30 Ethical Issues: Addressing the Sensational Cases and Analyzing the Clinical Practice

Andrea L. Kalfoglou and Glenn McGee

Key Points

- Oocyte and embryo donation have always been controversial because of public divisiveness regarding sensational cases and the social concerns that attend changes in conventional reproductive patterns, capacities, and roles.
- A growing body of empirical data is accumulating on issues, such as the potential psychological effects oocyte and embryo donation has on donors, families, and offspring, to further inform our ethical discussions.
- Values that govern medical practice must also be extended to women who are willing to donate oocytes.
- It is incumbent upon physicians to treat oocyte donors with as much care and respect as they normally extend to patients for whom their goal is to cure.

A.L. Kalfoglou, Ph.D. (✉)
Health Administration and Policy Program, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle PUP 212, Baltimore, MD 21250, USA
e-mail: akalfogl@umbc.edu

G. McGee, Ph.D.
Graduate Department of Bioethics, Kansas City University for Medicine and Bioscience, 1101 Walnut Street 1303/4, Kansas City, MO 64106, USA
e-mail: glenn.mcgee@stanford.edu

Oocyte and embryo donation have long been lightning rods for controversy about assisted reproduction, both because of public divisiveness regarding sensational cases and because of the social concerns that attend changes in reproductive patterns, capacities, and roles. In particular, there is much discussion regarding the minimization of physical risks to oocyte donors, the iteration and development of consensus around what ought to be included in information provided to donors before they give consent to oocyte or embryo donation, and both whether and what children have a right to know about their genetic origins [1].

Among the most dramatic changes in the social perception of oocyte and embryo donation is the presence of a growing body of empirical data to shed light on issues such as potential psychological outcomes of oocyte and embryo donation for donors, families, and offspring [2–4] to inform our ethical discussions.

In the USA and many other countries, there is also now legal precedent and legislation that helps predetermine legal parentage and other potential disputes about oocyte and embryo donation as well as other forms of third-party reproduction.

Multiple professional associations like the American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) and not-for-profit organizations such as the National Research Council-Institute of Medicine (NAS-IOM), the California Institute of Regenerative Medicine advisory committee, New York Stem

M.V. Sauer (ed.), *Principles of Oocyte and Embryo Donation*,
DOI 10.1007/978-1-4471-2392-7_30, © Springer-Verlag London 2013

Cell Foundation ethics committee, New York Task Force on Life and the Law, the Nuffield Council, and UK's Human Fertilisation and Embryology Authority (HFEA) have provided guidance on many of the ethical and legal issues surrounding the donation of oocytes and embryos for reproductive and research purposes.

Across these three changes in the environment and institutions of assisted reproduction, five trends and technological advances have altered the ethics landscape for oocyte and embryo donation most recently.

First, the number of fresh oocyte donor cycles has more than doubled from 1997 (4,498 cycles) to 2010 (9,866 cycles), and the number of frozen embryo transfers with donor oocytes has increased fivefold (from 1,482 cycles in 1997 to 6,665 cycles in 2010) [5]. Fully 12 % of all IVF cycles in 2009 used donor oocytes [6]. This growth in the use of donor oocytes is due to the fact that regardless of age, cycles using fresh embryos from donor oocytes result in a live birth 47–52 % of the time, whereas fresh embryos using the intended mother's oocytes result in an average live birth rate of 30 % [5]. For women of advanced reproductive age who have virtually no chance of having a live birth using their own oocytes, the use of donor oocytes or embryos improves their odds of a live birth to that of most 20–30-year-olds.

Second, there has been an explosion in embryonic stem-cell research. In the late 1990s, although embryo research was occurring, it was mostly to improve the outcomes of assisted reproductive technologies in private clinics. Embryonic stem-cell research was in its infancy, and no one at that time could envision that the National Institutes of Health (NIH) would eventually fund embryonic stem-cell research. The development and growth of embryonic stem-cell research and the need for donors to supply gametes for research purposes have created additional demand for oocytes.

