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Endocrine features of primary mitochondrial diseases

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Purpose of review
Primary mitochondrial diseases are one of the most prevalent groups of multisystem genetic disorders. Endocrinopathies associated with mitochondrial diseases may have clinical features that are distinct from the more common forms. We provide an overview of mitochondrial disorder genetics and phenotypes, focusing on recent studies regarding identification and treatment of associated endocrinopathies.

Recent findings
Known endocrine phenotypes of mitochondrial disorders continue to expand, and now include growth hormone deficiency, hypogonadism, precocious puberty, hypoparathyroidism, hypo- and hyperthyroidism, diabetes, and adrenal insufficiency. Recent studies suggest several genotype-phenotype correlations, including those related to nuclear variants. Diagnosis is important, as special considerations should be made in the management of endocrinopathies in mitochondrial patients. Finally, new mitochondrial replacement strategies may soon be available for women interested in preventing mitochondrial disease transmission to offspring.

Summary
Patients with multiple endocrinopathies or atypical endocrinopathies should be evaluated for primary mitochondrial disease, as a diagnosis may impact management of these individuals.

Keywords
diabetes mellitus, endocrinopathy, growth, Kearns–Sayre syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, maternally-inherited diabetes and deafness, mitochondrial disease, sexual maturation

INTRODUCTION

Primary mitochondrial diseases are a heterogenous group of disorders that are individually rare, but collectively affect approximately 1 in every 5000 people [1]. Genetic testing is the current gold standard for diagnosis, as there are no validated biomarkers [2]. At present, there is one mitochondrial disorder (Friedreich ataxia) for which a targeted, FDA-approved therapy is available [3,4]. Supportive care and conventional treatment of disease manifestations remains standard of care; all treatments discussed here are either approved for a disease manifestation not specific to a mitochondrial disorder or used off label [2].

Mitochondrial diseases result from disruption of one or more of the hundreds of genes encoding mitochondrial components [5]. Because mitochondria provide energy for almost every cell type and are involved in varied cellular processes, mitochondrial disorders can involve nearly every organ system [6]. Postmitotic tissues most dependent on mitochondrial energy production are usually affected, including brain, eyes, heart, and skeletal muscles.

Our appreciation of endocrine involvement in mitochondrial diseases is expanding. Diabetes mellitus remains the most common and well established associated endocrinopathy [7]. However, analysis of large mitochondrial patient cohorts has revealed other endocrinopathies, including

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KEY POINTS

- Mitochondrial disorder genetics and phenotypes are complex and heterogeneous.
- Multiple endocrinopathies are associated with primary mitochondrial disease including diabetes mellitus, short stature, hypogonadism, hypoadrenalism, and hypoparathyroidism.
- There are few targeted therapies for mitochondrial disease; however, associated endocrinopathies may have atypical features or require specific treatment.
- Broadly available reproductive options for women with mitochondrial disease using maternal spindle transfer are on the horizon.

abnormal growth and sexual maturation, hypoparathyroidism, and adrenal insufficiency [8].

In this review, we summarize the genetics and phenotypes of mitochondrial diseases. We then discuss landmark papers regarding endocrine phenotypes in mitochondrial disorders, focusing on recent advances and treatment options. We anticipate that this review will serve as a primer for endocrinologists in identifying, understanding, and treating endocrine manifestations of primary mitochondrial diseases.

MITOCHONDRIAL DISEASES

Before the broad implementation of molecular diagnostics, mitochondrial diseases were diagnosed biochemically, often by evidence of disrupted respiratory chain function on biopsy, and clinically by phenotype [9]. The term 'primary mitochondrial disorder' traditionally referred to a genetic change that caused impairment of oxidative phosphorylation. Oxidative phosphorylation is performed by the electron transport chain and involves multiple chemical reactions including oxidation of NADH to NAD^+, generation of a proton gradient, and phosphorylation of ADP to ATP for cellular energy. Mitochondria also mediate several other interlinked metabolic processes such as fatty acid oxidation, single carbon metabolism, nucleotide homeostasis, iron sulfur complex biogenesis, cell cycle progression, and immune signaling [10]. With improvements in sequencing and our understanding of genes encoding mitochondrial proteins, the gold standard for diagnosis is now genetic testing [5]. Biochemical diagnostics and diagnostic biomarkers for mitochondrial dysfunction are a complex and evolving field; however at present expert consensus does not support the use of these assays for clinical testing [2,11▪▪]. Due to genomic sequencing, the definition of primary mitochondrial disease has expanded to include disorders that affect numerous other processes within mitochondria as well [12].

