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Mitochondrial replacement therapy for advanced maternal age and diminished ovarian reserve: Efficacy, challenges, and Vietnamese landscape

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ABSTRACT

Mitochondrial replacement therapy (MRT) has emerged as a disruptive frontier in reproductive medicine to address the challenges of advanced maternal age (AMA) and diminished ovarian reserve (DOR). These conditions are primarily driven by mitochondrial dysfunction, which leads to adenosine triphosphate (ATP) depletion, oxidative damage, and increased embryonic aneuploidy. Heterologous techniques, such as maternal spindle transfer (MST) and pronuclear transfer (PNT), have demonstrated high clinical efficacy, with studies reporting fertilization rates up to 88.4% and significantly improved blastocyst formation in patients with poor prognoses. While these methods show promise, autologous strategies utilizing stem cell derived mitochondria offer an alternative to maintain full genetic relatedness and avoid the ethical complexities of "three-parent" embryos. However, MRT remains an investigational procedure globally due to critical safety concerns, including mitochondrial "reversion" where maternal mitochondrial DNA (mtDNA) regains dominance and potential mitonuclear incompatibility. In Vietnam, where infertility affects approximately 7.7% of couples, there is a rising demand for such interventions despite significant gaps in national data and specific regulatory frameworks. Establishing a strategic roadmap that includes a national AMA/DOR database and modernized legal guidelines is essential to ensure the safe and ethical integration of MRT into Vietnam's clinical landscape.

Keywords: Mitochondrial replacement therapy; Mitochondrial dysfunction; Mitochondrial donation; Advanced maternal age; Diminished ovarian reserve

1. Introduction

The global trend toward delaying childbearing has led to an

increasing number of women seeking fertility treatment. Women with advanced maternal age (AMA) and diminished ovarian reserve (DOR) represent one of the most challenging groups in assisted reproduction, with steep declines in oocyte quantity, euploidy, and live birth rates despite optimized *in vitro* fertilization (IVF) protocols. Central to this decline is progressive mitochondrial dysfunction in oocytes and granulosa cells reduced mitochondrial DNA (mtDNA) copy number, impaired oxidative phosphorylation, ATP depletion, and accumulating oxidative damage that together drive meiotic errors and aneuploidy[1–3].

Mitochondrial replacement therapy (MRT) has emerged as a disruptive strategy to address these defects by replacing or bypassing defective ooplasm. Heterologous techniques such as maternal spindle transfer, pronuclear transfer, polar body transfer and germinal vesicle transfer transplant the patient's nuclear genome into the cytoplasm of younger donor oocytes, aiming to restore bioenergetic competence while maintaining nuclear genetic relatedness[1,4,5]. Early human and animal data show that spindle and pronuclear transfer can increase blastocyst formation, improve morphokinetics, and substantially raise euploidy and pregnancy rates in highly refractory AMA/DOR patients who otherwise produce no euploid blastocysts[1,4–6]. At the same time, concerns about heteroplasmy, donor mtDNA carryover, long term safety,

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and complex ethical regulatory issues mean that MRT remains investigational in most jurisdictions[1,3–5].

In Vietnam, the prevalence of infertility remains a significant concern, with an estimated rate of approximately 7.7%[7]. Moreover, both the utilization of assisted reproductive technology (ART) and maternal age at first birth are rising, but local data on mitochondrial-targeted interventions are scarce and regulatory frameworks for germline manipulation are still evolving. This review summarizes the biological rationale and efficacy evidence for MRT in AMA and DOR, discusses technical, ethical and regulatory challenges, and outlines the current and potential implementation landscape in Vietnam within its sociocultural and legal context.

2. Methods

2.1. Search strategy and data sources

This narrative review was conducted through a comprehensive and multi-layered literature search to evaluate the efficacy and socio-legal landscape of MRT. We performed an extensive search across major electronic databases, including PubMed/MEDLINE and Google Scholar, as well as the Google search engine to capture grey literature and policy documents up to January 2026.

The search was executed using a combination of Medical Subject Headings (MeSH) terms and targeted keywords, including ("mitochondrial replacement therapy" OR "mitochondrial donation" OR "maternal spindle transfer" OR "pronuclear transfer") AND ("mitochondrial dysfunction" OR "infertility" OR "advanced maternal age" OR "diminished ovarian reserve" OR "IVF"). To specifically address the regulatory context, additional search strings were employed: ("bioethics" OR "legal frameworks" OR "Vietnamese healthcare regulations"). To minimize the risk of missing relevant studies, a manual "snowballing" technique was applied by screening the reference lists of all identified primary articles and clinical reviews.

2.2. Eligibility criteria and study selection

2.2.1. Inclusion criteria

We included original research articles, comprehensive reviews, and case reports. Recognizing the emerging nature of MRT, conference abstracts, clinical guidelines, and bioethical policy analyses were also eligible for inclusion if they provided significant unique insights or preliminary clinical data.

