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ORIGINAL ARTICLE

Methylmalonic acidemia (MMA) in pregnancy: a case series and literature review

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Abstract
Introduction Women with inherited metabolic disorders, including those with previously life-limiting conditions such as MMA, are reaching child-bearing age more often due to advances in early diagnosis and improved pediatric care. Information surrounding maternal and fetal complications associated with the underlying disorders remains largely unexplored.
Methods Pregnancies affected by maternal MMA were ascertained through study 04-HG-0127 "Clinical and Basic Investigations of Methylmalonic Acidemia and Related Disorders" (clinicaltrials.gov identifier: NCT00078078) and via literature review. Prenatal and delivery records in study participants were reviewed.
Results Seventeen pregnancies were identified in women with isolated MMA, including three abortions, one termination, and 13 completed pregnancies [three cases with *cblA* (four pregnancies), four cases of *mut*- (one cobalamin responsive, three non-responsive), five cases with unknown type of MMA]. Seventeen percent (3/17) of the pregnancies resulted in a first trimester abortion, while 38.5 % (5/13) of the completed pregnancies resulted in preterm deliveries. A cesarean delivery rate of 53.8 % (7/13) was noted among the cohort. Fetal distress or nonreassuring fetal status was the indication for 57 % (4/7) cesarean deliveries. One patient was reported to have metabolic crisis as well as episodes of mild hyperammonemia. Malformations or adverse outcomes in the progeny were not observed.
Conclusion Although there have been a small number of pregnancies identified in women with MMA, the cumulative results suggest that the majority of pregnancies can be complicated by cesarean delivery and increased risk of prematurity. A pregnancy registry could clarify perinatal complications and define management approaches needed to ensure optimal maternal and fetal outcomes in this growing patient population.

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Introduction

Methylmalonic acidemia (MMA) is a group of inherited metabolic disorders with a common defect in the conversion of methylmalonyl-CoA to succinyl-CoA (Manoli and Venditti 2010). The disorder was first defined clinically in late 1960s in infants presenting with overwhelming acidosis and renal tubular dysfunction (Oberholzer et al 1967; Stokke et al 1967). MMA is most commonly caused by mutations in the mitochondrial localized enzyme, methylmalonyl-CoA mutase (*MUT*) or impaired transport and synthesis of the MUT cofactor, 5′-deoxyadenosylcobalamin due to mutations in the *MMAA*, *MMAB* or *MMADHC* genes (Chandler and Venditti 2005). Over the past four decades, treatment with amino acid/

protein precursor restriction, along with supportive care and supplementation with cobalamin in responsive patients, has led to improved survival (de Baulny et al 2005; Dionisi-Vici et al 2006; Hörster et al 2007).

With early diagnosis through newborn screening and improved pediatric care, women with inborn errors of metabolism are achieving reproductive age more frequently and are well enough to contemplate pregnancy (Langendonk et al 2011; Jacquemyn et al 2014). Patients with MMA who are pregnant or interested in becoming pregnant, as well as their health care providers, need information surrounding the risks to maternal and fetal health that may be associated with the disease state during pregnancy and monitoring guidelines to ensure optimal outcomes.

Because some inborn errors have known deleterious maternal or fetal effects in pregnancy (Koch et al 1993), gestation, parturition, and lactation can be challenging for the fetus, mother, and the medical teams. In urea cycle disorders, there is an increased risk of metabolic decompensation for the mother, especially in the peripartum period (Walter 2000). Maternal phenylketonuria has well-described teratogenic effects on the fetus, including intellectual disability, microcephaly, congenital heart disease, and intrauterine growth retardation, mandating tighter dietary management for women even prior to conception (Walter 2000). In addition to the inherent exposures from the maternal condition on the fetus, many conditions are treated with medical foods and supraphysiological levels of cofactors, vitamins, even though teratogenicity of these agents have not been studied.

