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BRIEF REVIEW

Pregnancy in women with mitochondrial disease—A literature review and suggested guidance for preconception and pregnancy care

Lisa Hui[1,2,3,4], Pema Hayman[5], Ali Buckland[6], Michael C Fahey[7], David A Mackey[8], Andrew J Mallett[5,9,10], Daniel R Schweitzer[11,12,13], Clare P Stuart[14], Wai Yan Yau[6] and John Christodoulou[15]

[1]Department of Obstetrics, Gynaecology and Newborn Health, University of Melbourne, Melbourne, Victoria, Australia

[2]Reproductive Epidemiology Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia

[3]Department of Perinatal Medicine, Mercy Hospital for Women, Melbourne, Victoria, Australia

[4]Department of Obstetrics and Gynaecology, The Northern Hospital, Melbourne, Victoria, Australia

[5]College of Medicine and Dentistry, James Cook University, Cairns, Queensland, Australia

[6]Department of Neurology, Perron Institute for Neurological and Translational Science, Perth, Western Australia, Australia

[7]Department of Paediatrics, Monash University, Melbourne, Victoria, Australia

[8]Centre for Ophthalmology and Visual Science, Lions Eye Institute, University of Western Australia, Perth, Western Australia, Australia

[9]Department of Renal Medicine, Townsville University Hospital, Townsville, Queensland, Australia

[10]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia

[11]Department of Neurology, Mater Hospital, Brisbane, Queensland, Australia

[12]Wesley Hospital, Brisbane, Queensland, Australia

[13]Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia

[14]Mito Foundation, Sydney, New South Wales, Australia

[15]Brain and Mitochondrial Research Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia

Correspondence: Prof. Lisa Hui, Dept of Obstetrics, Gynaecology and Newborn Health, University of Melbourne, Dept of Perinatal Medicine, Mercy Hospital for Women, Level 4, 163 Studley Rd Heidelberg, Vic. 3084 Australia.
Email: lisa.hui@unimelb.edu.au

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Mitochondrial donation to reduce the risk of primary mitochondrial disease transmission from mother to child is now permitted under Australian law as part of a clinical trial. The energy demands of pregnancy have the potential to worsen mitochondrial disease symptoms and severity in affected women. We conducted a systematic literature review on mitochondrial disease in pregnancy; five cohort studies and 19 case reports were included. For many women with mitochondrial disease, pregnancy does not have a negative effect on health status. However, serious adverse outcomes may occur. We provide suggested guidelines for preconception counselling and antenatal care.

KEYWORDS

assisted reproductive techniques, genetics, mitochondrial disease, pregnancy, pregnancy complications

INTRODUCTION

Mitochondrial conditions encompass various genetic disorders characterised by cellular energy deficiency.[1] These conditions result from abnormalities in the mitochondrial apparatus, which is influenced by both nuclear and mitochondrial DNA. Consequently, both autosomal and maternal inheritance patterns can occur. Mitochondrial disorders can affect multiple organ systems and vary in severity, ranging from mild to potentially fatal, depending on the specific mutation, tissue distribution and burden.[2] Overall, about one in 5000 Australian livebirths will develop a severely disabling form of mitochondrial disease.[3]

There is no cure for mitochondrial disease, and treatments focus on managing symptoms and improving overall function. Given the limitations of existing reproductive options—such as gamete donation or prenatal diagnosis followed by termination of affected pregnancies—many individuals seek alternatives to prevent the transmission of mitochondrial disorders to their children.

One proposed method for mitigating this risk in those with maternal inheritance patterns is *in vitro* fertilisation with mitochondrial donation. After extensive community consultation, the Australian Parliament passed the Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021 in March 2022. This law permits research under a clinical trial to use mitochondrial donation as part of assisted reproduction.[4] Australia is only the second country after the United Kingdom to legislate for this practice.[5]

Australia is preparing to commence its first clinical trial of mitochondrial donation in the MitoHOPE study, funded by the Medical Research Future Fund (MRFF).[6] However, clinicians and people with mitochondrial disease should be aware of the health implications of pregnancy, birth and parenthood. Pregnancy is associated with increased energy demands that can potentially exacerbate mitochondrial disease. Previous studies have reported serious deterioration of maternal health during pregnancy in association with mitochondrial disease, including respiratory failure, severe metabolic dysfunction and heart failure, as well as a higher rate of pregnancy complications such as preterm birth, stillbirth, and pre-eclampsia.[7]