2.2.2. Exclusion criteria

Studies were excluded if the full-text or essential data from the

abstract were inaccessible, or if they were redundant publications from the same study population.

2.3. Language and source priority

Priority was given to peer-reviewed sources published in English or Vietnamese.

2.4. Data extraction and synthesis

The identified literature was independently reviewed and synthesized to highlight the technological transition from heterologous to autologous MRT. Special emphasis was placed on aligning global clinical outcomes with the current legal and ethical infrastructure in Vietnam to provide a localized perspective on this advanced technology.

3. Overview

3.1. Introduction to mitochondrial replacement therapy

3.1.1. Definition and purpose of mitochondrial replacement therapy

Mitochondria are essential cellular organelles that play a central role in energy production through oxidative phosphorylation. In humans, mitochondria are almost exclusively maternally inherited *via* the oocyte; therefore, mitochondrial abnormalities or dysfunction can directly affect oocyte quality, embryonic development, and overall reproductive potential. In women of AMA or those with DOR, mitochondrial aging is frequently associated with a decline in reproductive function, leading to an increased risk of IVF failure[8].

MRT also known as mitochondrial donation, is an advanced ART designed to replace defective mitochondria in oocytes or embryos with healthy ones, with the aim of preventing or ameliorating mitochondrial related diseases[5]. Initially developed to prevent the maternal transmission of pathogenic mitochondrial DNA mutations, MRT involves transferring nuclear genetic material into donor cytoplasm containing healthy mitochondria, thereby minimizing the load of pathogenic mtDNA from the mother[9]. According to Dougherty *et al*, the primary objective of MRT is to prevent the transmission of severe mitochondrial diseases from mother to child conditions that often result in debilitating health complications or death, given the critical role of mitochondria in cellular energy production[10].

More recently, MRT has been explored as a potential strategy in infertility treatment, particularly for women of AMA or those with DOR. In this context, MRT is anticipated to enhance oocyte quality

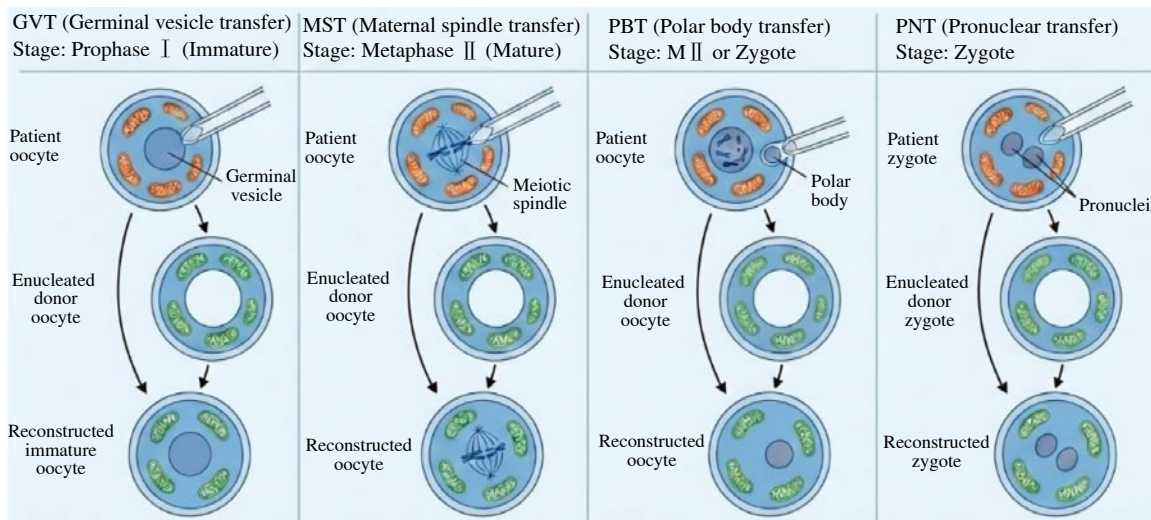


Figure 1. Major techniques for heterologous mitochondrial replacement therapies. Note: This figure was created with the assistance of NotebookLM.

by introducing healthier and more functional mitochondria, thereby improving the outcomes of ART[11].

3.1.2. Major mitochondrial replacement therapies

To date, several sophisticated microsurgical approaches have been developed to achieve mitochondrial replacement, primarily distinguished by the developmental stage at which the nuclear genetic material is transferred. The two most clinically established techniques are meiotic spindle transfer and pronuclear transfer.

