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Introduction

This guideline has been developed with the following aim: to offer information on best practice for antenatal care for women with mitochondrial disease.

Mitochondria provide 90% of our energy and have their own DNA (mtDNA). They produce ATP through oxidative phosphorylation. Mutations in the mtDNA can lead to impairment in energy production. As mitochondria are found in every human cell this can lead to a wide variety of clinical manifestations including muscle weakness, fatigue, epilepsy, cardiac problems and diabetes mellitus. For further information about clinical presentation and diagnosis of mitochondrial disease a comprehensive review is ‘Batteries not included: diagnosis and management of mitochondrial disease’ (J Intern Med. 2009 Feb;265(2):210-28.) or please see www.mitochondrialncg.nhs.uk.

Approximately 1 in 4000 women are clinically affected or are at risk for development of a mitochondrial mutation (Annals of Neurology. 2008 Jan; 63(1): 35-39.); many of those affected are of childbearing age. However, there is currently little information available for these women, or the clinicians looking after them, regarding the relationship between mitochondrial disease and pregnancy. Mitochondrial dysfunction has previously been implicated as an aetiological factor in the development of pre-eclampsia, although this remains contentious. In patients with severe mitochondrial disease, the increased metabolic demand during pregnancy and particularly at the onset of labour may lead to serious maternal and fetal complications.

There are a number of issues associated with pregnancy in mitochondrial disease:

1. The increased energy requirement of pregnancy makes this a time when mitochondrial disease may present for the first time. Unfortunately this may go unrecognized by healthcare professionals unfamiliar with these disorders, who might reasonably consider some of the clinical features of mitochondrial disease, such as fatigue and diabetes mellitus, as accepted complications of pregnancy.
2. Mitochondrial diseases are heterogeneous with variable clinical presentations and women may be affected variably in pregnancy.

3. Women with mitochondrial disease appear to be at increased risk of complications during pregnancy and labour such as gestational diabetes, pre-eclampsia, and preterm delivery.

Mitochondrial diseases are being increasingly recognized and it is important that health care professionals caring for pregnant women are aware of these diseases. Pregnancy in mitochondrial disease also presents a challenge, as the evidence base is limited to case reports, which, due to small numbers, are limited in their validity and reliability. Affected women should therefore have input from both the mitochondrial clinical team and the obstetric team when planning pregnancy care and in the event of complications arising.

**Women-centred care**

This guideline has been developed to offer expert consensus advice on the management of pregnancy in women with mitochondrial disease. It aims to provide information for use by clinicians and pregnant women with mitochondrial disease in order to make the best decisions about appropriate management during pregnancy and delivery. The care of these patients and their treatment should take into account patients’ needs and preferences, following full discussion with the healthcare professionals involved.

In accordance with NICE guidance the views, beliefs and values of the woman, her spouse/partner and her family in relation to her care and that of her baby should be sought and respected at all times. Good communication between healthcare professionals and pregnant women and their families should be supported by the best available information tailored to their individual needs. Information and support should be readily available for women and their families. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English. This information should include where they will be seen and who will undertake their care.
All pregnant women should have the opportunity to make informed decisions about their care during pregnancy. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines –‘Reference guide to consent for examination or treatment’ (2001), available from www.dh.gov.uk. Healthcare professionals should also follow the code of practice accompanying the Mental Capacity Act (2005).

**Key Priorities for Implementation**

We recommend that all women with mitochondrial disease who become pregnant should have an early initial obstetric assessment and close monitoring throughout their pregnancy. All women should have access to multi-disciplinary care between obstetrics, mitochondrial medicine and other medical specialties as indicated. Links with fetal medicine are also important since offspring of affected women can be symptomatic early in life and follow up of children may be important.

It is important that obstetricians are made aware of mitochondrial disease and its various presentations in pregnancy.

This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors such as patient preference and pragmatism.
1. Prenatal information

1.1. We recommend that women with a proven or suspected genetic defect (nuclear or mitochondrial) causing mitochondrial disease who are considering pregnancy are seen in a specialist mitochondrial disease clinic for pre-conception counselling to discuss the implications of the pregnancy for the mother and the fetus.

