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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.

Materials and methods

The current survey was approved by the Institutional Review Board of Saint Barnabas Medical Center (Protocol 13–11; 17 December, 2013). Thirteen parent couples were contacted by phone, email, or both, to request their participation in the study. Once consent was obtained, patients were asked to complete an online questionnaire (QuestionPro software) for each child that resulted from cytoplasmic donation. The parents of the quadruplets did not respond to repeated requests. Twelve parents completed surveys for 14 children, as one couple had dizygotic twins from the procedure and another patient delivered twins after transferring one embryo from cytoplasmic transfer and one from egg donation. The survey asked a series of questions designed with the purpose of assessing physical, emotional, mental and cognitive health and well-being of the child.

A standard matrix scorecard was part of the survey, and included 32 questions to assess incidence of childhood diseases, diagnosis of pulmonary, cardiac, liver and kidney dysfunction as well as physical, emotional and learning disabilities. In two instances, the parents were assisted by an independent study coordinator when their answers were incomplete or ambiguous. When participants completed the programme before correcting errors such as gender, the study coordinator allowed them re-entry to the survey during an online consultation. Answers were tallied and validated by the software tool provided by QuestionPro. A second request for information went out to the parents in response to *Reproductive Biomedicine Online*'s editorial review process. Participants were asked to provide grade point average (GPA) and current height and weight. The Child and teen calculator, provided by the Centers for Disease Control and Prevention, was used to calculate BMI (https://nccd.cdc.gov/dnpabmi/calculator.aspx).

Results

The period between first participation request and last completed survey lasted 22 months. Reminder emails and repeated phone calls were necessary to remind patients to complete the surveys. In one case, a survey was started 6 months before it was completed; however, in most cases, once the survey was started, it was usually completed in less than 1 h. Information of patients with delivery after cytoplasmic transfer is provided in **Table 1**. The patient with quadruplets (patient 9 in **Table 1**) did not respond to repeated invitations. The survey questions are outlined in **Tables 2 and 3**. One set of twins are girls from mixed procedure origin (Patient 16 in **Table 4**). As maternal origin was not determined, information on both girls is included in **Table 3** and **Table 4**. Shortly after birth, the mother had considered fingerprinting to determine which twin was from egg donation. Once the children became older, she decided against testing because one girl's features were strikingly similar to the mother. We studied multiple photographs, including those of the mother when she was a teenager, and although we agreed that there was a strong resemblance between the mother and one twin, we concluded that this method was not full proof and therefore data on both girls were collected and presented. The first child listed in **Table 4** from patient 16 is presumed to be the cytoplasmic transfer child. As a result, the group of children studied here consisted of nine girls and five boys; however, only 13 are from cytoplasmic transfer.

Parental background, pregnancy and delivery outcomes

All mothers had prenatal care throughout pregnancy. None of the mothers smoked or consumed alcoholic beverages during

Table 1 Clinical and laboratory information of patients with delivery after cytoplasmic transfer.

ID	*Maternal age at cytoplasmic transfer cycle (years)*	*Number of previous cycles*	*Number of embryos transferred/fetal heartbeat after cytoplasmic transfer*	*Testing for donor mitochondrial DNA (–) Patient did not consent*	*Babies*	*Survey (+) Patient participation (–) Patient did not respond*	*Heteroplasmy at birth (+) Heteroplasmy confirmed (–) No heteroplasmy detected*
14	39.5	4	3/1	a	1F	+	Not sampled
20	38.4	6	6/1	–	1M	+	Not sampled
18	37.6	9	5/1	–	1M	+	Not sampled
11	30.5	3	4/1	u,p	1F	+	+
8	37.2	3	2/1	a,p,u,b,bl	1M	+	+
15	35.7	4	5/2	a,p,u	1F	+	–
21	31.6	3	4/1	a,p,u	1F	+	–
22	34.1	6	3/1	p,u	1F	+	–
24	36.5	6	5/2	a[a],p,u	1F, 1M	+	–
9	33.8	4	6/4	p,u[b]	2F, 2M	–	–
23	34.8	10	4/1	a,p,u	1F	+	–
12	36.6	3	4/1	–	1M	+	Not sampled
16	36.3	3	4/2	–	1F	+	Not sampled

a, amnio; b,buccal; bl,blood; F, female; M, male; p, placenta; u, umbilical cord.
[a]Borderline positive for donor mitochondrial DNA in amniotic fluid samples for both twins.
[b]Negative for donor mitochondrial DNA in all four siblings.

Table 2 Disclosure information of couples to their children related to the use of IVF, egg donation and cytoplasmic transfer.