3.1.2.1. Germinal vesicle transfer (GVT)

This is an experimental mitochondrial replacement technique in which the germinal vesicle nucleus from an immature oocyte of the intended mother is transplanted into an enucleated immature donor oocyte at the same GV stage. The reconstructed oocyte is then subjected to *in vitro* maturation to reach metaphase II, followed by fertilization and embryo culture (Figure 1). Human and mouse studies show that GVT reconstructed oocytes can resume meiosis, extrude the first polar body, and often display normal metaphase II karyotypes, indicating preserved chromosomal integrity[12,13]. By placing the maternal genome into the cytoplasm of a young donor oocyte, GVT aims to rejuvenate oocyte quality and reduces the risk of mitochondrial dysfunction[4,12]. Nevertheless, efficiency remains limited, with relatively low blastocyst and live birth yields in animal models and no established clinical application in humans so far[4,13].

3.1.2.2. Pronuclear transfer (PNT)

PNT is performed shortly after fertilization. The procedure entails the microsurgical extraction of the pronuclei containing the nuclear DNA from both the mother and the father from a patient derived zygote. These pronuclei are subsequently transferred into an enucleated donor zygote (from which the original pronuclei have

been removed). The reconstructed zygote is then cultured *in vitro* and transferred into the uterus at the optimal developmental stage (Figure 1)[14]. Historically, PNT gained significant recognition when it received regulatory approval for clinical use in the United Kingdom in 2015, marking a milestone in the governance of MRT[15]. The first successful live birth utilizing PNT for infertility marked a significant milestone in reproductive medicine. In this landmark case, the procedure was employed to overcome embryonic developmental arrest, resulting in the delivery of a healthy child[16]. This clinical success underscores the potential of PNT to address complex reproductive failures, extending its utility beyond the primary scope of preventing mitochondrial disease transmission.

Regarding its technical efficiency, optimized PNT protocols have demonstrated high precision in limiting mitochondrial carryover. A study indicated that the average maternal mtDNA carryover in PNT derived blastocysts was approximately 1.68%. Notably, 79% of blastocysts exhibited less than 2% carryover, without reported cases exceeding 5%[17].

3.1.2.3. Maternal spindle transfer (MST)

MST is performed prior to fertilization, involving the extraction of the spindle chromosome complex from the patient's oocyte and its subsequent transfer into an enucleated donor oocyte. The reconstructed oocyte is then fertilized and cultured to the blastocyst stage (Figure 1). Compared to PNT, MST is often associated with a lower risk of mtDNA carryover and fewer ethical concerns regarding embryo manipulation[14]. The first live birth following MST was achieved in Mexico for a patient carrying Leigh syndrome[18]. Typically, the proportion of maternal mtDNA carryover in MST derived embryos is exceptionally low, with an average of approximately 0.3%-0.4%. Furthermore, studies have shown that carryover often remains below 2% at the embryonic or embryonic

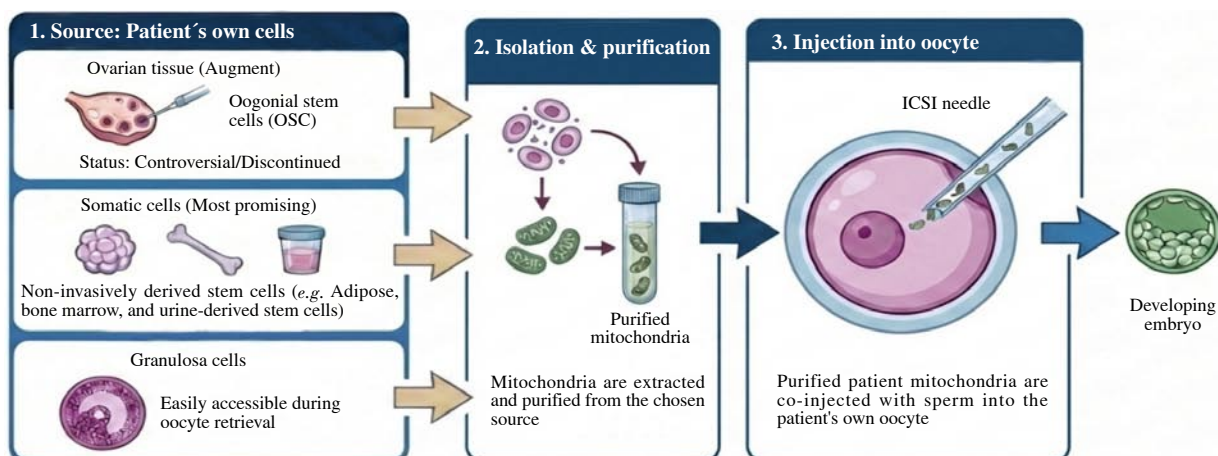


Figure 2. Schematic representation of autologous mitochondrial replacement therapy strategies and procedural workflow. Note: This figure was created with the assistance of NotebookLM.

stem cell (ESC) stage, with maternal mtDNA frequently becoming undetectable in ESC lines after multiple passages[17].

