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Title	Mitochondrial replacement techniques and Mexico's rule of law : on the legality of the first maternal spindle transfer case
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Citation	Journal of law and the biosciences, 4(2), 384-390 https://doi.org/10.1093/jlb/lsx015
Issue Date	2017-05-09
Doc URL	https://hdl.handle.net/2115/68152
Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	lsx015-1.pdf

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Journal of Law and the Biosciences, 384–390
doi:10.1093/jlb/lsx015
Advance Access Publication 9 May 2017
Peer Commentary

Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case

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In 2016, a group led by Dr. John Zhang, New Hope Fertility Center New York city, briefly reported translational research on a type of mitochondrial replacement technique (MRT), resulting in a childbirth in Mexico at the American Society for Reproductive Medicine (ASRM) meeting.[1] Regarding the first clinical use of experimental MRT (specifically, spindle nuclear transfer: SNT), César Palacios-González and María de Jesús Medina-Arellano[2] conducted an in-depth legal study, pointing out the possibility that those involved in the SNT broke the Regulations of the General Health Law on Health Research 1987[3] (the Regulations).

Palacios-González and Medina-Arellano asserted that Zhang et al. violated the Regulations primarily because the SNT research was implemented in order to prevent maternal transmission of a mitochondrial disease to offspring, which can hardly be interpreted as admissible research 'to solve sterility problems that could not be otherwise solved',[4] as stipulated in the Regulations. Although the authors appear to have effectively accused Zhang et al. of regulatory violation, the scientists might offer a counterargument against the authors. More importantly, the authors' legal interpretation

[1] John Zhang et al., *First Live Birth Using Human Oocytes Reconstituted by Spindle Nuclear Transfer for Mitochondrial DNA Mutation Causing Leigh Syndrome*, 106 FERTIL. STERIL. e375–6 (2016). DOI: 10.1016/j.fertnstert.2016.08.004.

[2] César Palacios-González & María de Jesús Medina-Arellano, *Mitochondrial Replacement Techniques and Mexico's Rule of Law: On the Legality of the First Maternal Spindle Transfer Case*, J. LAW BIOSCI. (2017). doi:10.1093/jlb/lsw065.

[3] CÁMARA DE DIPUTADOS DEL H. CONGRESO DE LA UNIÓN, REGLAMENTO DE LA LEY GENERAL DE SALUD EN MATERIA DE INVESTIGACIÓN PARA LA SALUD (1987), http://www.diputados.gob.mx/LeyesBiblio/regley/Reg_LGS_MIS.pdf (accessed Mar. 27, 2017).

[4] *Id.* See Article 56.

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paradoxically suggests that research on experimental SNT will be admissible to solve 'sterility problems' at fertility clinics in Mexico.

The present commentary first considers possible counterarguments to the judgment by the two authors. It then discusses some legal and social implications of MRTs for infertility treatment, indicating the potential for reproductive tourism suggesting that MRTs may be a last resort for treating intractable female infertility.

MITOCHONDRIAL REPLACEMENT TECHNIQUES

A small cellular organelle, the mitochondrion, is characterized by its own genome (termed mtDNA) and energy production and prevention of deleterious free radical production through cellular respiration. Although the vast majority of mitochondrial proteins are encoded by the nuclear genome, some subunits of respiratory chain complexes in the organelle are derived from its own mtDNA.[5] Thus, the mitochondrial functions are coordinately exerted by the precision molecular apparatus formed through the gene expression from the dual genomes. The human egg is abundant in mitochondria and contains 200,000–300,000 copies of mtDNA per cell. Meanwhile, the paternal mitochondria in sperm cells are specifically degraded after fertilization.[6] Therefore, mtDNA is maternally inherited in children, forming at least 30 mtDNA haplogroups.[7] Some mtDNA mutations in eggs can cause infertility, miscarriage, or mitochondrial diseases in the resultant children.[8]