Most mitochondrial components are encoded by nuclear genes, and disorders associated with these genes follow Mendelian inheritance patterns [5]. There are 37 genes encoded by the mitochondrial genome, which is maternally-inherited [13]. Diseases result from point mutations or mtDNA deletions, such as in Kearns–Sayre (characterized by progressive external ophthalmoplegia and pigmentary retinopathy) or Pearson syndrome (characterized by sideroblastic anemia and exocrine pancreas dysfunction). There are hundreds to thousands of mitochondria per cell that are randomly distributed during cell division. For this reason, variants often occur in a fraction of gene copies, and the percentage of mutant mitochondrial genes is termed *heteroplasmy*. Measuring this proportion remains challenging because even within an individual, heteroplasmy can differ across cells, tissues, and throughout the lifespan [14,15]. Higher proportions of heteroplasmy are anticipated to result in more severe disease phenotypes. There may be no symptoms until heteroplasmy exceeds a disease-specific threshold, although how to define such thresholds remains unclear (Fig. 1, top) [13]. Because of this heterogeneity, the same mitochondrial variant can cause different phenotypes even among family members, and different variants can result in overlapping syndromes [6].

Clinical features of mitochondrial disorders may include encephalopathy, developmental delay, myopathy, stroke-like episodes, hypotonia, failure to thrive, cardiac dysfunction, hepatopathy, endocrinopathy, and renal failure (Fig. 1, bottom) [6]. In addition, there are several classical clinical syndromes associated with mitochondrial gene mutations: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); Leber hereditary optic neuropathy (LHON); myoclonic epilepsy with ragged red fibers (MERRF); maternally-inherited diabetes and deafness (MIDD); and neuropathy ataxia and retinitis pigmentosa syndrome (NARP). While there are no FDA-approved treatments for the vast majority of mitochondrial disorders, management guidelines and supportive care may improve outcomes [2].

ENDOCRINOPATHIES IN PRIMARY MITOCHONDRIAL DISEASES

Multiple endocrinopathies are associated with mitochondrial disease (Fig. 2). For many endocrinopathies, there are established genotype-phenotype correlations (Table 1).