3.1.2.4. Polar body transfer (PBT)

PBT is a MRT technique that utilizes the nuclear material contained within the polar bodies small, nonfunctional byproducts of asymmetric oocyte division. This approach can be categorized into first polar body transfer (PB1T), performed before fertilization, and second polar body transfer (PB2T), conducted after fertilization. In PBT, the polar body is extracted and transplanted into an enucleated donor oocyte or zygote (Figure 1). The primary advantage of PBT lies in its potential to minimize mitochondrial carryover, as polar bodies contain significantly fewer mitochondria compared to the spindle chromosome complex or pronuclei[19]. While PBT has shown promising results in preclinical animal models and human research settings, leading to the development of viable blastocysts, its clinical application remains more limited than MST or PNT. Research suggests that PBT could serve as a complementary or alternative strategy for patients with limited oocyte yields, further expanding the technical repertoire of mitochondrial replacement therapies[19–21].

3.1.2.5. Autologous mitochondrial replacement therapies

In contrast to the aforementioned heterologous approaches, autologous strategies as shown in Figure 2 aim to rejuvenate oocytes using the patient's own mitochondria. By utilizing endogenous sources, these methods avoid third party genetic contribution and significantly minimize concerns regarding mitochondrial heteroplasmy and the ethical implications of using donor material[22–24].

The best-known strategy, autologous germline mitochondrial energy transfer (AUGMENT), isolates putative oogonial precursor cells from ovarian cortex, extracts their mitochondria and co-injects them with sperm at ICSI to boost oocyte bioenergetics in women

with poor ovarian response, advanced maternal age or recurrent IVF failure[22,24–26]. Early uncontrolled or historically controlled series reported higher fertilization and pregnancy rates and several live births, but these studies lacked robust controls and were prone to bias[22,25,26]. A subsequent randomized, triple blind trial in poor prognosis IVF patients found no improvement in blastocyst formation, euploidy, mitochondrial DNA content or live birth versus conventional ICSI, and even lower day 5 blastocyst rates in the AUGMENT arm, leading to discontinuation of this procedure as a clinical add-on[22,24,27].

Granulosa cells (GCs) play a vital role in supporting oocyte development and can be easily harvested from follicular fluid or during oocyte decumulation. Since 2004, Kong *et al* suggested that transferring GC derived mitochondria could enhance embryo quality in aging patients[28]. However, a significant limitation is that GCs age in synchrony with the oocyte within the same follicular environment. Consequently, their mitochondrial potential may not be optimal for achieving full rejuvenation in advanced maternal age cases.

Newer autologous concepts focus on mitochondria from non-invasively obtained or easily accessible stem cells such as urine-derived mesenchymal stromal cells (USCs), adipose-derived stem cells (ADSCs), and other mesenchymal populations. USC mitochondria show oocyte like morphology, high activity, low oxidative stress and relative resistance to aging; *in vitro* transfer into human oocytes improved mitochondrial content, membrane potential and, Ca^{2+} homeostasis. In older or cryopreserved oocytes were associated with enhanced embryo morphology and higher euploidy rates[4,29]. ADSC derived mitochondria have restored oocyte quality, embryo development and fertility in aged or cryopreserved oocyte mouse models, though results are not uniformly positive across studies and human data are still lacking[24,25].

Overall, autologous MRT remains experimental, with heterogeneous and sometimes conflicting outcomes; large, well

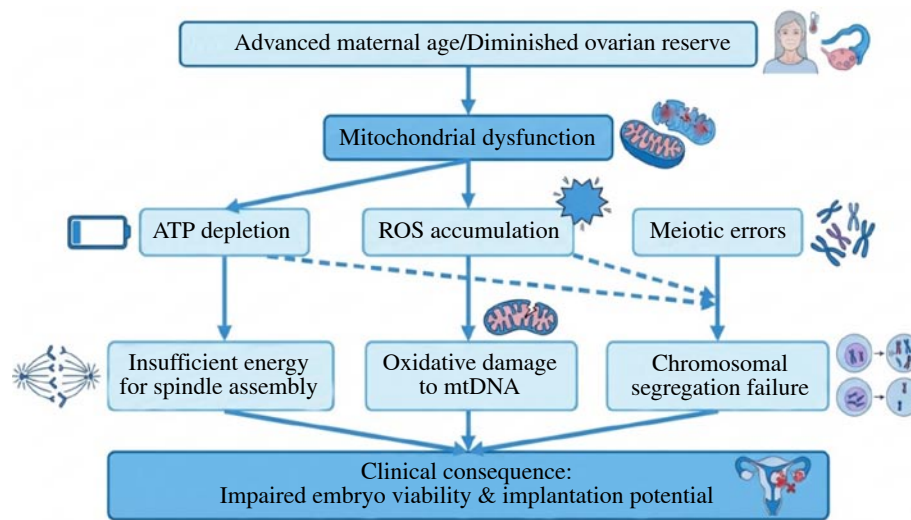


Figure 3. Mitochondrial-mediated pathways leading to impaired embryo viability in AMA and DOR patients. AMA, advanced maternal age; DOR, diminished ovarian reserve; mtDNA, mitochondrial DNA; ROS, reactive oxygen species. Note: This figure was created with the assistance of NotebookLM.

designed randomized trials and long-term offspring follow up are required before routine clinical use can be justified.