In 2015, the UK became the first jurisdiction to permit the clinical use of two types of MRTs: SNT and pronuclear transfer (PNT), in order to prevent the maternal transmission of serious mitochondrial diseases to offspring.[9] To reduce the prevalence of aberrant mitochondrial with mutated mtDNA in eggs, both MRTs employ the transfer of a karyoplast: a cellular nucleus (or nuclei) with a small amount of cytoplasm containing mitochondria.[10] In SNT, a karyoplast derived from a wife's egg is transferred to an enucleated egg from a donor, which is then fertilized using the husband's sperm cell. In PNT, a karyoplast containing two pronuclei from a fertilized egg derived from a couple is transferred to an enucleated fertilized egg created using a donor egg. Therefore, both MRTs involve karyoplast transfer and egg donation. Of particular note, karyoplast transfer only reduces the prevalence of aberrant mitochondria having mutated mtDNA in eggs, although the term 'MRT' denotes the replacement of mitochondria. Additionally, recent studies have suggested the importance of matching nuclear DNA and mtDNA in MRTs by considering mtDNA haplogroups.[11]

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5 Tetsuya Ishii, *Mitochondrial Manipulation for Infertility Treatment and Disease Prevention*, in HUMAN REPRODUCTION: UPDATES AND NEW HORIZONS. 206–9 (Heide Schatten ed., 2016).

6 *Id.* at 209.

7 For example, Mannis van Oven & Manfred Kayser, *Updated Comprehensive Phylogenetic Tree of Global Human Mitochondrial DNA Variation*, 30 HUM. MUTAT. e386–94 (2009).

8 See Hide Schatten et al., *The Impact of Mitochondrial Function/Dysfunction on IVF and New Treatment Possibilities for Infertility*, 12 REPROD. BIOL. ENDOCRINOL. 111 (2014).

9 Palacios-González & Medina-Arellano, *supra* note 2, at 2.

10 Ishii, *supra* note 5, at 218–220.

11 For example, Louise A Hyslop et al., *Towards Clinical Application of Pronuclear Transfer to Prevent Mitochondrial DNA Disease*, 534 NATURE 383–6 (2016); Mitsutoshi Yamada et al., *Genetic Drift Can Compromise Mitochondrial Replacement by Nuclear Transfer in Human Oocytes*, 18 CELL STEM CELL 749–54 (2016).

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POSSIBLE COUNTERARGUMENTS

According to the abstract by Zhang et al., SNT was employed for a Jordanian woman with an mtDNA mutation that might cause the mitochondrial disease, Leigh syndrome in her children. Indeed, two of her children had already died due to the syndrome.[12] After SNT, one resultant embryo was selected and transferred to her uterus, resulting in the birth of a healthy boy. The boy was followed up for 3 months after birth, and the average level of transmitted mother's mtDNA was less than approximately 2% in the baby's tissues.[13] Such results appeared indicative of the clinical success of SNT, at least at the time of the ASRM meeting.

Palacios-González and Medina-Arellano deliberately analyzed a wide range of Mexican regulations, including the Federal Constitution, federal laws, relevant regulations, and regional rules. They clarified that Mexico has no federal laws pertinent to human genome modification or specific to assisted reproduction. The authors then found that Article 314, chapter VIII of the General Health Law 1984 (the Law) defines a human embryo as 'the product of conception from the moment of it'.[14] They also addressed that Article 330, chapter II of the Law forbids the research use of human embryos (if viewed as 'the product of induced abortions').[15] Although PNT requires the creation and destruction of human embryos, Zhang's group employed SNT which does not require human embryo for MRT.

Eventually, they reached the Regulations and noted two insightful findings to consider when judging the legality of SNT in Mexico. The Article 56 stipulates that

> Research on assisted fertilization will only be admissible when it is applied to solve sterility problems that cannot be solved otherwise, respecting the couple's moral, cultural, and social point of view, even if these differ from those of the researcher.[16]

First, the authors judged that clinical research involving SNT for helping fertile women that have children without Leigh syndrome would violate Article 56 because the SNT research was not intended 'to solve sterility problems that cannot be solved otherwise'. Their assertion is based on the fact that the woman enrolled in SNT research could get pregnant and deliver a live baby.