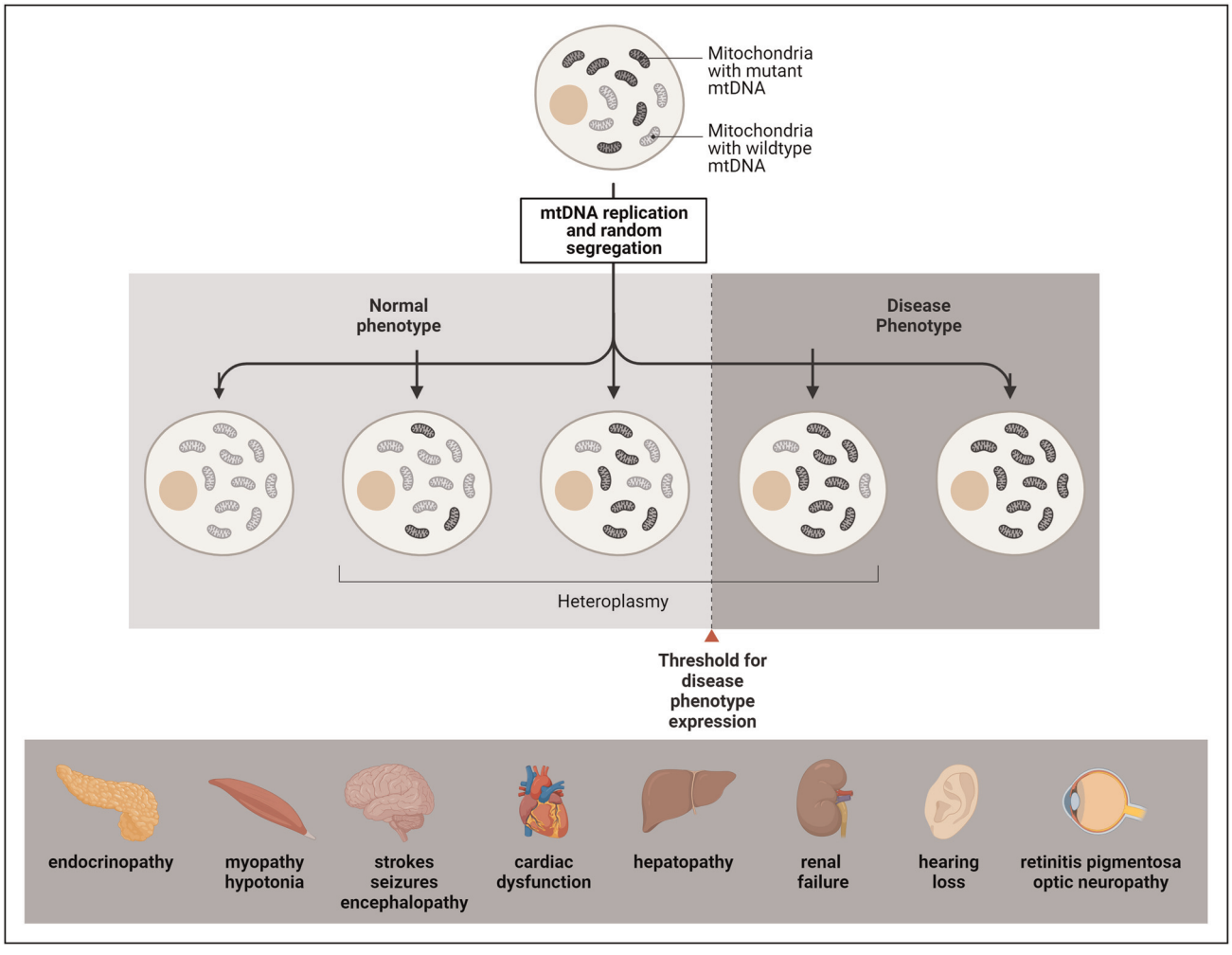

FIGURE 1. Mitochondrial disease genetics and phenotypes. Random distribution of mitochondria during cell division results in heteroplasmy, in which only a proportion of mitochondrial gene copies carry a mutation. Once heteroplasmy passes an ill-defined threshold in an individual, mitochondrial disease phenotypes are exhibited. For mitochondrial nuclear gene variants, biallelic pathogenic variants are usually required for disease expression. Adapted from 'Heteroplasmy', by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.

Diabetes mellitus

The link between mitochondrial mutations and diabetes was first published in 1992, when a family with maternally inherited diabetes and deafness (MIDD) was found to harbor an mtDNA deletion [16]. MIDD is now linked to a variety of mitochondrial variants, but ~80% of cases are caused by m.3243A>G, which likely alters the structure of tRNA-leu-1 encoded at this position, resulting in mitochondrial translation defects [17–19]. This variant is the most common heteroplasmic, pathogenic mtDNA variant and can result in MELAS or MIDD, among other manifestations [20].

Around 85% of individuals with m.3243A>G develop diabetes by the age of 70 [21]. The average age of onset is 38 years, with a range of 12–67 years within a large patient cohort [22]. The presence of comorbid sensorineural hearing loss, predating diabetes by an average of 6 years in this cohort, may be an important diagnostic clue [22]. Patients are almost invariably lean at presentation, with a mean BMI of around 20 in multiple studies [7,22]. The DM is typically not associated with autoimmunity, and may be insulin dependent or not, with 13% of patients requiring insulin at diagnosis and 58% requiring insulin after four years [7]. Rarely, diabetic ketoacidosis can occur [23].

Recently, MELAS syndrome was shown to be caused by variants in nuclear as well as mitochondrial genes [24,25▪]. However, DM appears to be more common in patients with mtDNA defects than in those with nuclear mutations (23% versus 4%), suggesting nuclear variants primarily act as modifiers rather than drivers of diabetes in MELAS/MIDD [8].

