International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Sukayogula M et al. Int J Reprod Contracept Obstet Gynecol. 2025 Jan;14(1):258-261
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20243964

Case Report

Mitochondrial disorders-challenges in pregnancy: a case report

Malini Sukayogula*, Tarakeswari Surapaneni

Department of Obstetric Medicine, Fernandez Hospital, Hyderabad, Telangana, India

Received: 01 November 2024
Accepted: 03 December 2024

***Correspondence:**
Dr. Malini Sukayogula,
E-mail: drmalinisukayogula@gmail.com

ABSTRACT

Mitochondrial disorders (MD) encompass a diverse group of genetic disorders affecting the intra-cellular energy-producing organelles. During pregnancy, these disorders present unique challenges that warrant special attention. Here, we report a case of a 28-year-old woman who presented with ptosis since, 11 years of age. Muscle biopsy revealed mitochondrial cytopathy, but genetic evaluation was not done. She presented to us in early pregnancy. Whole Mitochondrial genome sequencing showed no pathological / likely pathological variant. Whole Exome sequencing revealed a Homozygous missense variant in exon 6 of RRM2B gene (c.629 A>G;p.lys 210 Arg) associated with Mitochondrial DNA depletion syndrome 8A and 8B, which has an autosomal recessive pattern of inheritance. The review of literature discusses the implications of MD on pregnancy outcomes and explores the management strategies to optimize maternal and fetal outcomes.

Keywords: Mitochondrial, Myopathy, Pregnancy, Mitochondrial disorders, Mitochondrial DNA depletion syndromes

INTRODUCTION

Mitochondria are the cellular organelles responsible for generation of energy in the form of adenosine tri phosphate through oxidative phosphorylation. Alterations in the Mitochondrial Ribonucleic Acid translation, or defects in respiratory chain proteins and ancillary proteins, mutations that affect the Mitochondrial inner membrane lipid milieu or the Mitochondrial dynamics can result in MD. Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are a group of disorders caused by defects in mtDNA maintenance due to mutations in the nuclear genes. Depletion of mtDNA leads to impaired energy production in affected tissues and organs.[1,2]

CASE REPORT

We report a case of mitochondrial DNA depletion syndrome, who presented in pregnancy. A 26-year-old Primi, first born to third-degree consanguineous couple, who had a history of ptosis since 11 years of age. Ptosis was partial and gradual in onset and progressed till 15 years of age- static since then. Muscle biopsy done in 2011 was suggestive of mitochondrial cytopathy, the report itself was not available with the woman. She was non-compliant to the prescribed antioxidant medications. She did not have other symptoms of MD. She is in a non-consanguineous marriage and booked at 8 weeks. Her height was 152 cm and weight at booking was 42 kg (BMI 18.2). She had mild hypotonia of all limbs. Partial ptosis of both eyelids, central fixed gaze and normal sensory and motor functions were noted. Whole Mitochondrial genome sequencing showed no pathological/likely pathological variant. Whole Exome sequencing revealed a Homozygous missense variant in exon 6 of RRM2B gene (c.629 A>G;p.lys 210 Arg) associated with Mitochondrial DNA depletion syndrome 8A and 8B, which has an autosomal recessive pattern of inheritance. This is associated with progressive external ophthalmoplegia with mitochondrial DNA deletions. Husband tested negative for the mutation, hence prenatal testing for the fetus was not suggested. Family screening revealed the same mutation in RRM2B gene in heterozygous state in both her parents and her sibling. Hearing evaluation and electroneuromyography (ENMG) were not done during the pregnancy.

Trimester screening was low risk for aneuploidy and screen negative for preeclampsia. Screening for diabetes was done at 16 weeks and then at 26 weeks-which were both normal. She was under the care of a multidisciplinary team including physician, maternal and fetal medicine specialist and a plan was put in place for the management in pregnancy. She was reviewed by the anaesthesia and critical care team at 32 weeks and at 36 weeks. She developed gestational hypertension at 36 weeks and was started on Labetalol. Labour was induced at 37 weeks. She received epidural analgesia during labour delivering a baby boy, by vacuum assisted vaginal birth. The baby had good APGAR score with a birthweight of 3.1 kg. She was discharged on second postnatal day. Follow up at 6 weeks postpartum, she is doing well.

Table 1: Antenatal screening.