Second, they also asserted that Article 101 of the Law could apply to the violation of Article 56 of the Regulations, referencing the Article 101 that persons carrying out research on human beings in contravention of this law or other applicable provisions (in this case, the Regulations) are subject to sanctions. This is also based on the fact that the woman had experienced pregnancies, suggesting that SNT research possesses a central human element. Therefore, the two assertions depend on the premise that the enrolled woman had no 'sterility problems'.

I infer that Zhang et al. can offer some counterarguments against this judgment by Palacios-González and Medina-Arellano from both legal and clinical standpoints. First,

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12 See the ASRM abstract by John Zhang et al.

13 *Id.*

14 Palacios-González & Medina-Arellano, *supra* note 2, at 12. See also the General Health Law 1984.

15 *Id.*

16 *Id.*

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the scientists could rebut the accused violation of Article 56 of the Regulations, by indicating that there is no legal definition of 'sterility' in the Regulations or the Law.[17]

Next, the researchers could explain sterility using a textbook of obstetrics and gynecology as follows:

> After 18 months of unprotected sexual intercourse, the remaining couples have a low monthly conception rate without treatment, and many may have absolute defects preventing fertility (sterility).[18]

The researchers could emphasize that sterility is a state of difficulty in conceiving, which cannot be defined based solely on pregnancy and delivery. In addition, they could bring up the medical history that the woman 'had four pregnancy losses and two deceased children at age 8 months and 6 years'.[19] Pregnancy loss implies miscarriage. It is true that she was able to become pregnant at least seven times; however, researchers would have diagnosed her as having had 'sterility problems' at certain times in her medical history, suggesting that the SNT research can be viewed as 'research on assisted fertilization to solve sterility problems'.

In addition, they can explain that the condition cannot be solved otherwise because preimplantation genetic diagnosis is not effective due the high mutation load (>95% mutation load[20]). They could also assert that they respected 'the couple's moral, cultural, and social point of view' in the SNT research, as the Jordanian couple wished to undergo SNT rather than PNT 'for religious reasons'.[21]

Furthermore, the researchers are also likely to point out that their SNT research conformed to Article 47 of the Regulations which stipulates that

> 'Research in pregnant women, with therapeutic benefit related to pregnancy, shall be permitted when they are aimed at increasing the viability of the fetus, with minimal risk to the pregnant woman.'

Because miscarriage frequently occurs in women having eggs with the mutated mtDNA responsible for Leigh syndrome,[22] the SNT research can potentially increase the viability of the fetus and prevent miscarriage during pregnancy. Indeed, in the abstract in question, the woman delivered a healthy boy.

This commentator further addresses the legality of egg donation required for SNT research in Mexico, which Palacios-González and Medina-Arellano did not discuss in their analysis. There are no specific constraints regarding egg donation in the Law or the Regulations.[23]

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[17] In the Law, the word, 'esterilidad' (sterility in English) appears once at Article 231, without showing the definition. In the Regulations, the word, 'esterilidad' also appears once at Article 56, again, without the definition.

[18] Neville Hacker, Joseph Gambone & Calvin Hobel, Hacker and Moore's Essentials of Obstetrics and Gynecology (5th ed., Saunders Elsevier, 2009).

[19] See the ASRM abstract by John Zhang et al.

[20] *Id.*

[21] *Id.*

[22] For example, Sarah L. White et al., *Genetic Counseling and Prenatal Diagnosis for the Mitochondrial DNA Mutations at Nucleotide 8993*, 65 Am. J. Hum. Genet. 474–82 (1999).

