



Author's response to peer commentaries: Mexico's rule of law and MRTs

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We would like to thank Rebecca Dimond and Atina Krajewska,¹ Sandra González-Santos,² and Tetsuya Ishii³ for their thoughtful comments on our article.⁴ Here we will reply to their comments while at the same time we provide further clarificatory notes regarding what transpired in Mexico, in relation to the use of mitochondrial replacement techniques (MRTs).

WHAT'S IN A NAME?

MRTs are new reproductive techniques where the nuclear DNA of an egg, or zygote, that was housed in a cell with deleteriously mutated mitochondria is transferred to a donated enucleated egg, or zygote, that possesses healthy mitochondria.⁵ The term MRTs has been used to refer to two techniques: pronuclear transfer and maternal spindle transfer. In her commentary, from a science and technology studies perspective, González-Santos criticizes the use of this term. She argues that using it 'helps silence each technique's particular history, intended purpose, and technological and biological implications; it inaccurately suggests that what is being replaced is the mitochondria,

¹ Rebecca Dimond & Atina Krajewska, *Comment on MRT and the birth of the 'first,'* J. L. BIOSCI. 1–9 (2017).

² Sandra González-Santos, *Shifting the Focus on the Legality of the First Maternal Spindle Transfer Case*, J. L. BIOSCI. 1–5 (2017).

³ Tetsuya Ishii, *Mitochondrial Replacement Techniques and Mexico's Rule of Law: On the Legality of the First Maternal Spindle Transfer Case*, J. L. BIOSCI. 384–390 (2017).

⁴ 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*, 4 J. L. BIOSCI. 50–69 (2017).

⁵ For a detailed account of what are MRTs, see *Id.*

and it fails to highlight that the mitochondria are not the only thing involved'.⁶ She also criticizes the alternative term 'nuclear transfer' since it, just as MRTs, also blurs the role played by the oocyte provider.⁷ We agree with González-Santos in that the term MRTs is problematic—one of us has elaborated on this topic⁸—and we find it puzzling that in her comment she did not propose an alternative way of naming these techniques, independently and jointly, that addresses the issues that she so clearly pointed out.

DEVELOPMENTS IN MRTs

Three relevant things have happened since in September⁹ last year the news broke about the first baby born after an MRT procedure:

- i. John Zhang and his team published a paper about their experiment, and a critical editorial was published alongside it.¹⁰
- ii. MRTs have been used in order to aid an infertile couple, whose infertility was not related to a mitochondrial DNA disease, to have a genetically related child.¹¹
- iii. Zhang has set up a company to provide assisted reproductive services that might include MRTs.¹²

Some of the details provided in the editorial that accompanied Zhang's paper are important for our discussion of the legality of the first maternal spindle transfer case, specifically the details concerning where the MRT and embryo transfer took place:

⁶ González-Santos, *supra* note 2 at 5.

⁷ For similar arguments, see Stuart A. Newman, *Deceptive Labeling of a Radical Embryo Construction Technique*, THE HUFFINGTON POST (2014), http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r.b_6213320.html (accessed July 20, 2016); Françoise Baylis, *The Ethics of Creating Children With Three Genetic Parents*, 26 REPROD. BIOMED. ONLINE 531–534 (2013); Françoise Baylis, *Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush*, 31 BIOETHICS 7–19 (2017); Vardit Ravitsky, Stanislav Birko & Raphaëlle Dupras-Leduc, *The 'Three-Parent Baby': A Case Study of How Language Frames the Ethical Debate Regarding an Emerging Technology*, 15 AM. J. BIOETHICS 57–60 (2015); Stuart A. Newman, *FDA Asked to Approve Creation of Genetically Modified Children*, THE HUFFINGTON POST (2014), http://www.huffingtonpost.com/stuart-a-newman/fda-asked-to-approve-crea.b_4809876.html (accessed Sept. 18, 2016); Ainsley J. Newson & Anthony Wrigley, *Is Mitochondrial Donation Germ-Line Gene Therapy? Classifications and Ethical Implications*, 31 BIOETHICS 55–67 (2017).

⁸ César Palacios-González, *Mitochondrial Replacement Techniques: Egg Donation, Genealogy and Eugenics*, 34 MONASH BIOETHICS REV. 37–51, 40 (2016).

⁹ Jessica Hamzelou, *Exclusive: World's First Baby Born With New '3 Parent' Technique*, NEW SCIENTIST (2016), <https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/> (accessed Oct 3, 2016).

¹⁰ John Zhang et al., *Live Birth Derived From Oocyte Spindle Transfer to Prevent Mitochondrial Disease*, 34 REPROD. BIOMED. ONLINE 361–368 (2017); Mina Alikani et al., *First Birth Following Spindle Transfer for Mitochondrial Replacement Therapy: Hope and Trepidation*, 34 REPROD. BIOMED. ONLINE 333–336 (2017).