Disclosure information	*Yes*	*No*	*Undecided*
Has the use of an egg donor been disclosed to the child?	1	11	NA
If not, do you intend to disclose?	1	4	6
As you know, as a result of the procedure, there is a possibility that mitochondrial DNA from the donor might be in your child's cells. Has this been disclosed to your child?	1	11	NA
If not, do you intend to disclose?	0	3	8
Has the use of an egg donor been disclosed to others? (Others might be: siblings, extended relatives, or friends)	6	6	NA
If not, do you intend to disclose?	0	3	3

NA, not applicable.

Table 3 Emotional, mental, cognitive and general health history of children born after cytoplasmic transfer as assessed by their parents using the study survey.[a]

Health history of child	*Yes*	*No*
Do you consider your child in good health?	14	0
Does your child have any serious medical conditions? Now or in the past.[b]	1	13
Has your child had any injuries or accidents?	6	8
Has your child ever been hospitalized other than birth?	2	12
Has your child ever had any surgery?	4	10
Has your child ever had allergies?	7	7
Emotional and mental health		
Emotional and behavioral problems[c]	0	14
Depression or suicidal thoughts[c]	1	13
Emotional abuse[c]	0	14
Attention deficit disorder[c]	1	13
Are you concerned about your child's attention span?	3	11
Are you concerned with your child's emotional development?	1	13
Cognitive health		
Are you concerned about your child's cognitive development?	0	14
Has your child ever repeated a grade?	0	14
Has your child ever been in a special education or resource classroom?	2	12
Learning disabilities[c]	1	13

[a]Both twins from the mixed procedure origin cycle were included.
[b]Chronic migraine headaches.
[c]Part of standard matrix scorecard.

pregnancy, but two used medications for depression and anxiety, chronic migraine headaches or for asthma. Nine of the 12 deliveries were vaginal and three were by caesarean section. The length of labour varied from 5 to 34 h for the vaginal deliveries. All parents were white. All mothers had a university degree and three had a postgraduate degree. All fathers had a university degree and seven had a postgraduate degree. The mean household income was greater than or equal $100,000 per annum. Two of the 12 couples were divorced at the time of the survey.

Birth weight ranged between 1975 to 4281 g (**Table 4**). Birth height ranged from 43.2 to 57.2 cm, but two values were unknown. Those with assessed APGAR score had normal results ($n = 12$). Seven of the babies were born at term (40 weeks). All others were born between 36 and 40 weeks. No additional neonatal care was necessary, but one baby spent additional days in the neonatal intensive care unit because of jaundice.

Some contact with the parents of the quadruplets was maintained until 22 months after delivery but they declined participation in the survey. The babies were born at 32 weeks. Two male babies weighed 1446 and 1814 g. Two female babies weighed 1758 and 1985 g. The children are alive and are attending high school, but other information is currently unavailable.

Disclosure of egg donor role by parents to children

Only parents of one child had disclosed the use of an egg donor to their child (**Table 2**). Possible inheritance of mtDNA was also disclosed by these parents. Four couples reported having decided not to disclose treatment information. One reported intending to disclose in the future and the remaining six couples said they were undecided. The parents who reported that they would disclose egg donation at a future time answered that they were undecided about disclosure of cytoplasmic transfer. Six of the 12 couples disclosed the use of an egg donor to individuals other than their children. Three of the six who had not disclosed to anyone were undecided about disclosure in the future.

Perceived cognitive abilities and academic performance on record

The parent with boy/girl twins was concerned about the emotional wellbeing of her son and his ability to live independently and be a productive person. None of the parents were concerned about the cognitive development of their children. Three parents were concerned about the attention span of their children. School grades are reported in **Table 4**. All attended schools in the USA, hence grades provided in **Table 4** represent the US grading system which assigns letter grades A (4.0 points) to F (0 points) and GPA is calculated based on the points earned. The grades of the children in the study ranged from good (B) to excellent (A–A$^+$). Most of the children (11/13) had excellent grades. Conversion to grades of other countries can be found using a conversion formula from the World Education Services on http://www.wes.org/gradeconversionguide/index.asp. No child ever repeated a grade.

Health of children

All parents considered their children to be in good health at the time of the survey; however, one child was reported to

Table 4 Birth and development characteristics of children from ooplasmic transplantation.