Amongst women with MMA and related disorders, there are nine published cases of pregnancy affected by maternal isolated methylmalonic acidemia (Wasserstein et al 1999; Diss et al 1995; Deodato et al 2002; Boneh et al 2002; Adeyemi et al 2004; Brunel-Guitton et al 2010; Langendonk et al 2011; Lubrano et al 2013; Jacquemyn et al 2014). The paucity of information regarding management and outcomes of pregnancies affected by maternal MMA motivated a critical reappraisal of this topic when we participated in the care of several MMA patients evaluated as part of a natural history study who had previous pregnancies or became pregnant during the course of this study.

Patients and methods

A retrospective analysis was performed of patients enrolled through a natural history study at the National Institutes of Health, 04-HG-0127 "Clinical and Basic Investigations of Methylmalonic Acidemia and Related Disorders" (clinicaltrials.gov identifier: NCT00078078) and conducted in compliance with the Helsinki Declaration. Prenatal and delivery records were obtained for review and used to supplement patient assessments. The subtypes of MMA were determined by cellular biochemistry and/or genetic testing for all participants (Baumgartner et al 2014).

Two women enrolled in the natural history study were found to have three unpublished pregnancies. Additionally, another woman enrolled in the natural history study became pregnant and was followed prospectively. Two first trimester miscarriages were also identified; including one in a patient with another completed pregnancy.

To supplement the experience of our participants, a comprehensive literature review of reports indexed in PubMed describing pregnancies affected by maternal MMA was performed using the terms methylmalonic acidemia, pregnancy, and inborn errors of metabolism. The searches yielded 28 reports; upon further evaluation, three were relevant to our study for further review. Additional case reports were also identified after examining the citations within relevant papers. Only cases of isolated MMA were considered in subsequent analyses. The same literature search was repeated in October 2014 prior to final submission. The results of the published cases and the NIH patients were combined with the previously published reports to generate the case series presented here.

Results

Nine pregnancies affected by isolated MMA were previously published (Adeyemi et al 2004; Boneh et al 2002; Deodato et al 2002; Diss et al 1995; Jacquemyn et al 2014; Langendonk et al 2011; Lubrano et al 2013; Wasserstein et al 1999). In the review of patients enrolled in our clinical research protocol, four pregnancies in three women with forms of isolated MMA were identified, as well as two first trimester miscarriages. These latter pregnancies have not previously been reported. The results from the literature review and the retrospective chart review were combined for a total case series of 13 completed pregnancies (Tables 1 and 2); three first trimester miscarriages and one first trimester termination of pregnancy were also documented (Table 3).

Of the 12 women with MMA, several subtypes of MMA are represented. Five of the patients were unclassified. Four patients had *mut*$^{-}$ and three patients had *cblA* deficiency, one of whom had two completed pregnancies. The women manifested a range of MMA-related complications including optic atrophy, chronic pancreatitis, strokes, seizure disorders, history of coma, intellectual disability, and cardiomyopathy (Table 1).

Renal dysfunction is a common manifestation of MMA (de Baulny et al 2005; Hörster et al 2007) and patients in this cohort displayed a range of kidney disease from normal function to renal insufficiency and even renal transplantation (Table 1). As previously noted, but worth being emphasized, the woman reported by Wasserstein et al experienced a decrease in renal function during pregnancy from 51 ml/min in the first

Table 1 Published and unpublished pregnancies complicated by maternal isolated methylmalonic acidemia (MMA)