Third, a precedent-setting surrogacy case in California changed expectations about parental responsibilities in assisted reproductive activities and subsequent parentage, as a judge decided that a surrogate mother, pregnant with an embryo created from the intended parent's genetic material, was not the legal mother of the baby [7]. Because the intended parents were the gamete providers, they were awarded full custody of the resulting child. The judge referred to the woman who gestated the fetus as a "foster parent." As a result, many intended parents who use a surrogate mother believe there will be less maternal bonding and more support from the courts if the surrogate tries to keep the baby when the gestating woman does not provide the oocyte(s) that creates the fetus(es).

Fourth, the banking of reproductive material has expanded to include oocytes, in an environment where other banking and use is now better established. Sperm banks are routine. Embryos can be frozen, thawed, and transferred in later cycles, but success rates from previously frozen embryos were low until recent years. Oocyte freezing was purely experimental, and success rates – even in bench and preclinical research – were so low that it was not a viable option. A process called vitrification has radically improved the process of oocyte cryopreservation. This technological advance has changed the landscape of oocyte donation. Oocyte banks are increasing in number across the USA and the rest of the world claiming that cryopreserved oocytes are cheaper and faster to use than recruiting an oocyte donor and then cycling her with the recipient patient. Although many of the ethical issues related to oocyte banking are similar to sperm banking, this new technology has had little in the way of ethical analysis.

Similarly, though live birth success rates from frozen embryos are not as good as fresh embryos, they are climbing into the range of 35 % [5]. According to a 2002 RAND study, there were approximately 400,000 cryopreserved embryos in the USA [8]; however, fertility patients appear to be very reluctant to donate excess stored embryos to other couples for reproductive purposes [9, 10]. Fertility clinics and private companies have attempted to create embryo banks so that reproductive material is readily available to couples seeking fertility treatment; however, most of these ventures have been abandoned.

Fifth, an experimental technology that made a splash in the USA before the FDA shut down the

research in 2001 is now emerging in the UK. It has many names – cytoplasmic transfer, mitochondrial DNA transfer, maternal spindle transfer, and pronuclear transfer – but the research has two primary goals. In the UK clinical trials, the goal is to help a couple have a child that is free from mitochondrial disease; however, this is not the only target market for this technology. The larger market, should this technology prove safe and effective, is infertile women of advanced maternal age who want to have a child that shares their DNA. If this technology becomes widely available, it is possible that demand for oocyte donors will increase. It also creates new ethical questions because the resulting child will have genetic material from three rather than two individuals and the phenotype of the oocyte donor no longer matters. Like gestational surrogacy, oocytes could be obtained from women willing to accept much less in compensation, putting donors at increased risk of exploitation.

Across three technologies and five new kinds of problems, there are four important kinds of ethical concerns for practitioners working in the area of oocyte and embryo donation. These include the following: (1) Who gets to decide what happens to donor oocytes and embryos? (2) Who are the parents of children created from donor gametes? (3) Why are we still debating donor compensation? and (4) What new ethical dilemmas will we need to navigate as cytoplasmic transfer technologies improve?

Who Gets to Decide What Happens to Donor Oocytes and Embryos?

We have learned a great deal about how to improve the consent process for oocyte donors in the past 20 years. Research conducted by the New York State Task Force on Life and the Law [11] as well as at least one other study [7] have shown that donors were not always receiving all the necessary information they needed to make an informed decision about donating, and many were given no information about the potential uses of their oocytes. Should donors have a voice as to whom and how many people receive their oocytes for reproductive purposes? For instance, should a donor be able to specify that she only wants to donate to a Jewish, nonsmoking couple? We would not permit this with blood donation because it would feed into prejudice and racism, but is contributing to the creation of a child somehow different? Many donors feel a sense of stewardship over their reproductive potential and the children they help bring into the world; they want to know that the child will be raised by a loving family [12].

Because donors represent a resource that is in very high demand, they may have more power to make these kinds of requests than many donors realize. Some clinics are, in fact, willing to work within the constraints a donor places on her donation. If a clinic is unwilling to work with the donor, not only are there other clinics to choose from but some donors have turned to the Internet to appeal directly to infertile couples. In this open market, oocyte donors have negotiated higher compensation and more open relationships than what many clinics permit [12].