ID	Gender	Amnio centesis	Birth weight (g)	Birth height (cm)	Gestation (weeks)	Surgery	Age (years)	Height (cm)	Weight (kg)	BMI	Age adjusted percentile	Grade point average	Letter grade
24[a]	Male	Normal	3034	48.3	36	Ear tubes	16	180	60	18.1	12	3.6	A
24[a]	Female	Normal	2381	43.2	36	Tonsillectomy	16	168	64	22.6	71	3.6	A
16[a]	Female	Normal	1975	46	38	No	13	153	42	18.2	32	4.0	A
16[a]	Female	Normal	2041	47	38	No	13	160	50	19.5	51	3.4	B +
18	Male	N/A	3062	55.9	37	No	17	188	82	23.1	68	3.6	A
21	Female	Normal	3062	48.3	38	No	16	168	49	17.4	7	3.9	A
15	Female	(1) XO[b] (2) XX	3147	50.8	39	Removal of large birthmark on thigh (benign)	16	160	54	21.3	55	3.8	A
23	Female	Normal	3771		40	No	15	175	62	20.2	47	4.3	A +
8	Male	Normal	3345	53.3	40	No	17	173	59	19.8	25	3.7	A
14	Female	Normal	4281	50.8	40	No	18	165	86	31.6	95	4.0	A
20	Male	Normal[c]	3969		40	Shoulder tear	17	186	84	24.4	77	3.0	B
11	Female	NA	3572	50.8	40	No	17	173	57	19	21	3.2	B
22	Female	NA	3440	48.3	40	No	16	168	52	18.6	19	3.8	A
12	Male	Normal	4026	57.2	40	No	14	163	55	20.6	61	3.5	A

NA, not applicable.
[a]Twin pregnancy. Twin number 16 is from mixed embryo transfer of cytoplasmic transfer and an intact donor egg.
[b]One twin with XO was selectively terminated.
[c]Both amniocentesis and chorionic villus sampling carried out.

suffer from chronic migraine headaches. Accidents or injuries were reported for six children. Two children were hospitalized, one for Norwalk virus and one for a shoulder muscle tear. Three children had minor surgical procedures. Seven had allergies. Two children had been diagnosed with mild asthma, three had minor vision problems, three had minor skin problems. No liver, kidney, cardiac, lung or neurologic disorders were reported. No eating disorders or dental problems were reported; however, this information may be subjective. Height and weight measurements were used to calculate BMI (**Table 4**). Among male children, BMI ranged from 12–77 percentile, and in female children from 7–95 percentile. One female child is obese, but a family history of obesity exists. One male child from the male/female twin was diagnosed with borderline attention deficit disorder. He received special education for the pre-school year only. He also has had episodes of depression. A family history of depression was reported.

Willingness to participate in a second follow-up study

Three couples have stated their willingness to provide saliva samples for further studies. One couple has refused to participate in future studies, whereas eight were still undecided. Only two couples would allow an in-person clinical assessment of their children.

Discussion

On the basis of study size and design, the results of this survey must be considered to be descriptive only. Delivery appeared uneventful in the patients who responded to the survey. One early miscarriage before fetal heartbeat detection, however, was diagnosed as XO and another fetus was also diagnosed with XO. This fetus was selectively reduced in a twin pregnancy. Both pregnancies were reported previously (Barritt et al., 2001a). Non-disjunction events arise commonly during anaphase of the two maternal meiotic divisions (Hassold and Hunt, 2009). The two monosomies may have arisen by the lack of segregation of the sister chromatid pair during meiosis I or II. The micromanipulation procedure was only carried out on oocytes with a clear first polar body and hence if there is an association between the procedure and loss of a sex chromosome, it could have only occurred in anaphase II. As far as we know, this association does not exist after ICSI for assisted fertilization. Clinically relevant aneuploidies in humans are more commonly associated with events during maternal meiosis I (Hassold and Hunt, 2009; Nagaoka et al., 2012).

The grades reported by the parents show that the children are doing well in school; however, the parents from the quadruplet delivery did not respond to repeated requests for participation. This study is limited because the information from the quadruplet delivery is essential for providing firm conclusions. Initial follow-up with the quadruplet family after birth proceeded for nearly 2 years, but subsequently the parents did not respond to further contact. Participation or response rates vary between 31 and 77% in follow-up studies (Hammarberg *et al.*, 2001 [response rate 55%]; Johansson *et al.*, 2010; [response rate 55%]; Leiblum *et al.*, 1998 [response rate 31%]; Hjelmstedt *et al.* 2003 [response rate 68%]; McMahon *et al.*, 2003 [response rate 69–77%]; Sundby *et al.*, 2007 [response rate 42%]). A large group ($n = 899$) of parents with children ranging from 4–6 years of age responded to a survey request by a German team after ICSI (Ludwig et al., 2008). The response rate was 55.7%. The participation rate in the current study was 92% (12/13) and compares favourably to other studies.

None of the parents who completed the survey had any concerns about the physical health of their children. One should, however, be cautious about possible perception bias. When asked about the weight of their children, all parents responded that weight was within normal range. Upon further request for height and weight information, one female teenager had an elevated BMI at 95th percentile and one girl was borderline underweight at 7th percentile. Although these frequencies are within normal range (Skinner et al., 2016), it is known that obesity can be under-reported by parents, paediatricians and family doctors (Chaimovitz et al., 2008; Eckstein et al., 2006).