3.2. Mechanisms linking mitochondrial dysfunction to poor oocyte quality for patients with advanced maternal age and diminished ovarian reserve

DOR and AMA typically defined as age 35 and older are primary drivers of female infertility. According to the American College of Obstetricians and Gynecologists (ACOG), female fecundity begins to decline modestly at age 32, with a significantly more rapid decrease after 37. By age 40, the probability of natural conception per cycle falls to approximately 5%[30]. This trend is mirrored in ART outcomes; in women over 40, the live birth rate per IVF cycle is reported to be as low as 3.5%, underscoring the profound impact of reproductive aging[31].

Extensive evidence supports a strong association between diminished oocyte quality in AMA and DOR patients and mitochondrial dysfunction, often characterized by reduced mtDNA copy number and impaired bioenergetic capacity. As mitochondria are critical regulators of oocyte maturation, fertilization, and early embryogenesis, quantitative and functional decline may result in reduced ATP production and increased oxidative stress. These bioenergetic disturbances can compromise spindle stability and disrupt chromosomal segregation during meiosis, thereby increasing the risk of embryonic aneuploidy. Furthermore, energy insufficiency and oxidative stress are associated with fertilization failure, early embryonic arrest, and suboptimal morphological outcomes (Figure 3) [32,33].

3.3. Clinical efficacy and safety profile of mitochondrial

replacement therapy

3.3.1. Fertilization rate, blastocyst development, and euploidy rate

In 2009, Tanaka *et al* reported significantly higher rates of fertilization and blastocyst formation in MST oocytes compared to the control group (76% vs 59.2% and 28% vs 3.1%, respectively)[34]. In addition, Wu *et al* 2017 explored the clinical potential of PBT. Their study successfully generated 75 PB1T embryos, of which 25.3%(19/75) reached the blastocyst stage, with a euploidy rate of 52.6%(10/19). Notably, the average mtDNA carryover remained remarkably low at 0.26%. Similarly, PB2T yielded 51 embryos, with 27.5%(14/51) progressing to the blastocyst stage. Among these, 64.3%(9/14) were confirmed as euploid, with an average mtDNA carryover of 0.37%. These results further demonstrate that PBT techniques not only support embryonic development but also offer an effective strategy for minimizing mitochondrial DNA carryover[21]. A pilot study on MST of couples under 40 with idiopathic infertility, characterized by repeated IVF failures and poor oocyte quality leading to low fertilization or impaired embryo development yielded fertilization, blastocyst and euploidy rates of 75.9%, 62.4% and 45.2%, respectively[35].

A recent prospective cohort study has provided pivotal insights into the clinical efficacy of MRT for patients with DOR and AMA. In this study, 323 mature oocytes from patients (mean age: 39 years) underwent either PNT or MST. Post intervention, the fertilization rate reached a robust 88.4%. By day 3, progression to the 8 cell stage was observed in 97.2% of PNT and 94.2% of MST derived embryos. Furthermore, high quality blastocyst formation (graded AA, AB, BA, or BB) was achieved in 55.7% and 52.5% of the PNT and MST groups, respectively. Notably, preimplantation genetic testing for aneuploidy (PGT-A) identified euploidy rates of 60.3% in the MST

group and 56.9% in the PNT group. These findings underscore the superior developmental competence and reproductive potential attainable through spindle and pronuclear transfer[6].

On the other hand, autologous mitochondrial replacement techniques demonstrate the potential to enhance fertilization rates and embryo quality, particularly when utilizing mitochondria derived from granulosa cells or stem cells[26,28,29,36]. However, outcomes remain contradictory regarding the AUGMENT strategy[27,37].