In clinics with anonymous donation programs, most donors are told that their oocytes will be used to attempt to create a child for a deserving couple. Does the clinic or oocyte donor organization have an ethical obligation to inform the donor if embryos created with her gametes are going to be transferred to a surrogate or used by a single person or same-sex couple? During the consent process, should the donor be asked about her wishes for the disposition of excess embryos? Or does her right to make decisions about what happens to her oocytes end when they are removed from her body or combined with sperm? Many different organizations and ethics committees have made recommendations regarding the donor's consent to the disposition of her oocytes [12], but the New York Task Force on Life and the Law's guide *Thinking about being an egg donor? Get the facts before you decide!* makes that group's then articulated consensus for New York's State Health Department clear: "Once you donate your eggs, their fate is entirely up to the recipient. You have no say about what happens" [13]. It could be argued that this view can be extrapolated to the point of universal ethical norm

and that medical professionals who are informing potential oocyte donors have an ethical obligation, at a minimum, to let women know all the potential used of donated oocytes and embryos created with their oocytes based on individual clinic policies (e.g., some clinics routinely split oocytes between recipients if a minimal number are harvested).

Oocyte banking is one of the newest trends in third-party reproduction. Oocyte banks claim that banked oocytes are cheaper and faster to produce for infertile couples than waiting to match cycles with an oocyte donor, and they can provide a wider selection of donors. Some offer money-back guarantees if the recipient does not get pregnant [14]. How does donating to an oocyte bank differ from donating to a specifically matched couple or individual? In this case, a business "owns" genetic material that can be used to create life rather than it being controlled by individuals who might have more of a personal sense of stewardship over these cells. Certainly, this has been the case with sperm banks for many decades. It is unclear that there will be any differences for oocyte banks, but as we are discovering, there are implications for them. First, with growing improvement in success rates for single or double embryo transfers, there is the possibility that a single stimulation cycle could result in multiple children born into one or multiple families. Children created from sperm donation are now using the Internet to find half-siblings and sperm donors. Europe is moving toward more openness in gamete donation. In fact, those who donate gametes after 2005 in the U.K. are required to provide identifying information [15]. For many oocyte donors, it is especially important to know whether a child was born and the sex and birth date of that child. As donors age and become parents themselves, some have persistent concerns that their own children could end up in an incestuous relationship with a half-sibling, and they believe having this information would be reassuring [12].

Banking oocytes is not as simple as banking sperm. Donors go through medical procedures including hormone injections and invasive surgery. Although there is no clinical evidence that donating leads to long-term medical problems, some of these women are likely to experience short-term problems [16]. Clinicians have an obligation to both adequately inform women undergoing a stimulated cycle and to provide follow-up care. Eventually, a former oocyte donor will experience infertility and may blame it on the oocyte donation. If her oocytes are still in storage, she may want her oocytes returned. Does the donor have the right to demand that they be returned to her if they are still available? Should she have to pay for her own gametes? Should she be entitled to free fertility treatment? What if the oocytes are now embryos stored by another patient?

With the advent of oocyte banks, women have begun using them to expand their own reproductive options. Extend Fertility was the first prominent company to begin offering personal oocyte banking services, but it now has much competition [17, 18]. The most obvious use of these services is to preserve future fertility among women and girls who are undergoing treatments like radiation for cancer where they may be left infertile, but women who intend to postpone childbearing until they find the right partner or meet their career goals may be the larger market for this service. Is this option empowering to women, or is it an opportunistic chance to play on women's fears in order to make money [19, 20]?

Society will be faced with many of the same questions that have arisen from banked sperm: Do others, such as spouses or parents, have the right to use the oocytes to attempt to create children or the right to donated banked oocytes to research in the event the woman dies? One can envision a situation where a 14-year-old child dies from cancer and her own mother, now premenopausal, wants to use her daughter's oocytes to attempt to give birth to her own granddaughter. Does it make a difference if the woman who has banked the oocytes has specified her desires regarding the disposition of her oocytes prior to her death? The ethics committee of the ASRM recommends that gametes only be used for posthumous reproduction when there is an advanced directive from the provider granting consent [21]. Knowledgeable ART providers will ask these kinds of questions at the time oocytes are banked to help deal with

these inevitable requests and legal petitions. In a 2004 document, ESHRE argued that when the donor is a child or adolescent, the stored gametes should be destroyed upon the death of that child or adolescent. In adults, if there is prior authorization to use sperm for reproductive purposes, it can be donated or used by a surviving spouse. In 2004, ESHRE felt that because stored ovarian tissue or oocytes were both too experimental and would require the use of a surrogate, use after death, even if the oocyte provider gave consent, should not be permitted [22]. The ASRM practice committee outlines the elements of informed consent for women wishing to cryopreserve oocytes for their own use and stresses that this is still an experimental procedure [23].

