherited metabolic diseases and pregnancy: consequences for mother and child. Ned Tijdschr Geneeskd 147:235–240

Vockley J, Ensenauer R (2006) Isovaleric acidemia: new aspects of genetic and phenotypic heterogeneity. Am J Med Genet C Semin Med Genet 142C:95–103

Walter JH (2000) Inborn errors of metabolism and pregnancy. J Inherit Metab Dis 23:229–236

Winter SC, Linn LS, Helton E (1995) Plasma carnitine concentrations in pregnancy, cord blood, and neonates and children. Clin Chim Acta 243:87–93