3.3.2. Pregnancy and live birth rates

Zhang *et al* 2016 and Zhang *et al* 2017 reported the first live births achieved through MRT, conducted for the purposes of preventing mtDNA diseases using PNT and treating infertility caused by embryo arrest at the two cell stage using MST, respectively[16,18]. Subsequently, in 2023, a clinical trial on MST reported a 36.8% clinical pregnancy rate per transfer. The live birth rate per transfer was 31.6%, while the overall live birth rate per patient stood at 24%. These results further substantiate the clinical viability of MST in addressing severe cases of infertility related to oocyte quality[35]. Misyura *et al* also reported encouraging clinical outcomes for patients with AMA and DOR using MRT techniques. The clinical pregnancy rates were 56.9% for PNT and 52.2% for MST, while ongoing pregnancy rates reached 60% and 55%, respectively. Notably, the live birth rate (at ≥ 37 weeks gestation) was 44% in the PNT group and 40% in the MST group. Genetic validation confirmed that all offspring possessed nuclear DNA matching the intended parents. Furthermore, the mtDNA analysis revealed an average match rate of 89.51% with the donor, confirming successful mitochondrial replacement with minimal carryover from the recipient[6].

Furthermore, Morimoto *et al* conducted a study using autologous mitochondrial transfer derived from ovarian stem cells (OSCs) in 52 patients with a history of recurrent IVF failure. Their findings reported the birth of 13 healthy babies, achieving a live birth rate of 17.5%[26].

3.3.3. Safety considerations and potential risks: Heteroplasmy, nuclear–mitochondrial incompatibility, and congenital anomalies

MRT remains subject to several safety concerns and potential biological risks:

3.3.3.1. Heteroplasmy and reversion

A primary concern in MRT is heteroplasmy, the coexistence of maternal and donor derived mtDNA. While initial maternal carryover is typically minimal (often $<0.5\%$), studies on embryonic stem cells suggest that donor mtDNA may be gradually replaced over time by maternal haplotypes. This phenomenon, often referred

to as reversion, occurs because maternal mtDNA may be more functionally compatible with the recipient's nuclear DNA[17]. In the study by Misyura *et al* average heteroplasmy levels reached 9.21%, indicating potential mtDNA instability[6]. If heteroplasmy exceeds specific biological thresholds, there is a theoretical risk that mitochondrial disease could manifest in the offspring. In addition, sequencing of a study confirmed minimal maternal mtDNA carryover ($<1\%$ heteroplasmy) in all blastocysts from MST cycles that led to live births. This high degree of mitochondrial purity was consistently observed in five of the six established pregnancies; heteroplasmy levels in amniotic fluid and various neonatal tissues such as cord blood and saliva remained below the 1% threshold. Notably, mtDNA sequencing for one child identified a combination of donor and maternal haplotypes, indicating a degree of heteroplasmy[35].

3.3.3.2. Mitonuclear incompatibility

A significant consideration in MRT is the potential discordance between the recipient's nuclear DNA and the donor's mitochondrial DNA, which could theoretically impair cellular homeostasis. Nevertheless, longitudinal studies in rhesus macaques utilizing MST with mismatched mitochondrial haplotypes have demonstrated unremarkable growth, health, and reproductive development. These findings indicate that mitonuclear compatibility is likely maintainable across intra-species haplotypes, assuming maternal mtDNA carryover is kept to a minimum[38].

3.3.3.3. Congenital anomalies

Cytoplasmic transfer (CT), formerly employed to improve oocyte quality in patients with AMA, has been associated with elevated risks of chromosomal abnormalities and developmental disorders. Out of approximately 30 live births resulting from CT, incidences of Turner syndrome and autism spectrum disorders were recorded, prompting the U.S. FDA to suspend the procedure in 2001[39]. Conversely, refined MRT, such as PNT and MST, have demonstrated favorable safety profiles in animal models and preliminary human trials. These methods show no significant increase in chromosomal anomalies or systemic toxicity, with preclinical data suggesting a high degree of safety[40]. Nonetheless, experts underscore that longitudinal, large scale follow up of MRT conceived offspring remains imperative to fully validate its safety before widespread clinical implementation.

3.3.3.4. Chemical exposure risks

MRT procedures, specifically MST and PNT, necessitate the use of specialized reagents to ensure technical success. These include the HVJ-E (Sendai virus envelope) for facilitating karyoplast cytoplasm fusion, and cytoskeletal inhibitors and notably cytochalasin B and nocodazole to stabilize nuclear manipulation[39]. However, recent

evidence suggests that elevated concentrations of HVJ-E may compromise blastocyst quality and exacerbate oxidative stress. To address these concerns, alternative approaches such as pressure-assisted fusion are being explored; these methods aim to mitigate chemical-induced risks while maintaining high fusion efficiency[41].

3.3.4. Long term follow up outcomes

The assessment of long term health outcomes for MRT conceived offspring remains the most critical frontier in reproductive medicine. While initial clinical reports such as the first live birth *via* MST showed no immediate developmental concerns, the complexity of mitonuclear interactions necessitates decades of surveillance[18]. Potential risks that require longitudinal monitoring include mitochondrial carryover, where a small percentage of maternal mtDNA persists and may potentially revert to dominance—a phenomenon known as reversion. Such a shift could theoretically lead to the late-onset manifestation of mitochondrial diseases[11]. Furthermore, experts emphasize the need to monitor for epigenetic dysregulation and metabolic syndromes, as the manipulation of oocytes and embryos during sensitive developmental windows may influence gene expression patterns in adulthood[42]. Currently, the limited number of human cases means that our understanding of long term safety relies heavily on non-human primate models, which have shown normal growth and behavior, yet underscores the urgent need for a global, standardized registry to track the health, fertility, and multi-generational outcomes of MRT-conceived individuals[38].

