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Original research

Obstetric history of women with m.3243A>G: an observational cohort study

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Received 27 April 2025
Accepted 7 December 2025

ABSTRACT

Background Mitochondrial diseases are genetic disorders arising from pathogenic variants in nuclear or mitochondrial DNA (mtDNA) characterised by respiratory chain dysfunction. Clinical manifestations are diverse, and treatment is mostly symptomatic. Mitochondria are maternally inherited, but new reproductive technologies may prevent the transmission of pathogenic mtDNA. We decided to investigate the pregnancies of women with the m.3243A>G mtDNA variant.

Methods 16 women with m.3243A>G were included in this retrospective, observational cohort study. Medical records were screened for pregnancies managed at Oulu University Hospital (Oulu, Finland) during the years 1960–2020. Main outcomes were obstetric complications as well as maternal and neonatal morbidity. All eligible pregnancies (n=38) were reviewed for the course of pregnancy and delivery as well as maternal and neonatal health.

Results The median of maternal m.3243A>G load in muscle or buccal epithelium was 59% (range 30–76%). There were 30 deliveries and 31 born children. Among singleton pregnancies, gestational diabetes was present in seven (24%), gestational hypertension or pre-eclampsia in three (10%) and preterm delivery in two (7%). Mean birth weight was 3537 g (1020–5310 g), with a z-score of 0.80±1.37 for girls and 0.77±1.05 for boys. Seven newborns (12%) were treated in the neonatal intensive care unit.

Conclusion Women harbouring m.3243A>G may have an elevated risk for obstetric complications, such as gestational diabetes and gestational hypertension. Their babies may have an elevated risk of preterm birth and need for intensive care. Pregnancies of women with m.3243A>G should be followed carefully.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are few studies on pregnancy outcomes in women harbouring the mitochondrial DNA variant m.3243A>G, the most common cause of adult mitochondrial disease.

WHAT THIS STUDY ADDS

⇒ Women harbouring m.3243A>G may have an elevated risk for obstetric complications, such as gestational diabetes and gestational hypertension.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The pregnancies of women with m.3243A>G would benefit from standardised care protocol for the safety of the mother and child.

INTRODUCTION

Mitochondrial diseases are relatively common genetic disorders primarily characterised by respiratory chain dysfunction. These disorders may arise from pathogenic variants in either nuclear or mitochondrial DNA (mtDNA).[1 2] The mtDNA encodes 37 genes necessary for respiratory chain function, with over 200 pathogenic variants reported.[3] The clinical presentations are diverse, ranging from asymptomatic to severe multisystem manifestations and early death.[2 4] There are hundreds or thousands of mitochondria in a cell, each containing multiple copies of the circular mtDNA molecule. Heteroplasmy describes the presence of both variant and wild-type mtDNA in the same cell. Typically, the heteroplasmy level correlates with the severity of the mitochondrial dysfunction.[5 6] Despite the maternal inheritance pattern, mtDNA heteroplasmy level may change from mother to offspring, explained by the mitochondrial genetic bottleneck.[7] Random distribution of mtDNA during cell division and relaxed replication of mtDNA may result in further differences between tissues.[5 6] The most common pathogenic mtDNA point mutation in adults is m.3243A>G in the tRNA encoding *MT-TL1*. The estimated prevalence of clinically affected adults varies geographically from 3.5/100 000 in North East England and Southwest Finland, up to 5.7/100 000 in Northern Finland.[8–10] Only a minority of variant carriers present with the classical, severe phenotype of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome. Maternally inherited diabetes and deafness and variable non-syndromic presentations are more common.[11]

The treatment of mitochondrial disease is mostly symptomatic.[1] New reproductive technologies with mitochondrial donation or replacement treatment provide ways to help prevent the transmission of pathogenic mtDNA variants.[12] Mitochondrial donation was legally approved in the UK in 2015, with news of a first child born with mitochondrial replacement treatment in 2023.[13 14] Thus far, only a few studies have investigated the natural course of pregnancies and deliveries in women harbouring pathogenic mtDNA variants. Studies suggest that mitochondria play a vital role in the placenta, enabling cellular transport of nutrients and oxygen

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To cite: Kuikka P, Nikkinen H, Majamaa K, *et al*. *J Med Genet* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jmg-2025-110875

and participating in signalling for physiological adaptations and regulation of pregnancy progression.[15 16] Previous survey studies suggest an increased risk of obstetric complications among mildly affected or asymptomatic mtDNA variant carriers.[17–19] In this retrospective, cohort-based register study, our objective was to investigate the course and outcomes of pregnancies and deliveries, as well as the effects of maternal heteroplasmy on reproductive health among women harbouring the m.3243A>G variant.