In anticipation of the planned clinical trial of mitochondrial donation, we conducted a literature review of the published data on pregnancy outcomes for individuals with a mitochondrial disease. Comprehensive UK guidance on mitochondrial disease during pregnancy was published in 2011 and last updated in 2013.[8] In this paper, we summarise the recent literature on mitochondrial disease in pregnancy, and offer suggested guidance for pre-pregnancy and antenatal care.

MATERIALS AND METHODS

We conducted a systematic search of the Ovid MEDLINE database on September 15, 2023. We used the MeSH search terms 'mitochondrial diseases' AND ['Pregnancy; High risk' OR 'Pregnancy complications']. The search was restricted to human studies written in English, published from 2000 to 2023. We included original research studies and case reports that reported maternal and perinatal outcomes in women with a pre-pregnancy diagnosis of any type of mitochondrial disorder. Reports of fetuses with a mitochondrial disease born to unaffected mothers were excluded.

This research was exempt from ethics approval as data were collected exclusively from published literature.

RESULTS

Our MEDLINE search yielded 90 articles: 65 were excluded on title and abstract screening, and 25 articles were reviewed in full text. After full text screening, 24 studies met our selection criteria, including 19 case reports and five retrospective cohort studies. The search was repeated on 12 February 2024, and no new relevant studies were identified. Due to the heterogeneous nature of the included articles, we performed a narrative summary of the included articles rather than a quantitative analysis.

Cohort studies

The five included cohort studies collected pregnancy outcomes retrospectively using patient-completed questionnaires (Table 1).[9–13] A total of 322 women with a mitochondrial disease participated in these patient surveys.

Impact of pregnancy on maternal mitochondrial disease

Most women with mitochondrial disease in the cohort studies tolerated pregnancy well, although it was associated with exacerbations of gastrointestinal, constitutional, and muscular symptoms. In one study, more than 30% of respondents reported new onset or worsening of gastrointestinal dysmotility, gastro-oesophageal reflux disease, fatigue, muscle pain, muscle cramps, nausea, headaches, weight problems, memory problems, anaemia, balance problems, weakness, exercise intolerance, nausea, vomiting, and constipation.[9] A Friedreich ataxia cohort had equal proportions of women reporting that pregnancy made their disease symptoms better, worse, and unchanged.[12]

Obstetric complication rates

Self-reported pregnancy-related complication rates varied widely among the cohort studies (Table 2). One study that performed a subgroup comparison demonstrated statistically higher rates of pre-eclampsia and preterm birth in the m.3243A > G mutation

TABLE 1 Included cohort studies of mitochondrial diseases in pregnancy

					Mitochondrial disease group		Control group	
First author, year	**Country**	**Recruitment method**	**Response rate**	**Mitochondrial diseases included**	**No. of women**	**No. pregnancies**	**No. of women**	**No. of pregnancies**
Feeney 2019[11]	United Kingdom	UK MRC mitochondrial disease cohort	Not reported	(i) m.3243A > G (n = 28) (ii)'Other' (n = 39)	67	149	69	139
Kuleva 2019[10]	France	Single tertiary centre	60%	(i) mtDNA group (n = 31, MELAS, NARP, mt deletion) (ii) nDNA group (n = 31) (POLG, DGUOK) (iii) Women with family history only (n = 13)†	75	287	62	117
Karaa 2019[9]	United States	MitoAction (patient advocacy group)	28%	(i) Mitochondrial myopathy (n = 35) (ii) 'Multiple complex deficiency' (n = 15) (iii) Other†: (n = 53)	103	370	N/A	N/A
De Laat 2015[13]	Netherlands	National inventory	71%	m.3243A > G	46	96	National reference	N/A
Friedman 2010[12]	United States	Single tertiary centre	Not reported	Friedreich ataxia	31	65	N/A	N/A