[23] I surveyed articles relevant to the donation of human egg for research or reproduction. The word, 'óvulo' (ovum in English) appears only in Article 40, chapter IV of the Regulations to define the words of pregnancy and

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Taken together, although Palacios-González and Medina-Arellano highlighted the possibility of regulatory violation in the first clinical use of SNT in Mexico, the scientists may offer several counterarguments against their claims.

LEGAL AND SOCIAL IMPLICATIONS OF MRTS FOR INFERTILITY TREATMENT

Paradoxically, the judgment by the authors also suggested that SNT may be permissible for treating intractable infertility in Mexico. The website of New Hope Fertility Center New York, at which Dr. Zhang has served as the medical director, introduces the international network comprising New Hope Fertility Center NY, Mexico, and Beijing (China).[24] It is worth considering regulations that are relevant to MRTs in the USA and China.

Currently, it is legally impossible to obtain regulatory approval to perform MRTs at US clinics due to an appropriation bill rider, the Consolidated Appropriations Act 2016 Sec. 749.[25]

Next, we should consider relevant regulations in China. Dr. Zhang and colleagues performed PNT for the first time in the world to treat an unexplained infertility case in China, and reported the results at ASRM meeting 2003.[26] Although they positively reported that they conducted PNT and attained a triplet pregnancy in a patient in whom embryos had been all arrested after two in vitro fertilization (IVF) cycles, the pregnancy eventually resulted in no live births: the remaining two fetuses died after one was reduced. Subsequently, PNT research incurred regulatory interventions in China.[27] As a result, the Ministry of Health enacted the guidelines regarding assisted reproduction in 2003, prohibiting cytoplasmic transfer, nuclear transfer, and manipulation of the genes in human gametes, zygotes, or embryos to treat infertility.[28] The guidelines explicitly prohibit SNT as well as PNT in China because such MRTs transfer a nucleus (or nuclei) and cytoplasm to human germline.

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embryo. However, I found no articles specifically addressing the donation of human ovum (egg) in the Regulations and the Law.

24 See the website of New Hope Fertility Center NY: http://www.newhopefertility.com/contact/international/ (accessed Mar. 27, 2017).

25 Palacios-González & Medina-Arellano, *supra* note 2, at 2–3.

26 See two reports: John Zhang et al., *Pregnancy Derived from Human Nuclear Transfer*, 80 FERTIL. STERIL. e56 (2003). http://dx.doi.org/10.1016/S0015-0282(03)01953-8 (accessed Mar. 27, 2017); John Zhang et al., *Pregnancy Derived from Human Zygote Pronuclear Transfer in a Patient who had Arrested Embryos after IVF*, 33 REPROD. BIOMED. ONLINE 529–33 (2016).

27 For example, Tetsuya Ishii, *Germline Genome-editing Research and its Socioethical Implications*, 21 TRENDS. MOL. MED. 473–81 (2015).

28 See The Ministry of Health: The Human Assisted Reproductive Technology Specifications and the Human Assisted Reproductive Technology and Human Sperm Bank Ethical Principles. http://www.moh.gov.cn/mohbgt/pw10303/200804/18593.shtml (accessed Mar. 27, 2017). The Specifications 'prohibit the implementation of human oocyte-cytoplasmic transplantation and nuclear transfer techniques for the purpose of infertility treatment' by Article 7 and 'prohibit genetically manipulating human gametes, zygotes and embryos for the purpose of reproduction' by Article 9, Chapter 3. The Ethical Principles also stipulates that 'Medical personnel should not implement human oocyte-cytoplasmic transplantation and human oocyte-nuclear transplantation for the purpose of infertility treatment because the safety issues of human oocyte-cytoplasmic transplantation and human oocyte-nuclear transfer still remain unsolved' by 7, Article 3, Chapter 1.