Patient	Year of publication or delivery	Age	Enzymology/ complementation group	Molecular genetics	B12 responsive	Protein intake (trimester)	Treatments	Methylmalonic acid serum μM (trimester)	Methylmalonic acid urine mmol/mol Cr	Renal function Serum Cr μmol/L (trimester)	Complications of MMA
1 (Diss 1995)	1995	23	NR	NR	No	3.6 g/kg/day (1) 4.1 g/kg/day (2) 1.6 g/kg/day (3)	NR	16.4 (1) 7.5 (3)	2.59 mmol/day (1) 1.02 mmol/day (3)	NR	Convulsions
2a (this report)	1997	18	*mut*$^{-}$	*MUT* c.2150G>T p.G717V; 2nd mutation unknown	No	64 g/day	Carnitine	172 (postpartum)	NR	Serum creatinine 70.72 (postpartum)	Strokes, seizure
3a (this report)	1997	24	*cblA*	*MMAA* c.450dupG p.P151AfsX19 homozygous	Yes	up to 45 g/day	N/A	52 (postpartum)	NR	NR	None
3b (this report)	2008	35	*cblA*	*MMAA* c.450dupG p.P151AfsX19 homozygous	Yes	45 g/day (1–2) 80 g/day (3)	Carnitine, hydroxocobalamin IM 5 mg QOD, protonix, albuterol inhaler	214 (preconception) 39 (1) 45 (2) 15 (3)	N/A	Serum creatinine 120.22 (1) 97.24 (3) eGFR:56 mL/min/ A (3) Proteinuria: 280 mg/24 h (3)	None
4 (Wasserstein)	1999	20	*mut*$^{-}$	NR	No	40–55 g/day	Oral amoxicillin in first trimester then metronidazole; cornstarch in overnight formula; oral bicarbonate	1900 (1) 484 (2) 1059-1192(3)	NR	eGFR:51 ml/min/ 1.73 m^2 (1); 36 ml/min/ 1.73 m^2 (2) Proteinuria: 0.7 g in 24 h (2)	Optic atrophy, chronic pancreatitis, anemia
5 (Deodato)	2002	24	*mut*$^{-}$	NR	Yes	NR	Carnitine, vitamin B12 IM 5 mg per week	280 (D)	17,049 (1) 4177 (2) 3236 (3) 1148 (D)	Creatinine clearance: 67.5 ml/min/ 1.73 m^2	
6 (Boneh)	2002	16	*cblA*	NR	Yes	NR	Vitamin B12 IM 1 mg every 4 weeks increased to 1 mg every 2 weeks	3.7–9.7 (D)	210–600 (3) 277–1308 (D)	NR	None
7 (Adeyemi)	2004	23	NR	NR	Yes	Low Protein	Oral cyanocobalamin 500 umg BID	NR	NR	NR	Epilepsy
8a (Langendonk)	2011	24	decreased propionate incorporation	NR	unknown	45 g/day (1–2) 60 g/day (3)	Carnitine, oral vitamin B12 1 mg daily, folic acid, iron, calcium, potassium, vitamin D		758 (Pre) 1700–3886 (?)	Serum creatinine 50	None
9 (Langendonk)	2011	19	decreased propionate incorporation and methylmalonyl CoA mutase activity; reduced adenosyl-cobalamin synthesis	NR	No	35 g/day	Carnitine, multivitamin, vitamin B12 IM 1 mg every 4–6 weeks	120 (1) 37 (3)	2240 (1)	Serum creatinine 66 eGFR >90 mL/min/ 1.73 m^2	Intellectual disability (IQ 55)

Table 1 (continued)

Patient	Year of publication or delivery	Age	Enzymology/ complementation group	Molecular genetics	B12 responsive	Protein intake (trimester)	Treatments	Methylmalonic acid serum μM (trimester)	Methylmalonic acid urine mmol/mol Cr	Renal function Serum Cr μmol/L (trimester)	Complications of MMA
10 (this report)	2012	29	*mut*$^{-}$	*MUT* c.2150G>T p.G717V homozygous	No	47 g/day	Carnitine, vitamin D, C, folic acid	133 (Postpartum)	765	Serum creatinine: 85.75	Peripheral neuropathy, history of coma
11 (Lubrano)	2013	29	*cblA*	*MMAA* c.586C>T p.R196X homozygous		NR	Immunosuppression, beta-blocker	72–52 (2–3)	1208 (Pre);	Serum creatinine 114.92 (1) 123.76 (2) eGFR 55 mL/min/ 1.73 m^2 (1)	Kidney transplant, hypertrophic cardiomyopathy
12 (Jacquemyn)	2014	27	NR	NR	Yes	1 g/kg/day	Carnitine, zinc sulfate, calcium carbonate, Vitamin B12 IM 1 mg once daily	NR	NR	Serum creatinine 55.69	None

D Delivery, *NR* Not reported, *N/A* not applicable

trimester to 36 ml/min in the second trimester. Serum creatinine values ranged from 0.63 mg/dL to 1.36 mg/dL (Table 1). Renal indices are summarized in Table 1 and were not uniformly reported (n=9).