†Other named diagnoses included: chronic progressive external ophthalmoplegia, deoxyguanosine kinase; Leber hereditary optic neuropathy; mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; mitochondrial neurogastrointestinal encephalomyopathy; neuropathy ataxia retinitis pigmentosa; polymerase gamma; also included 'unsure, clinical or suspected diagnosis'. mtDNA, mitochondrial DNA; nDNA, nuclear DNA; UK MRC, United Kingdom Medical Research Council

group than the group with other mitochondrial diseases.[11] Most of the studies used live births as their denominator for obstetric complications, and stillbirth rates were not able to be pooled from these studies. Feeney noted four stillbirths among the 67 women with mitochondrial disease, but there were insufficient data on these pregnancies to include in their analysis.[11] De Laat et al reported four fetal deaths, two of which occurred in a triplet pregnancy.[13]

Case reports

The 19 case reports described outcomes of 21 pregnancies in women with a range of mitochondrial diseases (Table 3). Over half of the case reports described women whose pregnancies did not have a negative impact on maternal health or fetal outcome, but other reports noted the following serious adverse events.

- A 22-week antepartum stillbirth in a woman who was admitted for 25 days with severe metabolic derangements and neurological complications.[14]
- A 23-week stillbirth in a woman who was admitted to an intensive care unit with acute pulmonary oedema and severe ventricular dysfunction on a background of Wolff-Parkinson-White syndrome and ventricular hypertrophy.[15]
- A 25-week stillbirth following a prelabour preterm rupture of membranes and antepartum haemorrhage. Post-operatively the woman was diagnosed with a pulmonary embolism, provoked by prolonged immobilisation in pregnancy.[16]
- Severe immobility during pregnancy resulting in elective caesarean at 39 weeks gestation for severe pain, compromised ventilatory status and immobility.[17]
- Maternal status epilepticus at 14 weeks. Due to concerns regarding seizure control and high doses of anti-epileptic medications in pregnancy, the patient opted for an elective termination at 16 weeks gestation.[18]
- Deteriorating respiratory function requiring increases in non-invasive intermittent positive pressure ventilation to 20 and 24 h per day.[19,20]
- Prolonged hospitalisation due to severe myalgia, raised creatinine kinase, severe pain, compromised ventilatory status and immobility.[21]

TABLE 2 Rates of self-reported obstetric complications from included cohort studies

	Feeney		Kuleva	Karaa	De Laat	Friedman
Study population	**28 women with m.3243A > G**	**39 women with other mitochondrial diseases**	**31 women with mtDNA mutation**	**103 women with mitochondrial diseases**	**46 women with m.3243A > G**	**31 women with Friedreich ataxia**
Denominator for obstetric complication rate	62 live births	87 live births	59 live births	248 live births	96 pregnancies[†]	56 live births
Gestational diabetes	16%	3%	14%	7%	11%	2%
Hypertensive disorder of pregnancy	36%	13%	5%	7%	12%	6%
Preterm birth <37 weeks	53%	9%	14%	10%	23%	13%
Small for gestational age	No difference	No difference	22%	21%	13%	Not reported
Caesarean delivery	31%	18%	17%	32%	15%	22%
Postpartum haemorrhage	Not reported	Not reported	12%	3%	Not reported	Not reported

[†]Includes one triplet pregnancy and two twin pregnancies.

TABLE 3 Mitochondrial diseases described in case reports

Mitochondrial disease	First author
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) (m.3243A > G)	Heindryckx,[28] Sanchez,[15] Maurtua,[29] Moriarty,[4,30] Annaiah,[16] Chou,[31] Hosono,[24] Bell[14]
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Pappalardo[22]
POLG-related disorders (incl. SANDO)	Shi[18]
Glutaric aciduria type II deficiency/multiple acyl-coenzyme A dehydrogenase deficiency (MADD)[†]	Trakadis,[25] Williams[26]
Friedreich ataxia	Armstrong[32]
Thymidine kinase 2 deficiency (TK2d)	Yuan[19]
Kearns-Sayre syndrome (KSS)	Faris[23]
Very-long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD)[†]	Yamamoto[21]
Cytochrome C oxidase deficiency	Soccio[17]
Unspecified mitochondrial myopathy	Diaz-Lobato,[20] Dessole[33]

[†]Not primary mitochondrial disorders but cause secondary mitochondrial dysfunction.

