Mitochondrial disease in pregnancy: a systematic review

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Summary: Mitochondrial diseases are heterogeneous in clinical presentation and genotype. The incidence of known pathogenic mitochondrial DNA mutations in the general population is 1 in 500. Little is known about the implications of pregnancy for women with mitochondrial disease. We undertook a systematic review of the literature on mitochondrial disease in pregnancy. Ten case reports were identified. The most common complications were threatened preterm labour (5 women) and preeclampsia (4 women). Two women experienced magnesium sulphate toxicity. Pregnancy had a varied effect on mitochondrial disease with some women being asymptomatic; others developing mild symptoms such as exercise intolerance or muscle weakness which resolved postnatally; and others developed more serious, persistent symptoms such as symptomatic Wolff–Parkinson–White syndrome, persistent paraesthesia and focal segmental glomerulosclerosis. Women with mitochondrial disease appear to be at increased risk of complications during pregnancy and labour but further prospective cohort studies are needed.

Keywords: mitochondrial disease, pregnancy complications

INTRODUCTION

Mitochondria generate energy in the form of adenosine triphosphate (ATP) by oxidative phosphorylation. Mitochondrial diseases, in which this process is impaired, can present at any age with phenotypically heterogeneous manifestations that are characterized by multisystem involvement.¹ A general feature is that tissues with the highest energy requirement are predominantly affected. Typical features include: deafness, diabetes, proximal myopathy, external ophthalmoplegia, visual loss, gastrointestinal dysmotility, cardiomyopathy, cardiac conduction defects, epilepsy and in rarer cases encephalopathy and stroke-like episodes.¹

Mitochondria have their own genome which is maternally inherited.¹ This small circular DNA molecule (mtDNA) encodes two rRNAs, 22 tRNAs and 13 of the ~90 proteins that make up the respiratory chain; however, the remaining respiratory chain proteins, along with mitochondrial DNA maintenance proteins, are nuclear encoded. Mitochondrial diseases can therefore show a variety of inheritance patterns. Point mutations in the mtDNA molecule (such as the m.3243A > G mutation) show maternal inheritance; large-scale mtDNA re-arrangements (for example single deletions) arise sporadically, and typically are not passed on. Multiple mtDNA deletions, which arise gradually as a result of mutations of nuclear-encoded mtDNA replication and repair enzymes, show either autosomal dominant or recessive inheritance. At-risk mothers may therefore not have an obvious family

history of mitochondrial disease, and similarly, the risk to their fetus depends to a large degree on the mode of inheritance of their disease.

The range of possible clinical presentations is very broad, and diagnosis may be difficult. This is as a result of the large number of mtDNA mutations that have been described to date,^{2–29} and also the range of syndromes arising as a result of a given mutation. For example, the m.3243A > G mutation may cause both the relatively mild MIDD (maternally inherited diabetes and deafness) syndrome,¹⁶ or the far more severe MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) syndrome.²⁴ Important syndromes of mitochondrial disease and their associated genetic mutations are summarized in Table 1. Unfortunately, many patients do not fall into any clearly defined syndrome, or have an as yet undescribed mutation; in these cases diagnosis depends on the recognition of typical symptoms with supporting evidence from mtDNA sequencing, histochemical investigation (e.g. ragged-red fibres seen in muscle biopsy specimens) and biochemistry (measurement of mitochondrial enzyme activities).¹

The prevalence of mitochondrial disease is difficult to estimate. The first genetic defects were identified in 1988, and it was initially thought that mitochondrial disease was relatively rare. However, the incidence of known pathogenic mtDNA mutations in the general population has recently been investigated. These studies have shown that approximately 1 in 500 individuals carry the m.3243A > G mutation, which can cause severe neurological disease, with a similar figure observed for the m.1555A > G mutation, which causes aminoglycoside-induced deafness.^{30–32} Another approach to study the incidence of mtDNA disease is to document the number of clinically affected cases within a specific geographic region. This approach is limited because there is marked clinical variability which means many patients go unrecognized and

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Table 1 Important syndromes of mitochondrial disease (adapted from McFarland and Turnbull¹)

Syndrome	Presentation	Usual Genotype
Leigh	Brainstem or basal ganglia dysfunction (respiratory abnormalities, nystagmus, ataxia, dystonia, hypotonia, optic atrophy), developmental delay	Variety of biochemical and molecular defects ²
Kearns–Sayre	Ophthalmoparesis and pigmentary retinopathy, cardiac defects, deafness, myopathy	Large-scale single deletion or complex rearrangements of mitochondrial DNA ¹¹
Mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS)	Encephalopathy, lactic acidosis and stroke-like episodes	m.3243A > G mutation in <i>MTTL1</i> gene (>80% of patients) ^{12,24,29}
Maternally inherited diabetes and deafness (MIDD)	Sensorineural deafness and diabetes	Mutations in <i>MTND1</i> ¹⁵ and <i>MTND5</i> genes ²⁵
Neuropathy, ataxia and retinitis pigmentosa (NARP)	Developmental delay, retinitis pigmentosa, dementia, seizures, ataxia, proximal neurogenic muscle weakness and sensory neuropathy	m.3243A > G mutation in <i>MTTL1</i> gene ¹⁶
Mitochondrial neuro-gastrointestinal encephalopathy	Progressive external ophthalmoparesis, ptosis, gastrointestinal dysmotility, diffuse leucoencephalopathy, peripheral neuropathy and myopathy	m.8993T > G or m.8993T > C ^{26,27}
Chronic progressive external ophthalmoplegia	Slowly progressive paresis of eye muscles, bilateral ptosis, mild proximal weakness, fatigue and cardiac conduction defects	Mutations in <i>ECGF1</i> ²³ and <i>POLG</i> ⁴³
		Single, large-scale mtDNA deletions ^{20,28}