1.2. We recommend that women at risk of having inherited mitochondrial or nuclear mutations associated with mitochondrial disease are also seen in a specialist mitochondrial clinic. Due to the heteroplasmy seen in mtDNA mutations there may not be a clear maternal history of clinical disease and risk should be based on assessment of the pedigree. In autosomal recessive conditions such as mutations within the nuclear POLG1 gene, population frequencies are documented in the region of 1:100 and as such potential carriers may opt for genetic screening for themselves and their partners (see Genetic Counseling Guidelines).

1.3. The potential risks and benefits of current medications during pregnancy need to be considered and discussed prior to conception where possible. This is particularly relevant to the anti epileptic drugs (AEDs). This is best counselled by a specialist with knowledge of the underlying genetic cause and clinical phenotype. High dose (5mg/day) folate supplements are recommended in all patients taking AEDs during pregnancy.

1.4. Further guidelines on prenatal diagnosis and discussion are currently being developed. These will include a discussion of the reproductive and antenatal testing options available.
2. Antenatal care: Standard management for all pregnant women with mitochondrial disease

2.1. Who provides care?
2.1.1. Antenatal care for women with mitochondrial disease should be shared between an obstetrician, midwife- and GP-led models of care.
2.1.2. Patients with a potential new diagnosis of mitochondrial disease during pregnancy, based on family history or characteristic clinical features, should be referred to a specialist mitochondrial disease clinic. We recommend early discussion with a specialist so that appropriate counselling and management can be initiated.
2.1.3. Patients with an established diagnosis of mitochondrial disease should be referred to a high-risk obstetric clinic even if they are currently asymptomatic. We recommend that there is contact with mitochondrial specialist services if the patient is not currently under their care. Full documentation of the mitochondrial disease should be available for all clinicians looking after these patients.

2.2. Standard nutritional and lifestyle advice in accordance with the NICE guidance for antenatal care: routine care for the healthy pregnant woman.
   - Food hygiene
   - Smoking cessation, alcohol and recreational drug use advice
   - Antenatal screening.
2.3. Management of common symptoms in pregnancy

Management of nausea, heartburn, constipation, haemorrhoids, backache, and varicose veins should be in accordance with NICE guideline for pregnancy in healthy pregnant women.

2.4. Maternal nutrition during pregnancy.

Women should be encouraged to eat a healthy and balanced diet throughout their pregnancy. There is no evidence that an increased calorific input will compensate for the deficit in cellular energy as a result of the underlying disease. Women may benefit from a referral to a dietician. Weight loss should not be recommended during pregnancy.

2.5. Supplements

2.5.1. Coenzyme Q10 (ubiquinone) is a vitamin that works within the mitochondria. Although this supplement appears safe with no significant side effects, the safety of taking this supplement during pregnancy and breastfeeding is unknown and should therefore only be used with caution.

2.5.2. Folic acid supplementation has been proven to be safe in pregnancy and to significantly reduce the risk of occurrence of neural tube defects. There is no evidence of detrimental effect in mitochondrial disease and in fact folic acid may be of benefit to mitochondrial function. There is no evidence for or against higher dose (5mg/day) supplementation in mitochondrial disease so we adopt the recommendations of the NICE guidelines (CG62), reserving high dose supplementation for those patients taking AEDs.
3. **Guidance for antenatal screening in pregnant women with mitochondrial disease.**

3.1. Gestational Diabetes

Routine screening for gestational diabetes is recommended, regardless of other risk factors, as mitochondrial disease appears to be an independent risk factor for developing this condition. Increasingly metformin is being used in gestational diabetes however in patients with mitochondrial disease we advise the use of insulin therapy.

3.2. Anaemia

NICE guidance recommends offering screening early in pregnancy and at 28 weeks in normal healthy pregnancy. There is no evidence of an increase in anaemia in patients with mitochondrial disease. We recommend that usual screening is sufficient in patients with mitochondrial disease.

3.3. Hypertension and Pre-eclampsia

3.3.1. Preliminary studies suggests women with mitochondrial disease are at increased risk of pre-eclampsia.

3.3.2. Women with mitochondrial disease should be informed of this increased risk and made aware of the symptoms. They should seek immediate advice from a healthcare professional if they develop any of these symptoms.

3.3.3. Blood pressure measurements and urinalysis for protein should be carried out at each antenatal visit. We recommend a primip schedule of care as per the NICE Antenatal Care Guideline with visits at booking, 16/40, 25/40, 28/40, 31/40, 34/40, 36/40, 38/40, 40/40, 41/40 weeks gestation.
Hypertension and/or proteinuria may pre-exist in some patients with mitochondrial disease and prenatal measurements may be helpful for comparison.