¹¹ Peter Dockrill, *World-First in Ukraine as 'Three-Parent' Baby Born to an Infertile Couple*, SCIENCEALERT (2017), <http://www.sciencealert.com/world-first-in-ukraine-as-three-parent-baby-born-to-an-infertile-couple> (accessed July 5, 2017).

¹² Emily Mullin, *The Fertility Doctor Trying to Commercialize Three-Parent Babies*, MIT TECHNOLOGY REVIEW, 2017, <https://www.technologyreview.com/s/608033/the-fertility-doctor-trying-to-commercialize-three-parent-babies/> (accessed June 30, 2017).

[T]he ovarian stimulation cycles and oocyte manipulations were carried out at a private fertility clinic in New York, the vitrified embryo was then shipped to Mexico to be warmed and transferred to the patient at an affiliate clinic in Guadalajara.¹³

When we examined the legality of this case, we did so according to the information that at that time was available to us.^{14,15} At that moment everything pointed toward the fact that the MRT procedure and the embryo transfer took place in Mexico, and thus we concluded that Zhang's team had violated federal regulations on health research, specifically Article 56 of the Regulations of the General Health Law on Health Research (henceforth: the Regulations):

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 points of view, even if these differ from those of the researcher.¹⁶

Now we know that *the MRT procedure took place in the USA* and it seems that this *modus operandi* will not change in the foreseeable future, since Zhang was recently quoted stating this.^{17,18} After these revelations, *we must now rectify our original position*, which departed from a false premise, and assert that Zhang's team did not violate Article 56 of the Regulations. They did not do so given that the MRT procedure happened outside of Mexico. Given this, in what follows we will take the comments by Dimond and Krajewska, and Ishii and interpret them as talking about the overall legality of MRTs in Mexico.

It is important to emphasize that our general assessment of the legality of carrying out MRTs in Mexico still stands. This assessment is relevant at the present time, given that New Hope Fertility Center Mexico's Internal Review Board (IRB) not only approved the transfer of the reconstituted embryo, but also 'approved a general protocol that included spindle transfer, oocyte reconstitution, intra-cytoplasmic sperm injection (ICSI), and preimplantation (sic) genetic screening (PGS)'.¹⁹ This means that the IRB gave Zhang and his team the 'ethical green light' to move ahead with MRTs in their Mexican clinics.

WHO CAN ACCESS MRTs IN MEXICO AT THE MOMENT?

In our paper we provided an answer to the question: How can MRT research be legally carried out in Mexico? We asserted that MRT research would be legal, in principle, if it

¹³ Alikani et al., *supra* note 10, at 333.

¹⁴ Whereas Zhang's paper and the accompanying editorial were published on April 2017, our paper was accepted for final publication on December 2016.

¹⁵ Palacios-González and Medina-Arellano, *supra* note 4, at 51.

¹⁶ 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 July 8, 2017).

¹⁷ In an unpublished paper González-Santos has examined how the language used by Dr Alejandro Chavez Badiola, Medical Director and Founder of New Hope Fertility Center Mexico, during media interviews concealed the fact that the MRT procedure happened in the USA. For example: NOTICIEROS TELEvisa, NACIMIENTO DE BEBÉ CON ADN DE TRES PADRES EN MÉXICO - DESPIERTA CON LORET 1:10/2:00 (2016), <https://www.youtube.com/watch?v=0geikNjh9zI> (accessed Aug. 15, 2017).

¹⁸ Quoted in Mullin, *supra* note 12.

¹⁹ Alikani et al., *supra* note 10, at 333.

aimed at solving sterility problems that could not be solved otherwise. In his commentary on our paper, Ishii finds the above conclusion about the general legality of MRTs in Mexico problematic. He asserts that our 'legal interpretation paradoxically suggests that research on experimental SNT [spindle nuclear transfer] will be admissible to solve 'sterility problems' at fertility clinics in Mexico'.²⁰

Even though we share some of Ishii's worries about the use of MRTs for 'treating' infertility that is not related to mtDNA diseases, we must accept that in terms of the Mexican law MRT research for dealing with *all types* of sterility would be legal if they followed Article 56 of the Regulations. In other words, in Mexico researchers can offer MRTs to women, or couples, when such techniques are aimed at solving sterility problems that cannot not be solved otherwise, regardless of the underlying medical condition.

