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ARTICLE

A limited survey-based uncontrolled follow-up study of children born after ooplasmic transplantation in a single centre

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Abstract Experimental ooplasmic transplantation from donor to recipient oocyte took place between 1996 and 2001 at Saint Barnabas Medical Center, USA. Indication for 33 patients was repeated implantation failure. Thirteen couples had 17 babies. One patient delivered twins from mixed ooplasmic and donor egg embryos. A limited survey-based follow-up study on the children is reported: 12 out of 13 parents completed a questionnaire on pregnancy, birth, health, academic performance and disclosure. Parents of a quadruplet did not participate. Prenatal development and delivery were uneventful. School grades ranged from good to excellent. Children were of good health. Body mass index (BMI) was normal in 12 out of 13 children. One child had chronic migraine headaches, two mild asthma, three minor vision and three minor skin problems. One boy from a boy/girl twin was diagnosed with borderline pervasive developmental disorder – not otherwise specified at age 18 months, but with no later symptoms. One couple disclosed the use of egg donor to their child. One reported intention to disclose; six were undecided and four reported they would not disclose. This limited follow-up strategy presents a high risk of bias. Parents may not assent to standardized clinical analysis owing to lack of disclosure to their children.

KEYWORDS: cytoplasmic transfer, repeated implantation failure, survey, limited follow-up, disclosure to children

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Introduction

An experimental study was conducted at Saint Barnabas Medical Center, Livingston, New Jersey, USA, between 1996 and 2001. The study aimed to improve embryonic development after the insertion of ooplasm from oocytes of fertile donors into oocytes of patients who had experienced repeated implantation failure and poor embryo development. The ooplasmic transfer procedures were carried out in 33 selected couples suffering from infertility and repeated failure of implantation during several cycles of IVF. The study was approved by the Institutional Review Board of Saint Barnabas Medical Center in 1996. In the mid 1990s, IVF was moderately successful, but, in many instances, implantation failed even after transfer of multiple embryos. The relationship between oocyte aneuploidy and age has been described, but the incidence of aneuploidy in in-vitro derived embryos was still largely unknown (Lee et al., 2015; Munné et al., 1995). Because repeated failure of implantation in this group of patients was also associated with repeated poor embryonic development *in vitro*, it was hypothesized that the failure could be caused by cytoplasmic deficiency rather than nuclear/chromosome abnormalities.

At the same time, nuclear transplantation experiments in murine models had demonstrated feasibility of altering the ooplasm using oocytes, zygotes or blastomeres as a source of cytoplasm (Levron et al., 1995, 1996; Pratt and Muggleton-Harris, 1988). A preliminary experimental study in three couples who had previously experienced failed IVF attempts due to abnormal embryo development was conducted and involved methodologies typically used during nuclear transplantation. This included the use of membrane relaxants and electro-fusion of small anucleate donor egg cytoplasts with a mature recipient oocyte. Fertilization rate was normal, but at least one-half of the zygotes showed abnormal development patterns (Cohen et al., 1998). Similar abnormalities were recently described after transfer of metaphase spindles into enucleated oocytes using electrofusion, to avoid transmission of mitochondrial disease (Richardson et al., 2015; Tachibana et al., 2009). Ooplasmic transfer by cytoplast fusion was abandoned after the experimental electro-fusion attempts failed, and an intra-cytoplasmic injection approach was chosen instead (Cohen et al., 1997, 1998). This technique was selected because of its relative ease and success when used for injection of a single sperm into an oocyte for alleviation of male infertility (Palermo et al., 1992). At the time of the first ooplasmic donation attempt, it was estimated that more than 20,000 babies had been born after intracytoplaismic sperm injection (ICSI). A small sample of cytoplasm was extracted from anonymous donor eggs and injected into each of the patient's eggs along with her partner's sperm. Ooplasmic transplantation patients were counselled about the experimental nature of the procedure. The study was offered to over 100 patients during the 4-year period of investigation. Only a minority agreed to participate. Fourteen out of the 33 patients (37 attempts) became pregnant, three with twin pregnancies and one with a quadruplet pregnancy. One singleton pregnancy was lost before a fetal heartbeat could be detected and testing of the products of conception showed an XO karyotype (Barritt et al., 2001a). One twin pregnancy was the result of a mixed embryo transfer from cytoplasmic transfer and an intact donor egg. One fetus from another twin pregnancy was also diagnosed as XO and was selectively terminated. The other female fetus was delivered normally. The XO karyotypes were unexpected and were considered potential adverse effects of the procedure. In total, 13 couples delivered 18 babies who appeared to be healthy at the time of delivery. Seventeen of these children were from the cytoplasmic transfer procedure, and one baby was from egg donation without cytoplasmic transfer. A boy from a boy/girl twin was diagnosed with borderline pervasive developmental disorder of non-specific origin at 18 months of age (Barritt et al., 2001a).

As cytoplasm contains mitochondria, mitochondrial DNA (mtDNA) from the donors were also transferred into the recipient eggs. Embryos that were not suitable for transfer or cryopreservation were therefore tested for the presence of donor-derived mtDNA using a fingerprinting approach, analysing nucleotide sequences of the hyper-variable region in the D-loop of mtDNA (Brenner et al., 2000). About one-half of 4-day-old developmentally arrested embryos contained donor-derived mtDNA. Buccal smears from eight children were checked after birth (Barritt et al., 2001b). Two of the babies had mtDNA derived from the donor. Mitochondrial DNA, unlike nuclear DNA, does not determine phenotypic characteristics like eye colour, skin colour or height. As a third person (the egg donor), however, was involved in the assisted reproduction process, the popular press referred to these children as 'three parent babies', a provocative but inaccurate reference (Cohen and Alikani, 2013). The publication of the finding that two of the eight tested children retained some mtDNA from the egg donors generated further controversy and concern in the scientific community. These concerns led to a number of investigations in animal models to study the physiological effects of mitochondrial transfer from one animal to another (Acton et al., 2007; Cheng et al., 2009; Liang et al., 2009).

In 2001, the US Food and Drug Administration exerted jurisdiction over this technology by requiring that an Investigational New Drug application be filed in order to continue offering this procedure to patients. Saint Barnabas Medical Center began the application process and continued for 2 years, but abandoned it after loss of funding. No ooplasmic transplantation procedures were conducted after June 2001.

Our ultimate aim is to discover whether donor mitochondria have persisted in the children and to ascertain the general health and cognitive abilities of these children. This communication relays the limited findings of the first phase of our case series follow-up investigation in which the parents of the children participated in an online questionnaire about the health and development of their children. The Institutional Review Board requested that we conduct a survey study first. It was argued that the findings would provide insight into how many, if any, parents would participate in a more standardized and involved second phase study. The age of the children ranged from 13–18 years at the time of the study. The findings must be considered limited, because of the subjective nature of the survey, the lack of a standardized clinical follow-up and the broad age range. The information, however, is nonetheless important and may be of interest to the assisted reproduction technique community, particularly in view of current discussions surrounding mitochondrial replacement therapies.

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