MMA patients were largely unaffected by metabolic disturbances during the pregnancies. One report mentioned two episodes of mild hyperammonemia (up to 49 μmol/L) during pregnancy (Langendonk et al 2011). Patient 2 had two metabolic crises in pregnancy around 24 weeks gestation, which manifested with nausea, vomiting, and lethargy and resulted in the need for hospitalizations and IV hydration. Fortunately, she was without metabolic crises in the postpartum period.

Protein restriction continued to represent the mainstay of treatment for patients with MMA during pregnancy. Depending on the severity of the underlying enzyme deficiency, a variety of protein restriction methods were employed starting as low as 40 g of natural protein per day up to 80 g. Patient 2a was maintained pre-pregnancy on protein restriction at 64 g per day, which was maintained during pregnancy This patient is *mut*$^{-}$ and clinically vitamin B12 unresponsive. Her metabolic course was significant for repeat hospitalizations from age 6 months to 7 years for metabolic crises but was unremarkable after that. Pregnancy 3a and 3b, who are the same patient, had protein intake during pregnancy of 76–80 g per day.

Patient 3b preconceptionally was prescribed 40 g of protein per day, which as pregnancy progressed was gradually increased to 80 g per day although actual intake based upon her recall was about 70 g per day. Her plasma amino acids were evaluated each trimester and the diet was adjusted based upon those data. Serum methymalonic acid concentrations ranged from 66.23 μmol/L in the serum in the first trimester to 210 μmol/L in the third trimester.

In addition to protein restriction, the use of supplements such as vitamin B12 and carnitine were continued throughout pregnancy. Patients who have been previously successfully managed with supraphysiological doses of vitamin B12 have been maintained on their dosage throughout pregnancy. Patient 3b was maintained on hydroxycobalamin 5 mg intramuscular every other day throughout pregnancy and during labor and delivery (Table 1).

Specific to the experience with patient 3b in labor and delivery during an episode of acute stress due to possible placental abruption and preeclampsia, recommendations were to administer L-carnitine at 50 mg per kg per dose intravenously every 6 for 24 h and then decrease the dosage to 25 mg per kg per dose every 6 h intravenously until stabilized. Throughout pregnancy, the patient was maintained on a dose of L-carnitine 1500 mg twice per day by mouth. Seven of the 13 pregnancies were supplemented with carnitine.

Table 2 Published and unpublished pregnancies with maternal methylmalonic acidemia, pregnancy outcomes

Patient	Enzymology/ complementation group	Metabolic imbalance in pregnancy	Gestational age at delivery	Obstetrical complications	Method of delivery	Indication for delivery method	Birth weight (%)	Outcome of child
1 (Diss 1995)	NR	None	Term	Hyperemesis in first trimester	Vaginal	N/A	3500 g (25 %)	At age 3 years, normal development
2a (This report)	*mut*$^-$	Hospitalization and IV fluids twice at 24 weeeks	38 weeks	Postpartum infection	Cesarean	Fetal distress	3288 g (50 %)	At age 10 years, normal development
3a (This report)	*cblA*	None	42 weeks	Preeclampsia	Cesarean	Fetal distress	3714 g (50 %)	At age 14 years, normal development
3b (This report)	*cblA*	None	32 weeks	Preeclampsia, PPROM, gestational diabetes, placental abruption, uterine scar	Cesarean	Fetal distress, repeat cesarean delivery	1459 g (10 %)	At age 3 years, normal development
4 (Wasser-stein 1999)	*cblA*	None	36 weeks 4 days	PPROM, preeclampsia	Vaginal	N/A	3220 g (75 %)	At age 1 year, normal development
5 (Deodato 2002)	NR	None	38 weeks	None	Cesarean	Scheduled, elective	2940 g (25 %)	At age 2 years, normal development
6 (Boneh 2002)	decreased propionate incorporation	None	36 weeks	None	Cesarean	Fetal distress	Not reported	Not reported
7 (Adeyemi 2004)	decreased propionate incorporation and methylmalonyl CoA mutase activity; reduced adenosyl-cobalamin synthesis	None	34 weeks	PPROM, chlamydia	Cesarean	Failure to progress	1900 g (10 %)	At age 5 months, normal development
8a (Langendonk 2011)	NR	2 episodes of hyperammonemia (49μmol/L)	38 weeks	None	Vagnial	N/A	2850 g (10–25 %)	At age 5 years, normal growth and development
9 (Langendonk 2011)	*mut*$^-$	None	35 weeks	Intrauterine growth restriction (IUGR)	Cesarean	IUGR	1530 g (<3 %)	At age 1 year, normal growth and development
10 (This report)	*mut*$^-$	None	39 weeks	None	Vaginal	N/A	3095 g (25 %)	At age 3 months, normal appearance
11 (Lubrano 2013)	*cblA*	None	37 weeks	None	Vaginal	N/A	2480 g (10 %)	At age 30 months, normal development
12 (Jacquemyn 2014)	*cblA*	None	40 weeks	None	Vaginal	N/A	3300 g (50 %)	Follow up reported as normal