STERILITY AND THE MEXICAN LAW

The above section tells us that the concept of 'sterility' is of the utmost importance in order to determine who might legally access MRTs in Mexico. Ishii is right in that neither the General Health Law nor the Regulations provide a legal definition of sterility. When we wrote our paper we realized this, and this is why we provided the definition that appears in a clinical guideline of the Mexican Social Security Institute. In this clinical guideline, infertility and sterility are treated as synonyms, and are defined as: 'the failure to achieve clinical pregnancy after 12 months of regular unprotected sexual intercourse'.²¹ In our paper, we interpreted this to mean the *inability to produce and deliver live offspring*, and that once there is a live delivery women should no longer be regarded as sterile. In this sense, we were following the WHO's definition of 'primary infertility':

When a woman is unable to ever bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth she would be classified as having primary infertility. Thus women whose pregnancy spontaneously miscarries, or whose pregnancy results in a still born child, without ever having had a live birth would present with primarily infertility.²²

Ishii, on the other hand, argues that scientists working on MRTs could defend a different understanding of this concept. According to him 'researchers could emphasize that sterility is a state of difficulty in conceiving, which cannot be defined based solely on pregnancy and delivery'.²³ He cites the following textbook definition of sterility to support his case: '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)'.²⁴ From both these quotes, it is reasonable to conclude that Ishii's understanding of this term is close to the WHO's definition

²⁰ Ishii, *supra* note 3 at 384–385.

²¹ INSTITUTO MEXICANO DEL SEGURO SOCIAL, DIAGNÓSTICO DE LA PAREJA INFÉRIL Y TRATAMIENTO CON TÉCNICAS DE BAJA COMPLEJIDAD (2012), <http://www.imss.gob.mx/sites/all/statics/guiasclinicas/621GRR.pdf> (accessed July 8, 2017).

²² World Health Organization, WHO INFERTILITY DEFINITIONS AND TERMINOLOGY WHO (2017), <http://www.who.int/reproductivehealth/topics/infertility/definitions/en/> (accessed July 8, 2017).

²³ Ishii, *supra* note 3 at 387.

²⁴ Quoted in Ishii, *supra* note 3 at 387.

of 'secondary infertility':

When a woman is unable to bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth following either a previous pregnancy or a previous ability to carry a pregnancy to a live birth, she would be classified as having secondary infertility. Thus those who repeatedly spontaneously miscarry or whose pregnancy results in a stillbirth, or following a previous pregnancy or a previous ability to do so, are then not unable to carry a pregnancy to a live birth would present with secondarily infertile.²⁵

In order to provide legal clarity about how the term 'sterility' should be understood, we decided to search the online database of the 'Federal Judicial Weekly' for the concepts 'infertility' and 'sterility'; it is in this publication where the jurisprudences and relevant cases solved out by the Mexican Supreme Court of Justice and federal circuit courts are compiled.²⁶ At present time, there is no jurisprudence or relevant cases where these concepts are *extensively* defined. However, we found three relevant cases from the 1960s (pertaining to the state of Jalisco) where federal circuit courts provided a definition of 'sterility'.²⁷ In all three cases, the courts were solving out disputes of divorce, and in all three of them 'sterility' was simply defined, in women, as the inability to conceive. Although these cases favor our interpretation of 'sterility' over Ishii's one, it is important to note that such a definition is *not legally binding*, but that it should be regarded as a *relevant precedent*.²⁸ Furthermore, the ruling of the Inter-American Court of Human Rights in the case of Artavia Murillo et al. vs. Costa Rica, that is also binding for Mexico,²⁹ defines infertility just as the Mexican Social Security Institute does, thus providing no further clarity on this issue.³⁰ Given how the Mexican law is written at the present time, and these diverging possible understandings of the term 'sterility', we have to conclude that we will have to wait either (a) for the law to change and define sterility/infertility or (b) for a relevant case to be brought again to the courts where they are required to define these terms in more detail.

A further point that Ishii puts forward is that scientists offering MRTs, as part of research protocol, could try to defend the legality of their research by appealing to Article

²⁵ World Health Organization, *supra* note 22.

²⁶ Suprema Corte de Justicia de la Nación, SEMANARIO JUDICIAL DE LA FEDERACIÓN (2017), <https://sjf.scjn.gob.mx/SJFSist/paginas/tesis.aspx> (accessed June 12, 2017).

²⁷ AMPARO DIRECTO 4663/59. DÁMASO PARRA. 8 DE JUNIO DE 1961. CINCO VOTOS. PONENTE: MARIANO RAMÍREZ VÁZQUEZ; AMPARO DIRECTO 101/60. GABRIELA MERCEDES GALLARDO CABRERO DE AGUILERA. 14 DE OCTUBRE DE 1960. UNANIMIDAD DE CUATRO VOTOS. PONENTE: MARIANO RAMÍREZ VÁZQUEZ; AMPARO DIRECTO 101/60. GALLARDO CABRERO DE AGUILERA GABRIELA MERCEDES. 14 DE OCTUBRE DE 1960. UNANIMIDAD DE CUATRO VOTOS. LA PUBLICACIÓN NO MENCIONA EL NOMBRE DEL PONENTE.

