

Ethical Issues in Human Ooplasm Transfer Experimentation

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Areas of Concern in Ooplasm Transfer

- Safety and Efficacy
 - What threshold of Risk and Uncertainty?
 - KNOWNNS and UNKNOWNS
- Inheritable Genetic Modifications
- Oocyte Providers
- Social and Legal Ramifications

Safety and Efficacy – What are the UNKNOWNNS

- The defect OT is trying to correct
- What is doing “the work” in OT
- Whether OT techniques have adverse effects on transferred material
- Whether OT helps “actualize” abnormal embryos
- The effects on embryos, infants and toddlers with heteroplasmy

The UNKNOWNNS: What defect we are attempting to correct

- Many factors can lead to poor embryonic development, including chromosomal abnormalities, genetic defects, and cellular abnormalities.
- ... impaired [embryo] development may also be a consequence of other problems within the embryo or it in its immediate environment. NEJM

The Unknowns – What is doing “the work”

- The mechanisms involved are still enigmatic, and it remains unclear as to which cellular components are transferred in the donor ooplasm. Barritt
- The exact mechanisms and ... factors that help to rescue the function of defective oocytes remain unknown. ... It is not yet clear how ooplasm transfer works. Huang
- Specialized proteins or messenger RNAs ... may direct subsequent cell cycle events. It is also possible that ... donor mitochondria ... is providing the benefit... . Lanzendorf

The Unknowns: Can transfer techniques have adverse effects on transferred material?

- [B]ecause it is still not known what ... is being transferred to the recipient oocytes, it cannot be determined if cryopreservation may have an adverse effect on [these] factors.... Lanzendorf
- One concern we have ...is the risk of transferring donor chromosomes [from metaphase II oocytes of donors] into the recipient's oocytes. Huang
- [W]e feel ... validation is still required to provide absolute proof that donor nuclear DNA has not been accidentally transferred. Barritt

What are the effects on the embryos?

- Even though the use of cytoplasmic transfer has been employed in several IVF clinics – and pregnancies have resulted – it is not known definitively whether the physiology of the early embryo is affected. Barritt
- ... there may be an improved developmental potential of hybrid cytoplasm in chromosomally normal as well as abnormal embryos. Barritt
- Ooplasmic transfer can alter the normal inheritance of mtDNA resulting in sustained heteroplasmy representing both donor and recipient mtDNA.

What are the effects on the embryos, infants and toddlers with heteroplasmy?

- Because little is understood about the maintenance of mitochondrial heteroplasmy and its nuclear regulation during human development, the effects of potentially mixing of two mitochondrial populations are still being debated. Barritt at 430

What do we know?

- The incidence of chromosomal anomalies is higher than the rate of major congenital abnormalities observed in the natural population.
- 18 month old boy has been diagnosed with PDD.
- The mtDNA inheritance is changed in some children resulting in an inheritable genetic modification.

Inheritable Genetic Modifications

- Is this a case of “germline” genetic modification?
- Why are we concerned about IGM’s?
 - Duties to future generations
 - AAAS conclusions
 - International community

What does Heteroplasmy of this type mean?

- WE DO NOT KNOW
- There are diseases associated with mitochondrial heteroplasmy.
- Yet “there is no reason to consider the mtDNA heteroplasmy as harmful, because it is known to occur naturally in normal individuals.”

What does Heteroplasmy of this type mean?

- Since mt diseases associated with heteroplasmy can be early or late onset, we cannot know whether this heteroplasmy is benign until these children grow up.

Limitations of the Clinical Data

- Small sample size
- Incomplete information on the women in the experiment
 - Previous procedures
 - Reasons for failure
- Incomplete testing of the children who have been born
- Lack of long-term follow up – need for long term monitoring

What do the **KNOWN**S and **UNKNOWN**S tell us?

- How do you get meaningful informed consent given the lack of knowledge and the context?
- Is it appropriate to conduct this experiment in widespread fashion in fertility clinics in this country?

Should there be more animal testing?

- YES.
- All the studies rely on the use of animal studies for the assumptions and conclusions they make.

Must there be further human embryo experimentation before more embryos are implanted, and children born?

- YES.
- Although infertility can be a serious condition it is not life-threatening or fatal.
- We have a duty to children we help be born to do our utmost to see that they are born free from disease or impairment.