MATERIALS AND METHODS

We used the mitochondrial disease patient cohort at Oulu University Hospital (OUH, Oulu, Finland) to identify women who harboured the mtDNA variant m.3243A>G. Among these, we scrutinised the data of those women with least one pregnancy managed at OUH between the years 1960 and 2020.

The medical records of the identified women were reviewed for pregnancy outcomes, mode of delivery, neonatal health and newborn and maternal deaths. In addition, maternal age, body mass index and the highest heteroplasmy level of m.3243A>G in either muscle or buccal epithelium were used as variables. Medical records were used to estimate the functional status of the women using the Karnofsky Scale and the modified Rankin Scale.[20 21] The Newcastle Mitochondrial Disease Scale for Adults[22] could not be used as a measure for mitochondrial disease severity, because the scale was not in clinical use at OUH for most of the period studied.

Primary indicators of maternal health during pregnancy, including maternal diabetes mellitus (type 1, type 2 or gestational), gestational hypertension and pre-eclampsia, were recorded. Gestational diabetes mellitus (GDM) was defined as fasting plasma glucose ≥5.3 mmol/L, plasma glucose ≥10.0 mmol/L at 1 hour and/or ≥8.6 mmol/L at 2 hours in a 2-hour 75 g oral glucose tolerance test.[23–25] The majority of women with normal fasting glucose were not investigated with the oral glucose tolerance test. Gestational hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg after 20 gestation weeks without pre-existing hypertension, with or without signs of pre-eclampsia.[26] Core indicators of neonatal health were gestational age at delivery, prematurity (birth before 37 gestational weeks), birth weight, umbilical arterial pH, Apgar score at 5 min and need for neonatal intensive care.

Only singleton births were included in the analysis of the course of pregnancy, delivery and neonatal health, to minimise the confounding effect of high-risk multiple pregnancies. Results were compared with those in previous studies on pregnancy outcomes in women with m.3243A>G[17–19] and to national or Nordic perinatal statistics, and other published data on maternal and perinatal health in general Finnish population.[27–34] To minimise the variation between years when using perinatal statistics data, the calculated means of years closest to the median year in the study population were used for comparison.

RESULTS

We identified 16 women with m.3243A>G (table 1) and their 38 pregnancies that took place between the years 1976 and 2020 (median year 1992). There were 29 singleton pregnancies, 1 twin pregnancy, 2 miscarriages and 6 induced abortions. The mean maternal m.3243A>G heteroplasmy level was 59% (range, 30–76%). Six women (38%) had sensorineural hearing loss, including two with epilepsy and two with diabetes. None of the women presented with the MELAS syndrome. The small number of patients limited the potential to analyse the potential associations between the maternal characteristics and pregnancy outcomes. In the performed analyses, no significant associations were found.

Table 1 Maternal baseline characteristics of 38 pregnancies by women with m.3243A>G

Gravidity, median n (range)	2 (1–8)
Parity, median n (range)	1 (0–7)
Nulliparous, n (%)	16 (42)
Age, mean (range)	30 (17–42)
BMI, mean (range)	23 (15–29)†
ART pregnancies, n (%)	1* (3)
mRS=0 and Karnofsky score=100, n (%)	21 (55)
mRS≥1 and Karnofsky score<100, n (%)	17 (45)

*Artificial insemination with donor egg.
†Includes women whose score could be determined based on the medical records near the time of the pregnancy. Maternal BMI was available for 28 pregnancies (BMI≥25 for 7, BMI≥30 for 0).
ART, assisted reproductive technology; BMI, body mass index; mRS, modified Rankin Scale.