Because oocytes are such a valuable commodity for both reproductive and research purposes, perhaps we will learn how to harvest them – like organs – from young women who have died. Should society permit family members to harvest gametes in order to create children whose genetic mother is dead? We have plenty of examples where this is a natural reaction of grieving widows and parents who want to harvest sperm from dead men, and many institutions are now writing policies on how to handle these kinds of requests. Should gametes be treated like other organs of the body? If a woman has signed an organ donor card, or if her family agrees to organ donation, does this mean that ovaries are fair game for harvesting? What law should govern such protocols or should estate law be the paradigm for transfer? Or should society require explicit consent from potential organ donors because gametes' reproductive potential makes them much different than bone marrow or liver cells? Reviews of the literature show that oocyte donors do not think of oocytes the same way they think of the donation of other organs [24].

For the most part, as a matter of policy, clinics typically treat embryos created from donor gametes as the "property" of the intended recipient(s). When a couple decides they have completed their family and still have frozen embryos, it is often extremely difficult for them to make a decision about what to do with the frozen embryos [9, 25– 27]. There are three options for these leftover embryos: (1) Allow them to die and dispose of them, (2) donate them to others seeking fertility treatment, or (3) donate them for research purposes. When those making the donation decision are the providers of the gametes used to create the embryos, they still may wish to put restrictions on the types of research for which the embryos are used [28]. When embryos were initially created with donor oocytes, couples are more likely to donate rather than destroy excess embryos [29]. When the embryos were made from one or more donor gametes, there is no clear answer about whether or not gamete donors must be informed or provide their consent for options 2 and 3. It is possible to ask the oocyte donor, at the time of donation, whether she consents to having excess embryos donated for reproductive or research purposes, but is it ethically necessary to do so? This is not normal practice for sperm donation, and perhaps an oocyte donor's rights to determine the disposition of her oocytes end once they are fertilized. The National Research Council-Institute of Medicine (NRC-IOM) report states that for embryo research protocols, each of the gamete donors must provide explicit consent for that particular protocol [30]. This would mean that in order to donate excess embryos for research purposes, the oocyte donor would need to be recontacted, informed about the protocol, and provide consent. As a result, many studies using embryos recruit their own gamete donors because the NRC-IOM recommendation is unduly burdensome.

As well, new conflicts are arising as the result of third-party reproduction. For instance, what if a couple, who still has embryos in storage, divorces? Most courts in the USA have sided with the parent who does not want their embryos to be used to produce children, but what if the woman is no longer producing oocytes and the embryos are her only chance of having biological children? Should courts give the woman "custody" of those embryos but absolve the biological father from all parental responsibility? Of course, this still would not absolve the father from what society sees as a parental obligation that comes from the genetic relationship with the child. What if one or both of the gamete providers die while

embryos are in storage. Should other members of the family such as intimate partners or parents "inherit" the embryos? If there is documentation of the gamete providers' wishes for the disposition of the embryos in the case of death, should this trump family member's wishes or state legislation?

Fertility clinics and private companies have also attempted to create embryo banks so that reproductive material is readily available to couples seeking fertility treatment; however, it appears that all of these ventures in the USA have been abandoned. There is public discomfort with organizations "owning" and "selling" the seeds of human life [31–33]. Still, there is the possibility that embryo banks could become an accepted service provided by fertility clinics or private companies. Alternatively, couples who cannot contribute genetically to creating a child can now customize their child by selecting an oocyte and sperm donor. In any case, because obtaining oocytes requires the participation of a physician, physicians must ask themselves whether they are prepared to participate in providing this kind of service.

Who Are the Parents?