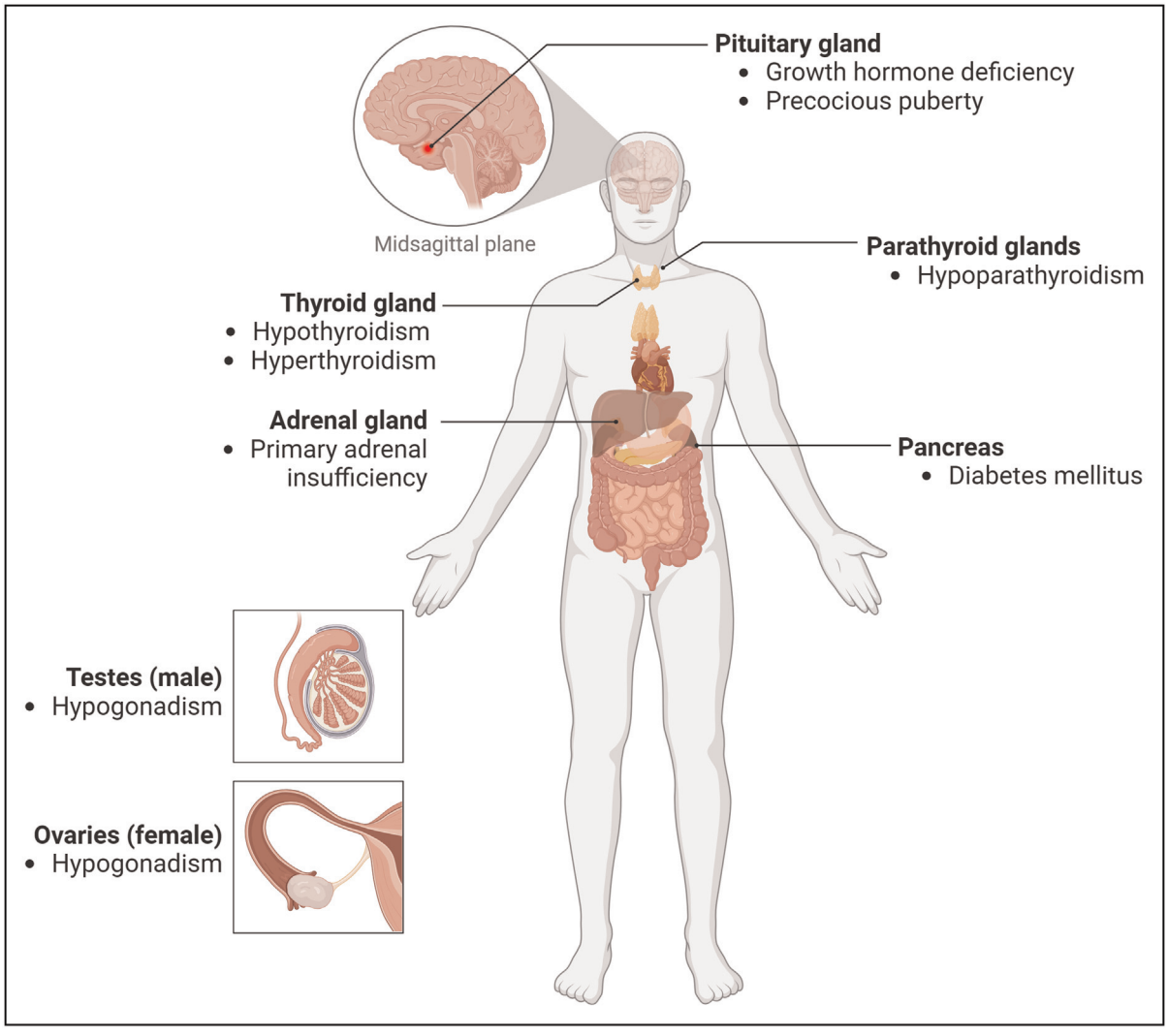

FIGURE 2. Endocrinopathies in primary mitochondrial disease. Endocrinopathies in mitochondrial disorders can affect primary or secondary endocrine organs. Underlying molecular mechanisms remain unclear. Adapted from 'Primary and Secondary Endocrine Organs', by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.