3.4. Ethical, legal, and social challenges of mitochondrial replacement therapy

3.4.1. Implications for ontological identity and parental rights

MRT raises a critical ethical debate: whether mtDNA significantly affects the identity or phenotype of the child. Some argue that mtDNA's primary role in cellular energy metabolism limits its influence on personal characteristics such as intelligence, behavior, or physical appearance. However, counterarguments suggest that mtDNA may influence physical performance, reproductive health, aging, and behavior factors that contribute to a person's identity[43]. Furthermore, MRT introduces the concept of a "three-parent baby", where a child inherits nuclear DNA from the biological parents and mtDNA from a donor. This scenario compels a redefinition of biological and legal parenthood, raising sensitive questions regarding individual identity and parental rights[44].

3.4.2. Slippery slope concerns and regulatory boundaries

One of the primary ethical objections to MRT is the "slippery slope" argument. Critics caution that legalizing any form of germline intervention for medical reasons could establish a precedent for

non-therapeutic applications, such as genetic enhancement or reproductive cloning. From this perspective, MRT is viewed as a gateway to "designer babies," where technology is used to select desirable traits rather than merely preventing disease[9]. However, practical experience suggests that these risks can be effectively managed through robust legal oversight. Instead of a total ban, clear and stringent regulations can create a functional barrier between medical necessity and elective enhancement. The regulatory frameworks in the United Kingdom and Australia serve as successful models; they demonstrate that well-defined legislation can facilitate the therapeutic benefits of MRT while strictly preventing the extension of genetic technologies into unethical territories[45].

3.4.3. Social acceptance and informed consent

A fundamental challenge in the discourse surrounding MRT involves a complex risk-benefit calculus. Beyond preventing hereditary disorders, there is growing interest in the application of MRT for AMA and DOR patients due to poor oocyte quality. In these cases, MRT acts as a form of oocyte rejuvenation, where healthy donor mitochondria compensate for the age-related bioenergetic decline of the maternal oocytes. For women facing age-related infertility, MRT offers a unique opportunity to preserve genetic maternity, providing an alternative to traditional oocyte donation where the maternal genetic link is entirely severed. However, this expansion into fertility enhancement rather than pure disease prevention intensifies ethical scrutiny. Critics argue that using MRT for infertility rather than to avoid lethal mitochondrial diseases may push the technology toward the commercialization of reproduction. Consequently, social acceptance remains contingent on whether the principle of beneficence applies equally to subfertility. Experts conclude that under stringent regulatory oversight, the ethical legitimacy of MRT can be maintained if the informed consent process clearly distinguishes between its life-saving therapeutic functions and its role in enhancing reproductive success for aging populations[4,9].

3.5. Mitochondrial replacement therapy: Current status and gaps in Vietnam

3.5.1. Statistics on infertility, DOR, and AMA

Vietnam is currently grappling with a substantial infertility burden, affecting approximately 7.7% of reproductive-age couples, equivalent to an estimated 700 000 to 1 million couples. A concerning trend within this demographic is that nearly 50% of these cases involve individuals under the age of 30. This issue is compounded by shifting social dynamics in major urban centers like Hanoi and Ho Chi Minh, where delayed marriage has led to a rise in the average age of conception. Consequently, there is an increasing

number of women seeking fertility treatment at an advanced maternal age and experiencing declining oocyte quality[7]. While comprehensive national data remain limited, the recent significant number of international publications suggest a growing prevalence of patients undergoing IVF who present with both AMA and DOR[46–52]. These local trends align with global concerns regarding reproductive longevity; for instance, the worldwide prevalence of premature ovarian insufficiency (POI/POF) in women under 40 is estimated at approximately 3.7%[53].

3.5.2. Current legal framework on assisted reproduction and germline modification

The regulatory environment for ART in Vietnam is governed by an updated legal framework, primarily Decree No. 207/2025/ND-CP and Circular No. 38/2025/TT-BYT, which standardize clinical infrastructure, specialized equipment, medical staffing requirements, and other relevant provisions. Under the 2014 Law on Marriage and Family, children conceived *via* ART do not establish legal parental relationships with gamete or embryo donors. Despite these advancements in reproductive law, human germline genome editing remains strictly prohibited due to bioethical standards. To contextualize this strictness, Vietnam's comprehensive biosafety regulations (including the revised Law on Biodiversity and Decree No. 43/2026/ND-CP) have already established mature frameworks for genetically modified organisms (GMOs) across multiple domains, heavily regulating agriculture, food, and contained biopharmaceutical research. In sharp contrast to this progressive stance on industrial GMOs, however, the Ministry of Health has yet to establish specific legal provisions that authorize or define MRT for clinical application, leaving it entirely outside the scope of approved medical practice in Vietnam.