One female child was diagnosed with an unspecified learning disability reported by the parent. As a result, she receives extra time when taking tests; however, her reported GPA indicates excellent performance. There may be a parental perception bias. Her twin brother was diagnosed with borderline attention deficit disorder. He was also tested at 18 months, when he was diagnosed with borderline pervasive development disorder – not otherwise specified; however, this initial diagnosis was not confirmed and, reportedly, no symptoms persist. The child excels in school subjects in which he has an interest, but achieves average or below average scores when he is not interested according to his mother. His reported grades, however, average A. The diagnosis of pervasive development disorder – not otherwise specified in children before age 3 years is not always confirmed later in life (Chawarska et al., 2007). Although short-term stability of the diagnosis is high, there are frequent exceptions, particularly when the first diagnosis is before age 3 years. It is possible that the male twin falls into the latter category. According to the Centers for Disease Control and Prevention, about 11% of children aged between 4 and 17 years (6.4 million) have been diagnosed with attention deficit disorder in the USA as of 2011 (http://www.cdc.gov/ncbddd/adhd/data.html). The incidence of this disorder is within the expected frequency in this small group of children from cytoplasmic donation.

Only one out of 12 parents disclosed the use of donor egg cytoplasm for IVF to their children. This incidence may be lower than the disclosure rate to children after the use of standard egg donation. Recommendations to recipients to disclose the use of gamete donation to their offspring has been long standing as per national and practice guidelines (ESHRE Task Force on Ethics and Law, 2002; American Society for Reproductive Medicine, 2004). For parents of children conceived through gamete donation, disclosure is a difficult decision (Klock and Greenfeld, 2004). An earlier study indicated that nearly 60% of parents disclose or plan to disclose whereas 40% plan not to disclose or are undecided (Greenfeld and Klock, 2004). This finding, however, was contradicted most recently by Isaksson et al. (2012) who reported 94% planning

to disclose, suggesting that these technologies are becoming more widely accepted and more openly discussed. The lack of disclosure after ooplasmic transplantation in this group of patients does not seem to have followed the recent trend. The underlying reason is unclear, but parental decisions may have been related to the fact that nuclear DNA is not inherited from donor eggs after cytoplasmic donation. For this reason, a direct comparison with egg donation cycles may not be appropriate. It is also possible that the use of an experimental procedure has had an effect on disclosure rate.

The effects of cytoplasmic transfer on embryonic and fetal development have been modelled experimentally in the mouse. Significant aberrations of development were reported (Acton et al., 2007; Cheng et al., 2009; Liang et al., 2009). The clinical procedure could not be duplicated in the mouse model, because cytoplasmic injection is technically difficult in mouse eggs. The studies involved transferring cytoplasm using electro-fusion, a technique that causes egg activation and may have affected development because of premature onset of the final stages of meiosis. All studies used inbred mouse strains, which were used to distinguish between recipient oocytes and cytoplasmic donor oocytes. Inbred strains are derived after dozens of sister–brother mating. Exposing the nucleus of an inbred mouse egg to mitochondria of another inbred strain is not an appropriate model for human reproduction as inbreeding in the human is both rare and unexpected. The current clinical findings contradict observations in animal models (Acton et al., 2007; Cheng et al., 2009; Liang et al., 2009).

In conclusion, we were not able to discern an effect of ooplasmic transplantation on children aged between 13 and 18 years, but the power of the investigation was low. The findings in this study are based on subjective assessment criteria and no standardized instruments were used. Given the low disclosure rate to children, only a limited survey could have provided an acceptable participation rate. It may be deduced that long-term follow-up of children undergoing mitochondrial replacement therapies to avoid mitochondrial disease may be of concern even when patients promise to participate before onset of treatment (Richardson et al., 2015; Wolf et al., 2015). On the basis of our findings, prolonged medical follow-up of children from experimental investigations is not a given even when parents are instructed or requested, agree to participate, or both. During the years after the first series of experimental preimplantation genetic screening and preimplantation genetic diagnosis, patients consented to undergo chorionic villus sampling or amniocentesis, and signed a consent form stating their approval. They agreed with this procedure at the time of IVF, but many patients refused to undergo the test once they became pregnant after their initial consent. Patients can change their mind within a time-span of 3–5 months (unpublished observations). US Institutional Review Boards require that language is added to the consent form stating that participants may withdraw at any time without consequences to their standard of care. This language was used in the consenting process of ooplasmic transplantation patients. They cannot be legally (or ethically) bound to the letter of the consent even though this may be disappointing to the investigators. The information presented here may be of interest to the assisted reproduction technique community, particularly in view of current discussions surrounding mitochondrial replacement therapies.

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