No maternal deaths occurred, but there was one neonatal death at age 18 hours of a baby born at 28 weeks of singleton pregnancy. The mother harboured m.3243A>G at a heteroplasmy level of 75% in skeletal muscle. The child was delivered by caesarean section because of severe pre-eclampsia of the mother, weighed 1160 g and the Apgar score was 7 at 5 min. Prenatal or preimplantation diagnosis of m.3243A>G was not performed in any of the pregnancies.

Maternal GDM was present in seven (24%; 95% CI 12% to 42%) of the 29 singleton pregnancies, and pre-existing diabetes mellitus in two (7%) (table 2). Essential hypertension prior to pregnancy was found in one woman and gestational hypertension was present in three (10%) pregnancies. Two (7%) deliveries were preterm. GDM, gestational hypertension and preterm delivery were the most frequent pregnancy complications, and at least one of them was found in 10 (34%) of singleton pregnancies. None of the women experienced stroke-like episodes, seizures, new focal neurological symptoms or lactic acidosis during pregnancy. Three newborns (10%) were treated in the neonatal intensive care unit (NICU). In this study, we could not review the medical records of the neonates, and the data on neonate health are limited to those in maternal obstetric records.

DISCUSSION

In this retrospective, single-centre, register-based study, we reviewed the medical records of 38 pregnancies of 16 women harbouring the m.3243A>G mtDNA variant for pregnancy progression, delivery and neonatal health. We found that most pregnancies ended in live birth by spontaneous vaginal delivery. However, pregnancies of women with m.3243A>G were often complicated by impaired glucose metabolism, gestational hypertension or prematurity, and 10% of newborns needed NICU treatment. None of the newborn children were tested for the m.3243A>G variant.

In the Finnish healthcare system, predictive genetic testing of children is generally not performed. This is also the case for mtDNA disease. In this study, whether some of the offspring were tested later in life was not investigated. In a previous study, the mutation analysis from 13 mothers with 3243A>G and their 41 children gave a segregation rate of 0.80.[35] The mothers with heteroplasmy greater than 50% tended to have offspring with lower or equal heteroplasmy, whereas the opposite was

Table 2 Mode of delivery and neonatal data of the singleton pregnancies of women with m.3243A>G

	Variant carriers
n	29
Pregnancy duration, weeks, mean (range)	39 (37–41)
Spontaneous vaginal delivery, n (%)	16 (55)
Caesarean delivery, n (%)	8 (28)
Birth weight, g (range)	3537 (1020–5310)
Birth weight, z-score, boys	0.77±1.05
Birth weight, z-score, girls	0.80±1.37
Treatment at NICU, n (%)	3 (10)
Apgar 5 min*, mean (range)	8.9 (6–10)
5 min Apgar score <7*, n (%)	1 (4)
Umbilical a-pH <7.05†, n (%)	1 (7)

*Data available for 23 pregnancies.
†Data available for 14 singleton births.
a-pH, arterial blood pH; NICU, neonatal intensive care unit.

true for mothers with heteroplasmy less than or equal to 50% (p=0.0016). These results were based on anonymised mother–child pairs, and as the anonymisation code has since been destroyed, these data are unfortunately not available for further use.

Previous studies have also assessed the obstetric health and pregnancy outcomes of women harbouring m.3243A>G.[17–19] These studies differ somewhat in the methods used, as access to the original clinical data has been variable and some studies have relied on patient-reported outcomes (table 3). Particularly compared with the recent study using hospital data, we found similar frequency of preterm delivery and caesarean section. The reported frequencies of GDM vary between 11% and 32%. Based on our results and those from previous studies, increased incidence of gestational hypertension or pre-eclampsia, GDM and prematurity seem to be relevant challenges in the pregnancies of women with m.3243A>G.