²⁸ Here we do not have enough space to explain why these rulings are not legally binding, for an in-depth explanation of why this is so see, particularly in chapter 1: MARIA DE JESÚS MEDINA-ARELLANO, THE QUEST FOR STEM CELL SCIENCE REGULATION IN MEXICO: CONTROVERSIES IN A CONTESTED SECULAR STATE, June 2012, <https://www.escholar.manchester.ac.uk/api/datastream?publicationPid=uk-ac-man-scw:165929&datastreamId=FULL-TEXT.PDF> (accessed Aug. 12, 2016).

²⁹ Palacios-González and Medina-Arellano, *supra* note 4, at footnote 16.

³⁰ Inter-American Court of Human Rights, Case of Artavia Murillo et al. ('In vitro fertilization') v. Costa Rica, 21 para. 62 (2012), http://www.corteidh.or.cr/docs/casos/articulos/seriec_257_ing.pdf (accessed June 12, 2016).

47 of the Regulations, which states:

Research in pregnant women, with therapeutic benefit related to pregnancy, shall be permitted when: (...) II. They are aimed at increasing the viability of the fetus, with minimal risk to the pregnant woman.³¹

We contend that Ishii is mistaken regarding this point, the source of his error is that this article *does not apply* to research scenarios where the woman is not already pregnant, as would be the case when MRTs are first offered.³²

HEALTH RESEARCH/CLINICAL PRACTICE

In their commentary to our paper, Dimond and Krajewska do two things: they elaborate on the international significance of the first live birth following an MRT and they offer an alternative interpretation of the legality of MRTs in Mexico, by focusing on the distinction between health research/clinical practice. Here we will only focus on their second point. Dimond and Krajewska note that if we can prove that MRTs do not fall within the remit of *health research*, then Article 56 of the Regulations would not apply to them, and thus MRTs could be offered across the board. In order to do exactly this, they start by raising the question of how is it that preimplantation genetic diagnosis (PGD) became approved in Mexico, and they assert that:

[It is not possible] to identify the precise moment, in which it became a fully acceptable clinical procedure. This is because the clear distinction between research and clinical practice stipulated in legal documents remains almost impossible to maintain in practice. This fluidity is exacerbated in the case of novel reproductive technologies, the full consequences of which will not be known for years, or even generations, to come.³³

The above assertion, in a more general sense, seems to point toward the fact that there are three possible ways in which to understand the status of assisted reproductive technologies within the Mexican law: that all assisted reproductive technologies fall within the remit of health research; that there is a point, or period, from where a reproductive technique no longer falls within the remit of health research (this is the interpretation that we endorsed in our paper); and that all assisted reproductive technologies can be regarded as being part of clinical practice from the outset.

Of these possible interpretations they seem to favor the first one, suggesting that all ARTs can in a sense be regarded as part of research. Now, if we, for sake of argument, accept Dimond and Krajewska's interpretation, then what would actually follow, *contra their conclusion*, is that in Mexico both PGD and MRTs are part of health research and thus fall within the remit of Article 56 of the Regulations. This follows because the definition of 'health research' provided in the Regulations is *really broad*, Article 3 asserts that: 'Health research entails carrying out actions that contribute: (...) III. To the prevention and control of health problems'.³⁴ We thank Dimond and Krajewska for noting

³¹ CÁMARA DE DIPUTADOS DEL H. CONGRESO DE LA UNIÓN, *supra* note 16.

³² César Palacios-González, *Are There Moral Differences Between Maternal Spindle Transfer and Pronuclear Transfer?*, MED. HEALTH CARE PHILOS. 1–9 (2017).

³³ Dimond & Krajewska, *supra* note 1, at 2–3.

³⁴ CÁMARA DE DIPUTADOS DEL H. CONGRESO DE LA UNIÓN, *supra* note 16.

this alternative interpretation of the status of assisted reproductive technologies within the Mexican law. Their interpretation further shows the urgency of legislative reform on the regulation of assisted reproductive techniques and health research in Mexico.

We want to conclude this article by stating that with the looming prospect of international MRT tourism ahead, we would greatly benefit from a global discussion on the ethics and regulation of new reproductive technologies that can inform both regional and international policy making.³⁵

³⁵ While this papers was under review (on August 4, 2017) the US Food and Drug Administration sent a very strongly-worded letter to Dr. Zhang. In that letter the FDA listed -in a non all-inclusive way- the violations to US regulations incurred by Zhang's team, and also asked him to stop marketing MRTs in the US. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/UCM570225.pdf> (accessed 19 Sept. 2017).