3.3.4. In patients with chronic hypertension who are taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) they should be informed that these drugs are contra-indicated in pregnancy. Alternative antihypertensive treatment should be discussed with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

3.3.5. Aspirin is recommended for women at high risk of pre-eclampsia from 12 weeks until delivery (NICE Hypertension in pregnancy guideline CG 107). There is no evidence to support the use of aspirin in women with mitochondrial disease alone (and without additional risk factors), but if there is a history of previous pre-eclampsia then we recommend the use of aspirin in subsequent pregnancies.

3.4. Fetal growth and well-being

There is currently insufficient evidence as to whether these women’s babies are at increased risk of fetal growth restriction; however we would recommend all women with mitochondrial disease have growth scans at 28-30 weeks and 32-34 weeks. Involvement of fetal medicine specialists should be considered.
4. Advice regarding specific complications of mitochondrial disease in pregnancy

4.1. Myopathy

Patients experience a variable clinical course during pregnancy ranging from a negligible difference in their exercise tolerance to the development of severe fatigue. There is no evidence to suggest that pregnancy has a deleterious effect on overall clinical course, and pregnancy is usually well tolerated. Severe myopathy may affect the preferred route of delivery (see ‘Delivery’ below).

4.2. Respiratory

Respiratory function should be checked routinely in patients with mitochondrial disease (see Respiratory Guidelines at www.mitochondrialncg.nhs.uk) and significant respiratory impairment should be monitored throughout pregnancy. In most cases this does not significantly affect the pregnancy. In severe cases or where respiratory failure has been documented, diaphragmatic splinting by the gravid uterus may lead to deterioration in respiratory function, possibly requiring intervention. Discussion with a respiratory specialist is recommended. Where severe respiratory dysfunction is known it is preferable to counsel the patient prior to conception.
4.3. Mitochondrial cardiomyopathy

4.3.1. Patients with mitochondrial disease may have cardiac disease including disturbances of cardiac rhythm and cardiac hypertrophy (Refer to Mitochondrial Cardiac Guidelines at www.mitochondrialncg.nhs.uk). Please refer to European Society of Cardiology guidelines for management of cardiovascular disease during pregnancy (European Heart Journal (2003) 24, 761–781). There is currently no evidence in patients with mitochondrial disease to suggest a need to deviate from this guidance.

4.3.2. Most women with cardiac disease have successful pregnancies, yet experience of the management of these patients is limited, particularly with regard to patients with cardiac involvement in mitochondrial disease. All patients with known or suspected cardiac disease should therefore be referred for assessment to a specialist centre, ideally prior to consideration of pregnancy.

4.3.3. Women with other hypertrophic cardiomyopathies usually tolerate pregnancy and limited evidence suggests that patients with mitochondrial disease and cardiomyopathy is similar. Beta-adrenergic receptor antagonists should be continued in pregnancy to lower the risk of symptomatic tachycardias, particularly in patients with diastolic dysfunction.

4.3.4. In other forms of pre-existing dilated cardiomyopathy the risk of significant deterioration in left ventricular systolic function during pregnancy is high. Limited data is available for cardiomyopathy due to mitochondrial disease, but the risks are likely to be similar. The risk of peripartum cardiomyopathy is known to be increased in women with a family history of dilated
cardiomyopathy. Where this is known to be due to mutations in the mtDNA, knowledge of the mutation and heteroplasmy levels may help quantify the approximate risk in an individual. Advice from specialized mitochondrial centres should be sought.

4.3.5. Symptomatic arrhythmias occur during pregnancy and management should be as conservative as possible, reserving definitive treatment for the post-partum period if it is safe to do so. Beta-adrenergic receptor antagonists are safe for use in pregnancy. If a class 3 drug is needed, then amiodarone is the agent of choice. Definitive treatment with radio-frequency catheter ablation and device implantation can be performed during pregnancy, although this is not straightforward due to issues around the use of fluoroscopy.

4.3.6. ACE inhibitors and angiotensin II receptor antagonists are contraindicated during pregnancy. Specialist advice should be sought regarding the use of all pharmacological treatments for cardiomyopathy in pregnancy.