We observed GDM in seven (24%) of the 29 singleton pregnancies of women with m.3243A>G. In the general Finnish population, the prevalence of GDM has increased considerably over time. Comprehensive national guidelines for GDM were introduced in 2008, recommending oral glucose tolerance test screening to the majority of pregnant women.[36] Previous screening guidelines were typically risk factor based and locally variably applied. Following the introduction of the national guidelines in 2008, the proportion of pregnant women screened for GDM increased from 28% in 2006 to 51% in 2010. The prevalence of GDM was estimated to be as low as 1.3% in 1987–1988, increasing to 9.1% in 2006, 11% in 2010 and 21% in 2019.[27 33 35] As 90% of the pregnancies reported here occurred before 2010, the prevalence of GDM in women with m.3243A>G at 24% seems considerably high compared with that in the general population. Higher prevalence of GDM among variant carriers compared with pregnancies in the general population would not be unexpected, given that impaired glucose metabolism and diabetes mellitus are common clinical manifestations of m.3243A>G.[11]

Gestational hypertension was observed in 10% of the women harbouring m.3243A>G. In the general Finnish population, the prevalence of hypertensive disorders during pregnancy has been reported considerably lower (5.5%).[32] Our results thus suggest that variant carriers may be at a higher risk of pregnancy-related hypertensive disorders. The observed association between a mitochondrial disease and gestational hypertension suggests a potential role of mitochondrial dysfunction in disorders associated with pre-eclampsia and warrants future study.

Previous studies have suggested a high rate of preterm delivery among women with m.3243A>G (table 3). In our study, the observed rate of preterm delivery did not differ much from that in the general Finnish population (7% vs 5.2%).[28 29] The need for NICU care in neonates of m.3243A>G carriers was slightly higher compared with pregnancies in the general population (10% vs 7.8%).[29–31] The risk of prematurity may be associated with the higher incidence of diabetic pregnancies and gestational hypertension. In addition, other mechanisms, such as placental dysfunction due to deficient mitochondrial energy production, may also contribute.[15–18]

The use of detailed patient record data in this study increases the reliability of the findings. These data also enabled us to present a more detailed account on the course of pregnancies, deliveries and early neonatal health in the pregnancies of women harbouring m.3243A>G. However, as the reviewed pregnancies in this observational, single-cohort study span over five decades, the clinical practices of pregnancy follow-up and obstetric care as well as standards of medical documentation have changed. In addition, changes in the prevalence and diagnostic criteria of GDM create challenges in comparing the investigated women with m.3243A>G to the general population.

CONCLUSION

Our results suggest that women with m.3243A>G have an increased risk for GDM and hypertensive disorders during pregnancy, and that their offspring may be at a higher risk for prematurity and need for intensive care after birth. Genetic counselling of women with m.3243A>G should take these findings into

Table 3 Studies reporting pregnancy outcomes in m.3243A>G cohorts

	Present study	de Laat *et al*[18]	Feeney *et al*[17]	Sanchez-Lechuga *et al*[19]
Data source	Hospital data	Questionnaire	Questionnaire	Hospital data
Women, n	16	46	28	26*
Pregnancies, n	38	91	62	66
GDM, n (%)	7 (24)†	9 (11‡)	10 (16)	21 (32)
Premature delivery, n (%)	2 (7)†	23 (25)	33 (53)	9 (14)
Caesarean section, n (%)	8 (28)†	15 (15§)	19 (31)	13 (20¶)

*Includes one woman with 12258C>A variant.
†Data presented for the 29 singleton pregnancies.
‡Per 85 pregnancies.
§Per 95 children born.
¶Per 64 deliveries.
GDM, gestational diabetes mellitus.

consideration. The pregnancies of women with m.3243A>G would benefit from standardised care protocol for the safety of the mother and child.

Contributors PK: data collection, writing the first draft, editing and revision of the manuscript text. HN: planning of the study, data collection, editing and revision of the manuscript text. KM: planning of the study, editing and revision of the manuscript text. MHM: initial idea and planning of the study, editing and revision of the manuscript text, guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer This work was generated within the European Reference Network for Neuromuscular Diseases and the European Reference Network for Rare Neurological Diseases.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This retrospective register-based study was approved by the Medical Director of the Hospital District (25/2021).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Individual patient data cannot be shared. All data that can be shared are in the manuscript.

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