Antenatal screening		
Gestational diabetes (GDM)	High risk phenotypes and those at risk for GDM should be screened with oral glucose tolerance test (OGTT) at 16-20 weeks and if normal, test to be repeated at 24-28 weeks.[9,15]	Insulin therapy is recommended over Metformin for management of GDM /DM in women with MD due to the risk of worsening or precipitating lactic acidosis.[9]
Hypertension and preeclampsia	Women with MD are at increased risk for hypertension and preeclampsia. Regular blood pressure (BP) monitoring to be suggested.	Routine use of aspirin for prevention of preeclampsia is not recommended.[19] Magnesium sulphate for seizure prophylaxis was associated with toxicity at therapeutic levels in two case reports, hence, close monitoring for magnesium toxicity is essential regardless of the serum levels.[16,17]
Anaemia	MD does not confer an increased risk for anaemia in pregnancy.	
Fetal growth	No evidence to say that women with MD are at increased risk for fetal growth restriction.	It is a good practice to monitor fetal growth from 28 weeks.[9]

Table 2: Specific complications of MD in pregnancy.

Complications		
Myopathy	Pregnancy is usually well tolerated. Splinting effect of the gravid uterus on the diaphragm may lead to deterioration of her condition. Severe myopathy may affect the route of delivery.[9]	Respiratory function should be checked in all women with MD.[9,18]
Cardiomyopathy	May manifest as conduction abnormalities or cardiomyopathy.[19]	12 lead ECG and 2D Echo Complications managed as per standard guidelines.

DISCUSSION

The true prevalence of mtDNA disease is difficult to estimate. The prevalence of mitochondrial disease in a population over 14 years of age was 5.7 per 100,000 and minimal birth prevalence of primary mitochondrial disorders was 6.2 per 100,000 births. The m.3243A>G mutation in the MT-TL1 gene is the most common mutation identified.[3-5] The disorders due to mitochondrial DNA defects were more common than those due to nuclear DNA defects.[6] MD can manifest with a varied range of clinical phenotypes. Tissues with high energy requirements such as brain(encephalopathy), heart(cardiomyopathy), skeletal muscle (mitochondrial myopathy) are preferentially affected. It can be an isolated or a multisystem involvement. Many affected individuals are of childbearing age and hence the clinicians should be aware of the implications in pregnancy. MD show a variety of patterns of inheritance based on the mutations involved. Point mutations in the mtDNA (m.3243A >G mutation) show maternal inheritance. Large mtDNA re-arrangements (single deletions) arise sporadically, and are not passed on. Multiple mtDNA deletions, which arise as a result of mutations of nuclear-encoded mtDNA replication and repair enzymes, show either autosomal dominant or recessive inheritance. Thus, the risk to the fetus depends on the mode of inheritance of the disease in the mother.[7,8]

Due to the increased energy requirement, mitochondrial disease may present for the first time during pregnancy. Diagnosing MD in pregnancy is challenging as some of the symptoms such as fatigue and conditions like diabetes mellitus tend to overlap.[9,10] Some of the symptoms like headaches, muscle cramps and gastrointestinal dysmotility of MD are exacerbated in pregnancy.[10] Management of

MD in pregnancy is a challenge as the evidence is based on case reports and few retrospective case series. A retrospective survey of 103 women with MD showed increased incidence of miscarriages as compared to general population (29.2% vs 8.2%). A higher incidence of preeclampsia and gestational diabetes (GDM) (5.2% and 6.8%) compared to national data was noted. There was no increased incidence of life-threatening complications.[10] Pregnancies in women with m.3243A>G mutation had significantly increased risk of GDM, breathing difficulties, hypertension, preterm birth, low birth weight babies and operative deliveries compared to women with other mutations or women without MD.[11,12]

Preconception care

Where a genetic diagnosis is not available, it is recommended to identify the mutation so that the risk to the fetus can be defined. Partner screening and screening of other family members needs to be addressed. Current medications must be reviewed. Shared decision-making involving the patient, family and the health care team is essential.

Antenatal care

Women with MD should be under multidisciplinary team care involving mitochondrial disease specialist, maternal and fetal medicine specialist. Standard nutritional and lifestyle advice is given. There is no evidence to support an increased calorific input to compensate for the deficit in cellular energy.[9] Routine medications used in antenatal period are safe including corticosteroids for fetal lung maturity.[13] A plan for labour analgesia and delivery should be discussed by anaesthesia team. Drugs that can potentially be toxic to mitochondria like chloramphenicol, aminoglycosides, linezolid, valproic acid, and nucleoside reverse transcriptase inhibitors and volatile aesthetics to be used with caution. Prolonged propofol use (>30-60 minutes) to be avoided.[14] Specific care is discussed in Tables 1 and 2.

Delivery

MD is not a contraindication for vaginal birth. Cesarean section should be done for obstetric indications with preference to regional anaesthesia. Adequate hydration, pain relief and calorific intake are important to prevent a catabolic state. Active management of the third stage of labour is recommended. Postnatally, gastrointestinal dysmotility and pseudo-ileus should be promptly recognised and addressed.[8] Breastfeeding is encouraged.[9] Neonate should also be screened when indicated.