However, disease exacerbation was not universal among the case reports. There was one report of drastic spontaneous improvement of gastrointestinal symptoms during pregnancy, which was attributed to placental production of the patient's deficient mitochondrial enzyme.[22]

Most case reports documented a return to pre-pregnancy baseline function almost immediately after delivery. The one exception was a woman with worsening fatigue and respiratory acidosis due to inadequate home non-invasive intermittent positive pressure ventilation use in the postnatal period as a consequence of the physical demands of early motherhood.[19]

The perinatal outcomes in these case reports included 17 live births, three stillbirths, and one termination of pregnancy. Four births were preterm: three due to spontaneous labour at 36 weeks, and one following induction of labour at 33 weeks for pre-eclampsia.[19,22–24] There were ten caesarean sections (CS), six vaginal deliveries and one with missing data. Most CS were for obstetric indications, but four women had CS due to maternal medical indications, including severe immobility, compromised respiratory status, metabolic decompensation, and cataplexy.[17,20,25,26]

DISCUSSION

The limited published literature on mitochondrial disease in pregnancy suggests that successful pregnancy outcomes, including vaginal birth of term infants, are possible for many women. Our results confirm that pregnancy has variable impacts on maternal health, with substantial symptom overlap with normal pregnancy, including fatigue and breathlessness. As expected, the degree of maternal compromise and tolerance of the physiological demands of pregnancy were related to pre-pregnancy function, especially of the respiratory, cardiac, and muscular systems.

The single study that compared women with the m.3243A > G mutation with women with a range of other mitochondrial diseases showed a higher rate of preterm birth, pre-eclampsia, and gestational diabetes. This suggests that these women are a higher risk group that warrants pre-eclampsia prophylaxis and early screening for gestational diabetes mellitus (GDM). It is also important to note that the rates of CS and GDM among women with mitochondrial disease were similar to, or even lower than, the national rates in our population (CS 38% and GDM 18% in 2021).[13] This lowers the generalisability of these findings.

Overall, the quality of the included studies was low — all the cohort studies were retrospective questionnaires, and hence subject to selection bias, small sample sizes, recall bias, confounding, and unknown accuracy as responses were not verified against medical records.

While the case studies cannot be used to determine complication rates, they are instructive in their detailed description of severe adverse outcomes, including respiratory failure, status epilepticus, severe immobility, lactic acidosis, and venous thromboembolism. Not all disease phentoypes were represented in the published literature, presumably due to their rarity (eg mitochondrially inherited tubulointerstitial kidney disease and other mitochondrial-associated kidney disorders). Women with mitochondrial disease planning pregnancy should ideally receive preconception medical assessment and counselling by a multidisciplinary team with genetics, obstetric medicine, mitochondrial disease, and maternal fetal medicine expertise (see Table 4 and Figure S1).

Pre-pregnancy counselling should include a discussion about the various reproductive options, especially where pregnancy is considered a significant risk to maternal health.[8] Friedman et al reported that about one in two women diagnosed with Friedreich ataxia before their first pregnancy were concerned or extremely concerned that their symptoms would worsen with pregnancy.[12] A similar proportion were concerned or extremely concerned that