An additional regulatory and ethical challenge relates to donor oocyte procurement. In this regard, Chin *et al* highlighted that extending MRT to women with age-related infertility and poor oocyte quality raises ethical concerns and necessitates rigorous patient counseling to ensure informed consent, stringent regulations governing egg donation, and an appropriate ethical and regulatory framework[54]. These considerations are particularly relevant in Vietnam, where oocyte donation is strictly regulated and permitted only on a voluntary and non-commercial basis. Current regulations require donor screening for genetic disorders, infectious diseases, and conditions that may impair decision-making capacity, while donor anonymity is protected by law. Furthermore, donated oocytes may only be used under specific regulatory conditions to ensure ethical practice. Therefore, any future clinical application of MRT in Vietnam would require careful consideration within the existing legal framework governing oocyte donation and ART.

3.5.3. Clinical trials or research on mitochondrial replacement therapy

To date, no published evidence of ongoing or completed clinical trials investigating MRT for AMA or DOR patients in Vietnam has been identified by the authors. This observation is consistent with searches of the international literature and major Vietnamese medical journals, such as Vietnamese Journal of Obstetrics and Gynecology, Ho Chi Minh City Journal of Medicine, and Vietnam Medical Journal, where no relevant MRT studies were found. Based on the currently available literature, MRT appears to remain at a conceptual or exploratory stage in Vietnam and has not yet been widely reported within formal clinical research programs.

3.5.4. Limitations and future directions

In light of the aforementioned facts, the current situation in Vietnam reveals several substantial limitations. First, there is a notable lack of comprehensive national data on the prevalence of AMA and DOR, despite a burgeoning body of research reflecting the intensifying academic and clinical interest in these patient groups. Second, a significant legal gap persists, as Vietnam has yet to establish a regulatory framework or specific Ministry of Health legislation governing MRT. Finally, there is no evidence of local clinical trials or MRT research specifically targeting the AMA/DOR demographics. These collective challenges pose significant hurdles for policymakers striving to strike a balance between patient needs, scientific advancement, and complex ethical-legal considerations.

Consequently, several future directions may be considered to address these existing challenges. Rather than solely following global developments, Vietnam could benefit from a strategic roadmap focused on two key pillars: first, establishing a national database for AMA and DOR to create a foundation of real-world evidence; and second, modernizing the legal framework to align with international standards, such as the ISSCR (International Society for Stem Cell Research) guidelines. By launching pilot research initiatives under rigorous ethical supervision, Vietnam may be able to evaluate the feasibility and safety of MRT through appropriately regulated research programs. This approach may facilitate the ethical evaluation and potential future application of emerging reproductive technologies while maintaining appropriate regulatory oversight and patient protection.

4. Conclusion

MRT represents an emerging approach in reproductive medicine that may provide a potential strategy to the challenges of AMA and DOR. By addressing the core issue of mitochondrial dysfunction which drives cellular energy depletion and embryonic genetic errors,

techniques such as MST and PNT have demonstrated significant potential in improving outcomes for patients with previously poor prognoses. While using donor material shows high clinical efficacy, autologous strategies using a patient's own stem cell derived mitochondria provide a promising alternative to maintain complete genetic relatedness and bypass the ethical complexities of "three-parent" embryos.

However, MRT remains an investigational procedure globally. Critical safety concerns, particularly mitochondrial "reversion" where a small amount of maternal mtDNA may regain dominance and the long term impact of potential incompatibility between donor and recipient DNA, necessitate rigorous, multi-generational follow up. These biological risks, alongside ethical debates regarding germline manipulation, mean that the technology requires strict regulatory oversight before widespread implementation.

In Vietnam, the rising burden of infertility and delayed childbearing highlight growing interest in novel reproductive technologies. Currently, the country faces significant gaps in national data and lacks a specific regulatory framework to govern MRT. To bridge this gap, a strategic roadmap is essential, focusing on establishing a national database for AMA/DOR and modernizing legal guidelines in alignment with international standards. By initiating pilot research under strict ethical supervision, Vietnam may be able to evaluate the feasibility, safety, and potential role of MRT within its clinical and regulatory context.

Conflict of interest statement

The authors declare that there are no conflict of interest.

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Data availability statement

Not applicable.

Authors' contributions

Van Thanh Ngo and Thanh Luan Nguyen conceptualized and

coordinated the study. All authors performed the literature search, drafted, and critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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