Contraception

There are no contraindications to standard forms of contraception. Advice should be tailored to individual needs.

CONCLUSION

Pregnancies with MD pose unique challenges to obstetricians. Comprehensive prenatal care, accurate diagnosis and multidisciplinary management are the key to optimizing outcomes. Mitochondrial medicine is a fast-developing specialty. Future research will help refine understanding and the approach to this complex disorder.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Anisha Gala Shah and Dr. Usha Ravishankar for their assistance and guidance in the final version of the manuscript.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Spinazzola A, Invernizzi F, Carrara F, Lamantea E, Donati A, Dirocco M, et al. Clinical and molecular features of mitochondrial DNA depletion syndromes. J Inherit Metab Dis. 2009;32(2):143–58.
2. El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013;10(2):186-98.
3. Arpa J, Cruz-Martínez A, Campos Y, Gutiérrez-Molina M, García-Rio F, Pérez-Conde C, et al. Prevalence and progression of mitochondrial diseases: A study of 50 patients: Study of Mitochondrial Diseases. Muscle Nerve. 2003;28(6):690–5.
4. Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain J Neurol. 2003;126(8):1905–12.
5. Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol. 2015;77(5):753–9.
6. Barca E, Long Y, Cooley V, Schoenaker R, Emmanuele V, DiMauro S, et al. Mitochondrial diseases in North America. Neurol Genet. 2020;6(2):402.
7. Say RE, Whittaker RG, Turnbull HE, McFarland R, Taylor RW, Turnbull DM. Mitochondrial disease in pregnancy: a systematic review. Obstet Med. 2011;4(3):90–4.
8. Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nat Rev Genet. 2005;6(5):389–402.
9. Pfeffer G, Blakely EL, Alston CL, Hassani A, Boggild M, Horvath R, et al. Adult-onset spinocerebellar ataxia syndromes due to MTATP6 mutations. J Neurol, Neurosurg Psych. 2012;83(9):883-6.

10. Karaa A, Elsharkawi I, Clapp MA, Balcells C. Effects of mitochondrial disease/dysfunction on pregnancy: A retrospective study. Mitochondrion. 2019;46:214–20.
11. Feeney C, Lim A, Fagan E, Blain A, Bright A, Maddison J, et al. A case-comparison study of pregnant women with mitochondrial disease – what to expect? BJOG Int J Obstet Gynaecol. 2019;126(11):1380–9.
12. De Laat P, Fleuren LHJ, Bekker MN, Smeitink JAM, Janssen MCH. Obstetric complications in carriers of the m.3243A>G mutation, a retrospective cohort study on maternal and fetal outcome. Mitochondrion. 2015;25:98–103.
13. De Vries MC, Brown DA, Allen ME, Bindoff L, Gorman GS, Karaa A, et al. Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus. J Inherit Metab Dis. 2020;43(4):800–18.
14. Goldstein A, Falk MJ. Single Large-Scale Mitochondrial DNA Deletion Syndromes. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, et al editors. GeneReviews®. Seattle (WA): University of Washington. 1993. Available at: http://www.ncbi.nlm.nih.gov. Accessed on 21 August 2024.
15. Overview. Diabetes in pregnancy: management from preconception to the postnatal period. Guidance. NICE. 2015. Available at: www.nice.org.uk/guidance. Accessed on 23 August 2024.
16. Moriarty KT, Mcfarland R, Whittaker R, Burch J, Turnbull HE, Taylor RW, et al. Pre-eclampsia and magnesium toxicity with therapeutic plasma level in a woman with m.3243A>G melas mutation. J Obstet Gynaecol. 2008;28(3):349.
17. Nakamura E, Ushijima J, Samejima K, Akashi K, Hotta D, Kadowaki K, et al. Pregnancy with mitochondrial disease complicated by threatened preterm labor and preeclampsia. Hypertens Res Pregnancy. 2016;4(1):38–41.
18. Newcastle mitochondrial disease guidelines anaesthesia & peri-operative care in adult patients: Screening and Subsequent Management. Available at: www.mitochondrialncg.nhs.uk. Accessed on 22 August 2024.
19. Newcastle mitochondrial disease guidelines cardiac involvement in adult mitochondrial disease: screening and initial management. Available at: www.mitochondrialncg.nhs.uk. Accessed on 25 August 2024.

Cite this article as: Sukayogula M, Surapaneni T. Mitochondrial disorders-challenges in pregnancy: a case report. Int J Reprod Contracept Obstet Gynecol 2025;14:258-61.