

EDITORIAL

New challenges in *in vitro* fertilization and assisted reproductive technology: Genetic and epigenetic modificationsJacek Z. Kubiak^{1,2*}¹Institute of Genetics and Development of Rennes, UMR 6290 CNRS/University of Rennes, Faculty of Medicine, Rennes, France²Laboratory of Molecular Oncology and Innovative Therapies, Military Institute of Medicine-National Research Institute (WIM-PIB), Szaserow 128, Warszawa, Poland

Since the birth of the first *in vitro* fertilization (IVF) child in 1978, assisted reproductive technologies (ARTs) have evolved from a single, relatively straightforward procedure into a broad toolkit of interventions. They are capable of manipulating gametes and embryos at increasingly fine molecular resolution. Two recent developments illustrate both how far this evolution has progressed, and how far ahead of regulatory and scientific consensus it now runs. The first concerns direct genetic modification at the level of mitochondrial DNA (mtDNA), where fertility clinics are offering unproven interventions outside the context of disease prevention. The second concerns a subtler, but no less consequential, layer of risk: the epigenetic reprogramming of offspring that can result from the embryo culture and transfer procedures inherent to ART itself. Together, these two threads, the first genetic, the second epigenetic, define the emerging ethical and scientific frontier of reproductive medicine.

The genetic dimension of this emerging frontier is exemplified by the uncontrolled expansion of mitochondrial replacement therapy (MRT). Originally developed and validated as a means of preventing mothers with disease-causing mtDNA mutations from transmitting them to their children, MRT uses techniques such as maternal spindle transfer and pronuclear transfer to combine the nuclear genome of the future parents with mitochondria of a donor egg.¹⁻³ The first MRT-conceived child was born in 2016.⁴ Since then, it has been demonstrated that the technique involving transfer of the nuclear genome from an oocyte or embryo into an enucleated donor oocyte carrying healthy mitochondria could produce healthy babies free of maternal mitochondrial disease, though with some residual mtDNA carryover in a subset of children that researchers are continuing to monitor.³ This success, however, has opened the door to a far more contentious application: marketing MRT to a broader population of IVF patients, particularly older women, as a general fertility enhancer rather than a disease-prevention tool.⁵

According to recent investigative reporting, clinics in several countries are now advertising MRT, sometimes euphemistically as “oocyte rejuvenation,” on the premise that mitochondria from young egg donors can restore the developmental competence of aging oocytes. The scientific basis for this claim remains uncertain. Only a handful of small, uncontrolled studies have examined MRT specifically as an infertility treatment. It includes a 25-patient study with no control arm.⁶ Researchers who have reviewed the available clinic data describe the evidence as insufficient to justify commercial use. Prominent reproductive biologists have gone further, arguing that there is no established mechanistic rationale linking oocyte mitochondrial content to age-related infertility, and

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that the practice of charging patients, usually desperate for a viable pregnancy, for an experimental procedure is ethically suspicious. This situation exemplifies a broader challenge in the genetic dimension of ART. Indeed, techniques validated for one narrow, well-characterized indication can be rapidly repurposed and commercialized well ahead of the evidence needed to support their expanded use, blurring the line between legitimate innovation and unregulated experimentation on the human germline.⁵ This tension recalls the parallel controversy over nuclear-genome base editing of human embryos, another genetic intervention whose clinical readiness remains far more disturbing to the general public.⁷

While mitochondrial replacement raises questions about deliberate genetic intervention, the epigenetic dimension of ART presents a second, more pervasive concern: the unintended epigenetic consequences of standard ART procedures themselves, e.g., embryo culture, embryo transfer, and the early postnatal environment, even in the absence of any genetic manipulation. This concern is not merely theoretical. A systematic review and meta-analysis of children conceived by IVF/intracytoplasmic sperm injection (ICSI) found an increased incidence of imprinting disorders and altered DNA methylation compared with spontaneously conceived children.⁸ Later work has linked ART specifically to an elevated risk of epimutation-mediated imprinting disorders in mothers aged 30 and above.⁹ Moreover, this is the age range of women targeted by MRT marketing discussed above. A recent study in mice (which I co-authored) provides an instructive model for how such effects can arise mechanistically.¹⁰ Using two genetically divergent mouse lines selected for high or low stress-induced analgesia, we performed reciprocal embryo transfer and cross-fostering to shed more light on the relative contributions of prenatal (uterine) vs. early postnatal (maternal care) environments to offspring physiology.

The results showed that both the prenatal and early postnatal maternal environments significantly shaped offspring phenotype, including body weight, body temperature, and pain-related stress responses. These traits shifted toward the values characteristic of the surrogate or foster mothers' lines rather than those of the biological parents. Notably, embryo transfer produced effects that persisted into the second filial generation, whereas cross-fostering effects did not.¹⁰ It suggested that the prenatal environment exerts a more durable, potentially heritable programming influence than the postnatal one. This finding aligns with the developmental origins of health and disease hypothesis, which holds that early-life environmental exposures, including the artificial conditions of *in vitro*

embryo culture and non-biological gestational carriage, can leave lasting epigenetic marks that shape adult physiology and, in some cases, propagate across generations.¹¹⁻¹³ One plausible mechanistic basis for such effects is that standard *in vitro* culture media lack sufficient methyl-donor supply and antioxidant protection during the very window in which genomic imprints are established and maintained, leaving the embryo more vulnerable to methylation errors than it would be *in vivo*.^{14,15}

Translated to the human clinical context, this animal model underscores a concern that has accompanied ART since its earliest applications: children conceived via IVF are gestated in physiological conditions that differ, sometimes substantially, from natural conception, and these differences may leave an epigenetic signature independent of any genetic change to the embryo itself. Unlike direct genome editing, these effects are diffuse, difficult to detect prospectively, and may only become apparent in longitudinal cohort studies spanning decades. Difficulties in detection of such potential troubles are reinforced by reports that ART-associated methylation defects remain inconsistently replicated across human cohort studies, likely owing to population heterogeneity and limited epigenomic coverage in earlier work.

The genetic and epigenetic challenges facing IVF and ART, though mechanistically distinct, share a common structural problem: both involve technologies whose safety and efficacy profiles are still being established, yet which are being deliberately or incidentally applied to populations broader than those for which they were originally validated. In the case of MRT, this manifests as premature commercialization of a genetically invasive procedure for an indication lacking robust supporting evidence. In the case of routine ART procedures, it manifests as an underappreciated background risk of epigenetic dysregulation inherent to the technology itself, revealed only through careful animal modeling of prenatal vs. postnatal environmental contributions.

Addressing both challenges will require closer alignment between clinical practice and the pace of rigorous evidence generation: mandatory trial-based evaluation before novel genetic interventions are offered commercially, and continued long-term, multigenerational follow-up, in both animal models and human ART cohorts, to characterize the epigenetic footprint of assisted reproduction. As ART techniques continue to diversify, the central task of the field is not merely technical refinement, but ensuring that innovation in the genetic and epigenetic manipulation of human reproduction does not overtake the evidence needed to use it responsibly.

Conflict of interest

Jacek Z. Kubiak serves as one of the Editors-in-Chief of this journal. The author declares no competing interests related to this editorial.

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