It is important to differentiate mitochondrial DM from other causes to improve patient management and surveillance for other symptoms. Around 1–3% of patients with DM carry the m.3243A>G variant [26]. There are high rates of complications including peripheral neuropathy (58%), diabetic retinopathy (62%), and nephropathy (56%) [27]. In addition, several studies suggest metformin may not be preferred first-line treatment in mitochondrial patients. One recent study of 16 patients with m.3243A>G found those treated with metformin were 3.5 times more likely to exhibit neurologic manifestations, such as stroke-like episodes [28▪▪]. In at least one case, there was a notable temporal relationship between onset of symptoms and initiation of metformin. The authors suggest considering Dipeptidyl Peptidase IV (DPP-IV) inhibitors, Sodium-glucose Cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists as first-line agents. This study adds to four case reports of patients with m.3243A>G who had neurologic symptoms seemingly fomented by metformin initiation [29–32]. However, the association between metformin and neurologic symptoms remains statistically insignificant, and causality has not been established. Importantly, the incidence of metformin-induced lactic acidosis is similar in MELAS patients to that in the general population; this is an important consideration as patients with MELAS often have baseline lactic acidosis due to mitochondrial dysfunction [33]. Metformin is considered safe in primary mitochondrial disease by international consensus, but should be used with caution [2,34].

Table 1. Genotype–phenotype correlations in primary mitochondrial endocrinopathies

Endocrinopathy	Associated gene variants (mitochondrial, *nuclear*)	Other genotype–phenotype information
Diabetes mellitus	m.3243A>G	• Well established • Associated with MIDD and MELAS • Lean at presentation • High rates of complications • Potential neurologic complications with metformin
	POLG, DGUOK, SUCLG2, TRNT1, LOXHD1, KCNQ1, KCNQ2, NEUROD1, MYH7	Variants may contribute to MELAS/MIDD phenotype alone or in combination with m.3243A>G
Hypothyroidism	m.8619A>G m.3243A>G mtDNA deletions (Pearson and KSS)	• Case reports only, no significant link established • Both primary and secondary hypothyroidism reported
Hyperthyroidism	Leigh syndrome	• Case report of child with Grave's disease
Hypoparathyroidism	KSS m. 3243A>G	• Well established in KSS; Not autoimmune. Case report in m.3243
	IARS2	Case report
Short stature	*MT-TL1* (especially m.3243A>G), *MT-TLK*, mtDNA deletions (KSS, Pearson)	• Cases reported with and without GH deficiency • If GH deficient, may respond to supplementation
Hypogonadism	Leigh syndrome KSS m.8561C>G	• Usually hypogonadotropic, but hypergonadotropic reported in m.8561
	RRM2B, POLG, MRPS7 Perrault (*TWNK, CLPP, LARS2, HARS2, ERAL1, HSD17B4*)	• Case reports • Perrault syndrome is known to be associated with primary ovarian dysfunction and decreased fertility
Hypergonadism	Unknown (diagnosed by muscle biopsy)	• Elevated estradiol • Good response to GnRH agonists
Adrenal insufficiency	KSS m.3243A>G, m.12014T>C, m.8344A>G	• Well established in KSS. Antibodies negative when tested. • Case reports in mitochondrial point variants, associated with MELAS
	POLG, GFER, NDUFAF5, MRPS7, QRSL1, TR4, STAR, CYP11A	Associated with steroid biogenesis/metabolism or mitochondrial protein import.

KSS, Kearns–Sayre syndrome; MIDD, maternally-inherited diabetes and deafness; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; GH, growth hormone.

Given differences in complications and management of mitochondrial DM compared with other types, a diagnosis of a primary mitochondrial disorder should be considered in any patient with an atypical presentation, especially insulin-dependent nonautoimmune DM in a lean individual with a personal or family history of sensorineural hearing loss.

Hypoparathyroidism

Hypoparathyroidism is uncommon in mitochondrial disease but is a hallmark feature of Kearns–Sayre syndrome, an mtDNA deletion disorder. Kearns-Sayre syndrome also leads to encephalopathy, myopathy, ophthalmoplegia, retinitis pigmentosa, and heart block. Hypoparathyroidism was first reported in 1978 in a patient with Kearns-Sayre syndrome, and a more robust literature review in 1992 identified this condition in 14 out of 222 clinically-diagnosed cases of Kearns–Sayre [35,36]. A more recent study focused on the pediatric population found 3 out of 34 children with mitochondrial deletions had hypoparathyroidism [37]. The hypoparathyroidism does not appear to be autoimmune and the etiology remains unclear, though autopsy of two patients with Kearns-Sayre found absent or atrophied parathyroid glands [35,38–40]. In addition to primary hypoparathyroidism, Kearns–Sayre is associated with renal dysfunction that can worsen parathyroid abnormalities. Renal tubulopathy causes electrolyte loss in the urine including magnesium, calcium, and potassium. Low magnesium suppresses parathyroid hormone release, resulting in worsened hypocalcemia that is not responsive to magnesium supplementation [41].