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However, history is likely to repeat itself. The website of New Hope Fertility Center NY has already advertised SNT, termed 'Human Egg Rejuvenation (H.E.R.) IVF'.[29] Although the website explains that the primary use of H.E.R. IVF is to prevent the inheritance of mitochondrial diseases in offspring, it also suggests that 'other applications will be discussed in the future'. 'Other applications' will be likely to include infertility treatment in specific cases where there are no alternatives after IVF and preimplantation genetic screening fail, which may fall under 'when it is applied to solve sterility problems that cannot be solved otherwise' in Article 56 of the Regulations in Mexico. The future application of SNT can therefore assume a scenario that infertile patients in the USA and China would be invited to New Hope Fertility Center Mexico where SNT is legally provided.

More recently, a news report stated that a group led by Dr. Valery Zukin at a Ukrainian clinic used PNT for infertility treatment.[30] The PNT research resulted in two different pregnancies, which is similar to the case of PNT in China 2003. In 2017, one of the pregnancies led to a live birth. To my knowledge, there are no regulations relevant to human germline modification in Ukraine.[31] Thus, MRTs will be likely to emerge and prevail in reproductive tourisms.

CONCLUSION

Before the UK lifted the prohibition of MRTs in 2015, some had alerted that the legalization of MRTs for preventing mitochondrial diseases in the UK may encourage the initiation of MRTs for other purposes, including infertility treatment and the building of a genetic link among a lesbian couple and the children, in other countries.[32]

Although IVF involving egg donation may be effective in treating some female infertilities, some infertile women will view MRTs as a last resort for treating intractable infertility while maintaining genetic relatedness with their prospective children. However, the use of experimental MRTs for infertility treatment, which will likely promote its widespread use, is currently unjustifiable due to the potential health risks to fetuses (or offspring), as illustrated by the adverse event following PNT in China 2003.

Likewise the UK legalization, MRTs for preventing serious mitochondrial diseases could be permissible if the risk-benefit ratio in the prospective child is considered appropriate in a country. Regardless, MRTs should be appropriately regulated and gradually integrated into society due to their unknown risks associated with heteroplasmy or mismatching between nuclear DNA and mtDNA because of the different mtDNA haplogroups. Of particular note, Zhang et al. recently published their SNT research in a

[29] See the website of New Hope Fertility Center NY: http://www.newhopefertility.com/her-ivf-3-parent/ (accessed Mar. 27, 2017).

[30] See Andy Coghlan, *First Baby Born Using 3-parent Technique to Treat Infertility,* New Scientists, January 18, 2017. https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/ (accessed Mar. 27, 2017).

[31] See the Fundamentals of the Legislation of Ukraine on Health care 1992: http://www.moz.gov.ua/ua/portal/zn_19921119_2801.html (accessed Mar. 27, 2017), and the Ministry of Health Order No. 771 'the Instruction on Procedures for Assisted Reproductive Technologies' 2008: http://zakon2.rada.gov.ua/laws/show/z0263-09 (accessed Mar. 27, 2017). The Order No. 771 allows even anonymous females to donate eggs for reproduction if they are healthy and at the age of 20 to 32 by Article 5 and 6, Chapter 5.

[32] For example, Tetsuya Ishii, *Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification*, 29 Reprod. Biomed. Online 150–5 (2014); Françoise Baylis, *The Ethics of Creating Children with Three Genetic Parents*, 26 Reprod. Biomed. Online 531–4 (2013).

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peer-reviewed journal. However, the case report confessed that mtDNA haplogroup of the egg donor (L2c) was different from that of the patient (I) in the SNT.[33] Meanwhile, Dr. Zukin et al. have not yet published peer-reviewed articles regarding their MRT research in Ukraine.

Despite possible counterarguments, the comprehensive analysis on the legality of MRTs in Mexico by Palacios-González and Medina-Arellano will likely stimulate discussion regarding the appropriate regulation of MRTs in other countries.

[33] John Zhang et al., *Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease*, 34 Reprod. Biomed. Online 361–8 (2017).

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