because patients may not be referred to specialist centres. However, even these studies show there is a high disease burden with at least 1 in 10,000 of the adult population suffering from mtDNA disease.³³

At present, little is known about the risk of pregnancy complications for women with mitochondrial disease or how best to counsel them preconception. The physiological changes of pregnancy, with its increased respiratory demands, lead us to hypothesize that women who already have impaired mitochondrial function may be at risk of deterioration in symptoms and obstetric complications. However, just as mitochondrial diseases are heterogeneous it is likely women may be affected variably in pregnancy.

The aim of this review is to identify studies investigating the risks of pregnancy complications in women with mitochondrial disease, to summarize what is already known and identify future research opportunities.

METHODS

We searched Medline (1950 to present) to identify citations on pregnancy and mitochondrial respiratory chain disease (search terms: pregnancy, pregnancy complications, high-risk pregnancy, mitochondrial diseases, mitochondria, DNA mitochondrial) from inception until December 2010. The reference lists of all included primary research papers were examined to identify cited papers not identified by electronic searches and, when possible, papers citing them were identified electronically.

RESULTS

Ten case reports were identified. There were no published cohort studies. These reports were of women with a variety of mitochondrial disease phenotypes and genotypes (see Table 2). The women experienced different modes of delivery at a range of gestations: from 25 weeks to term. The most common complications were threatened preterm labour and preeclampsia (see Table 2). Two women experienced magnesium sulphate toxicity when given as tocolysis³⁴ or for

preeclampsia.³⁵ Some women experienced no complications in one or more of their pregnancies.^{36,37}

In these cases, pregnancy had a varied effect on mitochondrial disease with some women being asymptomatic.^{34,35,37} Other women developed mild symptoms that resolved postnatally such as exercise intolerance or muscle weakness^{37,38} and others developed more serious or persistent symptoms such as Wolff–Parkinson–White syndrome,³⁹ persistent paraesthesia⁴⁰ and focal segmental glomerulosclerosis.⁴¹ In some cases, symptoms led to obstetric intervention such as induction of labour⁴² or planned caesarean section.³⁹

DISCUSSION

Mitochondrial disease presents a challenge for obstetricians because little is known about the relationship between mitochondrial disease and pregnancy and the evidence base is limited to the case reports discussed in this paper. Case reports are limited in their validity and reliability by their small numbers and heterogeneous clinical situations. Nevertheless, this review has raised a number of important issues for clinicians.

Women with mitochondrial disease have varied clinical presentations and genetic defects making diagnosis challenging. Women with an established diagnosis of mitochondrial disease are likely to be referred to a high-risk obstetric or obstetric medicine clinic. However, some women may present for the first time with a complication during pregnancy such as the case reported by Lowik *et al.*⁴¹ It is therefore important that obstetricians are aware of mitochondrial disease and its varied presentations to facilitate diagnosis of a first presentation in pregnancy.

Women with mitochondrial disease are likely to experience a variable clinical course before, during and after pregnancy. The results of this review suggest that they may well be at increased risk of complications during pregnancy and labour such as preterm delivery and preeclampsia. With the exception of Folgero *et al.*, these studies did not report whether or not infants inherited mitochondrial disease. This will vary between mitochondrial diseases, but it would have been useful to know this, particularly when the genetic defect was unknown. More research is required to develop a better