Aside from individuals with Kearns-Sayre syndrome, hypoparathyroidism has also been reported in one patient with an mtDNA m.3243A>G variant,

who also had the classical diabetes mellitus, hearing loss, and muscle weakness [42]. Additionally, a case has been reported of a 14 year-old girl with severe hypoparathyroidism, red cell aplasia, delayed sexual development, and developmental delay who was found to harbor a homozygous pathogenic variant in *IARS2*, a nuclear gene associated with mitochondrial disease [43▪]. This case raises the possibility that hypoparathyroidism may occur in mitochondrial disorders related to nuclear DNA mutations rather than solely in mtDNA syndromes. However, as there is no evidence of the hypoparathyroidism occurring as a result of the *IARS2* variant, it may be an incidental finding.

Growth disorder associated with short stature

Short stature is a well established feature of mitochondrial diseases caused by mutations in both nuclear and mitochondrial genes including *MT-TL1*, *MT-TK*, mtDNA deletions, *IARS2*, *MTFMT*, *C12orf65*, *NDUFA4*, *SURF1*, *COX10*, *LRPPRC*, *OPA1*, *POLG*, *RRM2B*, *TWINK*, and *ECHS1* [44,45]. In fact, height has been suggested as a biomarker for disease burden in pediatric-onset mitochondrial disease because of its negative correlation with disease severity [45]. Boal *et al*. found adults with mitochondrial disease have a significantly decreased mean height (−0.49 SD), and 1 out of 10 had a height <2 SD below the mean. Severity and rate of progression are significantly correlated with adult height. People harboring m.3243A>G are particularly likely to have short stature [46].

The cause of short stature in mitochondrial disease is likely multifactorial. Children with mitochondrial disease may have placental dysfunction and low birth weight, dysphagia, GI dysmotility, reduced muscle mass, and chronic multisystem disease, all of which contribute to decreased linear growth [46]. There is also evidence of growth hormone (GH) deficiency in several mitochondrial disorders including mtDNA deletions, nuclear gene variants, and m.3243A>G; however, GH levels may also be normal [44]. GH deficiency might be due to hypothalamo-pituitary axis dysfunction, but the mechanism is not well established. One patient with MELAS had high levels of mutant mtDNA in the pituitary [47]; however, MRI imaging of the pituitary is often normal in mitochondrial disease [48].

In patients with mitochondrial disease and confirmed GH deficiency, treatment is recommended. In one study, 6 out of 8 patients with Kearns–Sayre and GH deficiency had improved height with therapy [49]. However, in previous studies, only 3 out of 11 Kearns–Sayre patients improved, and in patients with a variety of other mitochondrial disorders, only 3 out of 13 responded [50]. This lower response rate may be because not all patients were assessed for GH deficiency prior to treatment. Studies are ongoing. Recently, an 11.5 year-old girl with MELAS, short stature, and GH deficiency had improved growth from 4.2 to 6.5 cm/year after initiation of GH [51▪].

Altered sexual maturation and fertility

Hypogonadism, both hyper- and hypogonadotropic, has been described in 2% of patients with mitochondrial disease [8]. Hypogonadism in mtDNA deletion syndromes is usually due to hypothalamic or pituitary dysfunction rather than ovarian or testicular insufficiency; however, elevated FSH and LH have been reported in patients with mtDNA variants [36,52–54]. Hypergonadotropic hypogonadism has also been described in 2 of 23 patients with *C10orf2* mutations, as well as a few patients with Leigh syndrome or *POLG, RRM2B,* or *MRPS7* mutations [44]. *POLG* variants may also result in early menopause [55].

By contrast, a recent study also found a high incidence of precocious puberty among girls with mitochondrial disease. Among 140 girls with evidence of mitochondrial disease on muscle biopsy, 10 (7.1%) were diagnosed with central precocious puberty, much higher than the general prevalence of 55.9 per 100 000 girls [56▪▪]. There was no association between precocious puberty and neurologic symptoms, specific enzyme defects, disease onset, or disease severity, and brain MRI was normal in all. These patients were treated with GnRH agonists with favorable outcomes.