Table 3 Pregnancy loss in first trimester patients with MMA

Patient	Enzymology	Timing of pregnancy loss
2b	*Mut* – B12 unresponsive	First trimester spontaneous miscarriage
8b (Langendonk)	Not performed	Miscarriage at 5 weeks gestational age
8c (Langendonk)	Not performed	Termination of pregnancy at 10 weeks gestational age
13	*Mut* –B12 unresponsive	First trimester spontaneous miscarriage

Gestational diabetes complicated one pregnancy in our cohort. She was managed less vigorously than gestational diabetic patients without MMA would be to avoid hypoglycemia and catabolism. The goals set for the patient were to maintain blood glucose levels at 120 mg/dl to prevent catabolism. Despite the laxity in glucoregulation, the birth weight at delivery was 10th centile.

The literature review revealed four of the nine (44.4 %) pregnancies resulted in a cesarean delivery as well as four of the nine (44.4 %) resulted in preterm deliveries. One case report noted the development of preeclampsia in a patient who was reported to have renal insufficiency (Wasserstein et al 1999). Additional cases from the National Institutes of Health demonstrated three of the four pregnancies resulted in cesarean deliveries all with emergent indications of fetal distress. Two of the four pregnancies were complicated by preeclampsia.

Combining our case series with that of the literature review, 38.5 % of the completed pregnancies resulted in preterm deliveries. A cesarean delivery rate of 53.8 % (7/13) was noted among the cohort, which is higher than the United States national average of 32.8 % (CDC 2014). Fetal distress or nonreassuring fetal status was the indication for more than half (4/7) of the cesarean deliveries, and another report documented persistently nonreactive fetal heart tracings with reassuring biophysical profiles (Wasserstein 1999). An additional indication for cesarean delivery in the setting of maternal MMA was intrauterine growth restriction (Langendonk et al 2011).

The postpartum courses for the patients were unremarkable. Patients were hospitalized for 2–10 days postpartum. All were maintained with dextrose containing intravenous fluids. Patients 2a, 3a, 3b, 10 were slowly introduced to protein postpartum as tolerated. To our knowledge, there have been no published reports of metabolic decompensation postpartum in a mother with MMA.

Fetal growth and development appear to be unaffected by maternal elevations of MMA (Wasserstein et al 1999). Increased MMA levels in amniotic fluid have been reported in patients undergoing invasive prenatal testing. Malformations or adverse outcomes in the babies were not reported although persistence of high concentrations of maternal metabolites was documented in one case report (Wasserstein et al 1999; Deodato et al 2002).

Discussion

As more patients with inborn errors of metabolism not only reach child bearing age but feel well enough to pursue pregnancy, the clinical challenges of counseling and management will continue to become more common. In MMA, the information used to manage patients during pregnancy has been derived from case reports and assumptions made from the experiences of other inborn errors of metabolism. Although in some inborn errors of metabolism, such as phenylketonuria, elevated levels of biochemical precursors are clearly teratogenic, the same information has not yet been established for MMA. It should be noted that one infant born to a mother with MMA had IUGR (Langendonk et al 2011) and that protein limitation during pregnancy might be associated with serious iatrogenic complications, given that a low protein intake is associated with poor fetal growth in mothers who have malnutrition (Godfrey et al 1995). In addition to risk to the developing fetus, proper counseling needs to include any potential complications impacting maternal health, such as pregnancy related complications including preeclampsia and gestational diabetes mellitus (GDM).