Table 2 Summary of case reports included in this review

Author	Study design	Mitochondrial disease	Parity	Pregnancy complications	Pregnancy outcome	Effect of pregnancy on mitochondrial disease
Aggarwal <i>et al.</i> ⁴⁴	Case report	m.3243A > G MELAS mutation	POG1	Gestational diabetes	Spontaneous vaginal delivery of male infant 39/40 3875 g in good condition	Not specified
Berkowitz <i>et al.</i> ³⁸	Case report	Previous WPW syndrome type A (ablated), premature graying, tinnitus, deafness Mitochondrial myopathy diagnosed on muscle biopsy but affected enzyme pathway not identified. Presented prenatally aged 16 with exercise intolerance, lordosis and hearing loss Common single mtDNA deletion. Sporadic	POG1	Postpartum haemorrhage due to placenta accreta (4 unit transfusion) Preeclampsia in labour	Spontaneous vaginal delivery of male infant at term 2525 g	Mild exercise intolerance in pregnancy which resolved postpartum
Blake and Shaw ²⁶	Case report		POG1	None	Ventouse delivery at term (for slow progress in second stage of labour) of male infant 3850 g	Not specified
Dessole <i>et al.</i> ³⁷	Case report	No defect found biochemically. Diagnosed by ragged red fibres on quadriceps biopsy	P1G1	Uncomplicated first pregnancy	First pregnancy: spontaneous vaginal delivery at term	First pregnancy: none
Folgero <i>et al.</i> ⁴⁵	Case series	m.3243A > G	Not specified	Second pregnancy: postpartum haemorrhage (PPH) – atonic uterus requiring hysterectomy for disseminated intravascular coagulation Preeclampsia, Eclampsia Miscarriage Preterm birth Intrauterine death	Second pregnancy: admitted in spontaneous labour at 37/40 emergency caesarean section for failure to progress in first stage of labour. Severe PPH (see complications) Not specified	Second pregnancy: muscle weakness, exercise intolerance Not specified
Hosono <i>et al.</i> ³⁴	Case report	Late-onset diabetes mellitus and sensory deafness m.3243A > G	POG1	Pregnancy-induced hypertension Threatened preterm labour 23/40 treated with bed rest Adverse reaction to tocolytic ritodrine (nausea and palpitations) 32/40 Muscle damage after magnesium sulphate	Vaginal delivery of male infant 36/40 2714 g in good condition	None (CT brain, EEG, ECG, echo and EMG no change)
Kovilam <i>et al.</i> ⁴²	Case report	MELAS	P0-2-2-2 G5	Threatened preterm labour	Induction of labour 36/40. Vaginal delivery of infant 2100 g in good condition	Induction for unspecified worsening symptoms
Lowik <i>et al.</i> ⁴¹	Case report	m.3243A > G	Not specified	Recurrent UTIs Gestational diabetes Preeclampsia	Emergency caesarean section for fetal distress 27/40	Developed focal segmental glomerulosclerosis. Subsequently diagnosed with diabetes (poststeroids), asymptomatic hearing loss on audiogram and left ventricular hypertrophy
Moriarty <i>et al.</i> ³⁵	Case report	m.3243A > G MELAS mutation	POG1	Postpartum nephrotic syndrome Preeclampsia Prelabour rupture of membranes Magnesium toxicity	Emergency caesarean section for pathological CTG and meconium 4 cm Male infant 2900 g 38 ⁺⁵ /40	Asymptomatic

Rosaeg et al. ³⁹	Case report	Defect in complex III	POG1	First pregnancy: preterm labour	First pregnancy: female infant delivered vaginally at 25/40 died later from respiratory complications of prematurity Second pregnancy: emergency caesarean section for fetal distress 36/40. Live infant 2390 g requiring resuscitation at birth but discharged with no complications Third pregnancy: elective Caesarean section at 34 weeks. Live infant 2600 g in good condition	First pregnancy: female infant delivered vaginally at 25/40 died later from respiratory complications of prematurity Second pregnancy: emergency caesarean section for fetal distress 36/40. Live infant 2390 g requiring resuscitation at birth but discharged with no complications Third pregnancy: elective Caesarean section at 34 weeks. Live infant 2600 g in good condition	Symptomatic Wolff-Parkinson-White syndrome
Yanagawa et al. ⁴⁰	Case report	m.3271T>C (MELAS syndrome)	Not specified but implies POG1	Second pregnancy: threatened preterm labour 26/40 (treated with IV fluids and bedrest) Third pregnancy: threatened preterm labour 26/40 (treated with bed rest) Threatened preterm labour 27/40	Scheduled for eLSCS 38/40 due to WPW but presented in labour at 36/40. Metabolic acidosis during first stage of labour Threatened preterm labour 27/40	Spontaneous vaginal delivery of live male infant 38/40 3472 g	Asymptomatic until 17/40 when developed exercise intolerance and muscle cramps. By 27/40 had developed muscle weakness and paraesthesia of the extremities Symptoms improved postnatally but slight paraesthesia of lower limbs persisted

understanding and ideally quantify all these risks in order to counsel women preconception and to plan and deliver care during pregnancy and delivery. This can only be achieved by studying large cohorts of patients with mitochondrial disease, exploring their obstetric history and prospectively collecting data on future pregnancies.

Furthermore, women with mitochondrial disease may also not be suitable for routine obstetric care in the event of complications. For example, as magnesium may compete with calcium in mitochondria, interfering with oxidative phosphorylation³⁴ even at therapeutic levels,³⁵ women with mitochondrial disease appear to be at risk of toxicity if given magnesium sulphate for preeclampsia.

Mitochondrial medicine is a fast developing specialty¹ and, as mitochondrial disease already presents a number of challenges to obstetricians, it is likely that multidisciplinary care with colleagues from mitochondrial medicine, neurology and the other medical specialties is indicated. Links with fetal medicine are also important since offspring of affected women can be symptomatic early in life.

DECLARATIONS

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