4.4. Diabetes

Mitochondrial disease increases the risk of gestational diabetes. Gestational diabetes or pre-existing diabetes is treated according to clinical need and does not differ from the care offered to patients without mitochondrial disease.

4.5. Migraine

Migraine may vary in pregnancy. There is no evidence to suggest that this is any different in patients with mitochondrial disease. Medication should be kept to a minimum where possible, particularly in the first trimester.
4.6. Epilepsy

4.6.1. Seizure frequency

Certain mitochondrial diseases are associated with epilepsy. Epileptic control can vary during pregnancy and there is no evidence to suggest that this is any different in patients with mitochondrial disease.

4.6.2. Anti-epileptic drugs (AEDs)

Several of the anti epileptic drugs may increase the risk of developmental abnormalities in the fetus. Women taking AEDs should be offered a discussion with an experienced clinician about the best course of management for their epilepsy during pregnancy. Please see NICE guideline CG20 with regard to advice for epilepsy management in pregnancy. In patients at risk of stroke-like episodes associated with seizures (eg MELAS) there may be a greater onus on maintaining adequate control of seizures.

4.7. Pre-eclampsia

4.7.1. Health care professionals should be alert as to the increased risk of pre-eclampsia in mitochondrial disease.

4.7.2 Magnesium sulphate infusion is typically used to prevent progression to eclampsia. This also applies to patients with mitochondrial disease. It should be noted that magnesium toxicity at therapeutic laboratory levels has been reported in a patient with the m.3243A>G MELAS mutation (J Obstet Gynaecol. 2008 Apr;28(3):349), although this is an isolated report. If magnesium is administered to patients with mitochondrial disease and pre-eclampsia, clinical examination for magnesium toxicity is essential regardless of documented laboratory levels.
4.8. Delivery

4.8.1. Women with mitochondrial disease may be at increased risk of pre-term delivery

4.8.2. Vaginal delivery

Mitochondrial disease is not a contraindication to vaginal delivery and this should be considered the first option for delivery. Caesarean section should be reserved for obstetric indications or when it is agreed that the maternal complications of mitochondrial disease preclude vaginal delivery.

4.8.3. Caesarean delivery

Where possible, Caesarean should be performed using spinal anaesthesia. If a general anaesthetic is necessary there is no evidence against the use of propofol as an induction agent in patients with mitochondrial disease, however a continuous infusion should be avoided. An alternative induction agent such as thiopentone can be considered if it is available. Women at high risk of complications should be discussed with the anaesthetic team antenatally in order that a plan is clearly documented in the medical notes and hand-held maternity records.

4.8.4. Breast feeding recommendations

Breast feeding should be encouraged in accordance with NICE guidance. Fatigue may limit breast feeding in more severely affected patients. Certain medications (e.g. some anti-epileptic drugs) may be expressed in breast milk and this should be considered in the decision-making process.
4.8.5. Post-natal contraception

There are no contraindications to standard forms of contraception and advice should be tailored to the individual needs of the patient.
5. Research recommendations

5.1. A retrospective study of the obstetric history of women with mitochondrial disease.

An initial, as yet unpublished, study has compared risk of obstetric complications in patients with m.3243A>G MELAS mitochondrial DNA mutation and single deletions. This will need to be extended to examine the risk in women with different mitochondrial disorders and to determine whether the level of mutation and severity of mitochondrial disease is associated with an increased risk in complications in pregnancy.

5.2. A prospective study of pregnancy in women with mitochondrial disease

It is recommended that a database is formulated to look at pregnancy and the complications in pregnancy for patients with mitochondrial disease.

5.3. A study of the effects of maternal mitochondrial disease on the fetus in utero and in the immediate postnatal period.

This should examine whether risks are due to complications of pregnancy in an affected mother or due to the underlying disease in the fetus.

5.4. A comparison of placental mitochondrial function in patients with mitochondrial disease compared to controls.

Mitochondrial dysfunction has been implicated in the development of pre-eclampsia although this remains controversial. By examining mitochondrial
function in placental tissue from women with and without pre-eclampsia, in mitochondrial and non-mitochondrial cohorts, we may provide further insight into the underlying aetiology of pre-eclampsia.

6. Updating the guideline

The Newcastle Mitochondrial Guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence every 2 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may update the guidance prior to any scheduled changes.
Appendix A: The Guideline Development Group

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