TABLE 4 General principles of antenatal care of women with mitochondrial disease

	Recommended care
Pre-conception counselling	Review with specialists in mitochondrial disease and obstetric medicine for baseline medical, obstetric and psychosocial assessment (see Table S1 and Sue et al.[1]) Discuss the full range of options for having children: spontaneous conception +/− prenatal diagnosis +/− termination of affected pregnancies, gamete donation, and adoption Provide best practice in routine pre-pregnancy care, including reproductive carrier screening, weight and lifestyle optimisation, periconceptional vitamin supplementation, reducing risks of perinatal and vaccine-preventable infections[34]
Medication review	Discuss risks and benefits of current medication (esp. anti-epileptic medications,[35] antihypertensives). ACE inhibitors and angiotensin II inhibitors are contraindicated in pregnancy[36]
Folic acid	Recommend preconception and pregnancy high-dose folic acid supplementation for patients with diabetes[37] or on anti-epileptic medications[38]; other patients should have routine supplementation
Multidisciplinary antenatal care	Maternal fetal medicine, obstetric medicine, mitochondrial medicine, midwife, and general practitioner, with genetic counselling, cardiology, respiratory medicine, mental health, dietitians, and physiotherapists as needed
Management of nausea and vomiting of pregnancy (NVP)	All women should be asked about NVP at each visit and if present, severity should be assessed by PUQE-24 score, measurement of weight and hydration status. Due to the symptom overlap between mitochondrial disease and NVP, clinical assessment and care of women with severe NVP (PUQE-24 score ≥13) should involve the multidisciplinary team[39]
Gestational diabetes mellitus (GDM) screening	Perform early oral glucose tolerance testing at 20 weeks for women with mtDNA variants associated with diabetes (M.3243A > G, 14709 T > C); screen all women at 26–28 weeks as per usual care. Avoid metformin for treating GDM due to the risk of lactic acidosis[37]
Pre-eclampsia prophylaxis	150 mg aspirin nightly from 12 weeks for those with m.3243A > G or other risk factors[36]
Venous thromboembolism (VTE) prophylaxis	If prolonged immobility or other risk factors for VTE occur during pregnancy or in the postpartum period, consider physical +/− pharmacological thromboprophylaxis[40, 41]
Magnesium sulphate	If magnesium sulphate infusion is clinically indicated during pregnancy (eg for eclampsia or extreme preterm birth), vigilance for magnesium toxicity is advised[24,30]
Fetal growth surveillance	Growth scan at 28–30 and 32–34 weeks
Mode of birth	Mitochondrial disease is not a contraindication to vaginal delivery, and this should be considered the first option for delivery, monitoring maternal fatigue and hydration Caesarean section should be reserved for obstetric indications or when maternal complications of mitochondrial disease are severe
Anaesthesia	Caesarean should be performed using regional anaesthesia where possible. An anaesthetic plan should be discussed antenatally and clearly documented in the medical notes[42]
Breastfeeding	Breastfeeding should be supported in accordance with best practice with close monitoring for fatigue

Adapted from the Ref. [8].

they would have trouble caring for their baby, and about their own shortened life expectancy. These findings highlight the importance of addressing psychosocial support and reproductive options for these individuals and families.

One potential reproductive option may be participation in the mitoHOPE clinical trial of *in vitro* fertilisation with mitochondrial donation. This literature review did not find any studies reporting outcomes of assisted reproductive technology (ART) in women with mitochondrial disorders. Like pregnancy, ART may be associated with increased morbidity for some women with a mitochondrial disorder, depending on their disease severity and phenotype. The National Health and Medical Research Council (NHMRC) has provided an ethical framework on assisted reproduction for mitochondrial donation, including communication of clinical risks, and potential for unknown risks.[27] It states that the clinical team must provide participants with 'an appreciation of the risk of mortality, permanent disability or other serious morbidities that may result from ART procedures, and from medical complications in any resulting pregnancy, including those specific to mitochondrial disease.'

CONCLUSION

Maternal and perinatal outcomes for women with mitochondrial disease range from uncomplicated to devastating, mirroring the phenotypic variation in mitochondrial disorders. As with many medical disorders, disease severity and levels of daily functioning are significant factors informing pre-pregnancy and early pregnancy counselling. Antenatal care should be provided by a multidisciplinary team with appropriate expertise.

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AUTHOR CONTRIBUTIONS

Lisa Hui: Writing – original draft, supervision, conceptualisation, methodology. Pema Hayman: writing original draft, investigation. Ali M Buckland: conceptualisation, writing – reviewing and editing. Michael C Fahey: conceptualisation, writing – reviewing and editing. David A Mackey: conceptualisation, writing – reviewing and editing. Andrew J Mallett: conceptualisation, writing – reviewing and editing. A Daniel R Schweitzer: conceptualisation, writing – reviewing and editing. Clare P Stuart: conceptualisation, writing – reviewing and editing. John Christodoulou: conceptualisation, writing – reviewing and editing. Wan Yan Yau: conceptualisation, writing – reviewing and editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
Table S1. Suggested pre-pregnancy assessment for individuals with mitochondrial disorders.