It is unclear why the incidence of precocious puberty was so high in this group, but not in previous studies. It is likely that some participants had secondary rather than primary mitochondrial dysfunction, as participants were diagnosed by respiratory chain analysis only. Previous studies may also have inadequately evaluated for precocious puberty, as they were focused on postpubertal patients.

Mitochondrial disease is associated with normal fertility in large datasets [6]. However, variants in some nuclear-encoded mitochondrial genes are associated with gonadal failure and hypergonadotropic hypogonadism, such as those involved in Perrault syndrome, a disorder characterized by sensorineural hearing loss and primary ovarian dysfunction (*TWNK*, *CLPP*, *LARS2*, *HARS2*, *ERAL1*, and *HSD17B4*) [46].

Although mtDNA diseases are not associated with decreased fertility, family planning can be difficult because of complex inheritance. This year, a pilot study was completed regarding feasibility of

maternal spindle transfer [57▪▪]. The procedure involves transfer of metaphase II spindles from a patient's oocytes into enucleated donor oocytes, followed by intracytoplasmic sperm injection. The resultant fetus will inherit nuclear DNA from the patient, but mitochondrial DNA from the donor. This was a study of 25 infertile couples, and did not include women with mitochondrial diseases. Of the six resultant children, all nuclear DNA was inherited from both parents without any contribution from the donor. For five of the children, mtDNA was exclusively (>99%) from the donor, but one child had 30–60% maternal mtDNA haplotype. This study proved the efficacy of mitochondrial replacement strategies, and posed an important advance in family planning options for women with mitochondrial diseases. Indeed, eight years after first regulating such mitochondrial replacement therapies, in 2023 it was announced that five children have been born in the United Kingdom using this technology [58▪▪].

Adrenal insufficiency

Primary adrenal insufficiency was first described in Kearns–Sayre syndrome [59]. A recent literature review of 13 patients with primary mitochondrial disease reported to have adrenal insufficiency found 10 had mtDNA deletions, two had *POLG* variants, and one had *GFER* variants [60]. In the two cases tested, adrenal antibodies were negative. There have been case reports of children with MELAS due to m.3243A>G, m.12015T>C, or m.8344A>G who had adrenal insufficiency [61–63]. In addition, both adrenal insufficiency and mitochondrial dysfunction are associated with several nuclear genes involved in steroidogenesis and steroid metabolism (*TR4*, *STAR*, *CYP11A1*), as well as genes involved in complex I assembly or mitochondrial protein import (*NDUFAF5*, *MRPS7*, *QRSL1*, *GFER*) [44].

Thyroid dysfunction

There are several case reports of patients with mitochondrial deletions or mutations who also have primary or secondary hypothyroidism [37,64,65]. Recent case reports include an infant with a novel variant, m.8619A>G, who presented with complex V deficiency and subclinical hypothyroidism, and a three-year-old child with Leigh syndrome who developed hyperthyroidism [66,67]. However, the incidence of thyroid disease in large cohorts of mitochondrial patients is similar to that of the general population (6%) [68]. Further research is necessary to determine if there is a subset of mitochondrial diseases associated with thyroid dysfunction, or if incidence truly mirrors that in the general population.

CONCLUSION

Primary mitochondrial disorders are multisystem diseases with diverse phenotypes that arise from mitochondrial or nuclear genetic perturbations. Associated endocrinopathies include diabetes, short stature, hypogonadism, hypoadrenalism, hypoparathyroidism, and possibly thyroid disease. Endocrinopathy tends to occur more frequently in young patients with multisystem disease, so multidisciplinary care is essential [33]. Physicians should be suspicious of mitochondrial disease in any patient with multiple endocrinopathies or unusual features of disease, such as low BMI at the time of DM onset. At present, there are few mitochondrial disease-specific therapies; however, physicians can screen for endocrinopathies, with effective treatment available for many. Finally, there are new reproductive options for patients with mtDNA-linked mitochondrial disease that may become more broadly available in the future.

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Conflicts of interest

Dr M.A. Walker is a coauthor on patent application U.S. 17/928,696| for a diagnostic method for mitochondrial DNA diseases. Dr N. Gold is a paid consultant for RCG consulting.

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