A variety of subtypes of MMA were identified including three cases with *cblA* (four pregnancies), four cases of *mut*- (one cobalamin responsive, three non-responsive), two historical cases confirmed with only enzymology, and three cases with an unknown type of MMA (two B12 responsive and one unresponsive). The cases span several decades and therefore include varying methods of management of MMA as well as changing methods of pregnancy management. Although limited in its numbers, this case series presents published experiences along with a number of new cases to create the most comprehensive description of MMA in pregnancy to date and helps to provide the foundation for improved understanding, management, and counseling of MMA patients desiring pregnancy.

When reviewing all the cases together, we observed some possible trends. Pregnancy complications such as late preterm birth, preterm premature rupture of membranes, cesarean delivery, nonreassuring fetal status, and preeclampsia all have been documented in this small cohort, while birth weight and development despite exposure to methylmalonic acid in utero appears to be tolerated without incidence in the offspring. In support of this concept, there have been no reports of birth defects or intellectual disability related to exposure to elevated

levels of methylmalonic acid in utero; in fact, 11 of the 13 children, ranging in age between 3 months to 14 years, born to mothers with MMA have reported normal developmental outcomes.

In the postpartum period, no episodes of decompensation have been reported, although in theory this period may present the window of highest risk for metabolic decompensation based upon experiences with urea cycle disorders (Walter 2000; Langendonk et al 2011). The postpartum period is a time of catabolism with the involution of the uterus and the breakdown of protein. In theory, the excess amino acids generated during this time can increase BCAA oxidative flux and increase nitrogen load, and could contribute to the precipitation of a metabolic crisis.

Pregnancy is an anabolic state, which for some patients with inborn errors of metabolism might make control of their disease slightly easier. Dietary needs of protein increase naturally as the pregnancy progresses and increased dietary intake of protein would need to be maintained postpartum if the patient were to breastfeed. Although all cases but one thus far have reported normal fetal growth despite protein restriction, the risk of protein malnutrition for the mother and the fetus necessitates careful metabolic management. It has been our recommendation to serially follow fetal growth with ultrasounds throughout the pregnancy, and to adjust maternal and fetal protein needs using maternal biochemical parameters.

Vitamin B12 responsive patients are treated with supraphysiological doses of cobalamin. Although vitamin B12 deficiency can be adequately treated in pregnancy without adverse consequences related to treatment, it is not known where the upper limit of vitamin B12 treatment in pregnancy lies, if such a ceiling exists, and whether cofactors in high doses could contribute to an adverse pregnancy outcome. Of the pregnancies, 7/13 were supplemented with carnitine. Patients ingested high doses of carnitine with the same caveats that very little is known about carnitine supplementation in pregnancy (Winter et al 1995). The effect of carnitine supplementation on birth parameters needs to be studied further.

Optimization of the maternal condition prior to pregnancy and close dietary management combined with regular surveillance of maternal serum amino acids is important to ensure maternal nutrition and minimize dietary risk of catabolism. Delivery plans should be discussed with the patient especially in light of the increased rate of late preterm birth and cesarean deliveries. In the intrapartum period, avoidance of catabolism with intravenous dextrose should be maintained in labor and delivery. The most prudent approach to a pregnancy complicated by a maternal inborn error of metabolism is via a multidisciplinary team that includes a biochemically trained geneticist, metabolic dietitian, and maternal-fetal medicine specialist working together with an obstetrician.

In the case of maternal phenylketonuria, a pregnancy registry has proven invaluable to collect patient experiences and use the aggregate data to adjust practice patterns (Vockley et al 2014; Koch et al 1993). The information presented here should be useful in the continued surveillance and counseling of future patients, and will help stimulate the formation of a dedicated registry to define the natural history of pregnancy in MMA and related disorders.

Compliance with ethics guideline

Conflict of interest None.

Human and animal rights and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (National Institutes of Health, National Human Genome Research Institute) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients included in the study.

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