When the first child was born as the result of an embryo donation in 1984, the headlines of the *Los Angeles Times* read "Woman Delivers Donor's Baby." The headline made the assumption that genetics trumped both gestation and intention to parent in determining who the "real" mother was. With the advent of ART, there are potentially five different adults who can be involved in the creation of a child – the two providers of the genetic material, the adult(s) who raise the child, and the woman who gestates the fetus. Laws vary by state in terms of who is recognized as the legal parent(s) at various stages in the process, but usually there is a person or couple who are intending to raise the child. Advocates of fertility services have lobbied to change laws so that intended parents have legal parentage, but there are still debates about who are the rightful parents when disputes erupt.

Women and couples who avail themselves of oocyte donation and gestate the fetus typically do not have to be concerned about retaining custody. The fact that oocyte donation requires the participation of the medical community, compared to "do it yourself" sperm donation, creates an advantage for intended couples. In many cases, the recipients of the oocytes are completely anonymous to the donor. The donor is not even told if a child resulted from the donation. While clinics have claimed this is to prevent the donor from being concerned about her own fertility or feeling as though her efforts were in vain if a child is not born, the secrecy also serves to assuage any concerns that the recipients might have that the donor could attempt to become part of the child's life. There are no cases on record of oocyte donors attempting to fight for custody of children particularly when the gestating woman is also the intended mother.

Custody has only been disputed when oocytes or embryos from would-be intended parents have been mistakenly transferred into the wrong patient's uterus or intentionally misappropriated. Laboratory errors occur. Embryos were transferred into the wrong woman's uterus in Connecticut [34], Wales [35], Hong Kong [36], and Japan [37]. In the first three cases, the mistake was discovered immediately, and the women took the morning after pill to prevent the embryos from implanting. The woman in Japan was not informed until weeks into her pregnancy, and though there was actually a chance that the fetus was from her genetic material, she chose to abort the pregnancy [37].

In the most tragic case, a clinic in Ohio transferred the wrong embryos into Carolyn Savage's uterus in 2009 [38]. The clinic informed her of the error on the day they informed her she was pregnant. The clinic told her she had one of two options: Abort the fetus or carry the baby to term and permit the biological parents to adopt the child. As a deeply religious couple that believed life begins at conception, the Savages chose not to abort the fetus. Carolyn carried the fetus to term and gave the boy to his biological parents.

The ASRM has written an ethics statement to address medical errors. Although laboratories

have strict protocols to avoid mix-ups, humans make mistakes. The guidelines recommend that any medical errors be immediately disclosed to all parties affected by the error [39].

Perhaps the darkest events in the history of ART occurred at the University of California, Irvine's Center for Reproductive Health between the late 1980s and 1995. Two reproductive endocrinologists, Drs. Ricardo Asch and Jose Balmaceda, intentionally misappropriated fertility patients' oocytes and embryos and transferred them without consent into the uteri of other infertility patients, as well as provided embryos to embryo researchers. Once the misdeeds came to light, the two physicians fled the country, Asch to Mexico and Balmaceda to Chile, in order to avoid prosecution, where they continue to practice reproductive medicine to this day. The US government is still in the process of attempting to extradite them, but it is unclear as to what the actual criminal charges will be, since there were no specific laws covering gamete and embryo theft.

Medical records are sketchy, but it appears that approximately 15 children were born as the result of misappropriated embryos at the University of California, Irvine. Medical records show that Loretta Jorge was one of the women whose oocytes were used to create embryos and were transferred into another woman's uterus. The Jorges, who were never able to have their own biological children, know that another woman gave birth to twins using Loretta's eggs. The Jorges filed suit seeking custody of the children, but the recipients refused to allow a genetic test to determine whether the children were genetically related to the Jorges [40]. Similarly, medical records show that the embryos of Shirel and Steve Crawford were transferred into the uterus of another woman who gave birth in two separate pregnancies to a boy and a girl. The Crawfords hired a private detective to try and locate the children, who are now adults, but to no avail. They live with heartache believing they may never know their biological children. In all, UC, Irvine, has paid settlement claims for 137 separate incidents in which oocytes or embryos were either unaccounted for or given to other women without consent [41], and the decimation of this major reproductive medicine and research organization under the weight of scandal caused a collapse of faith in reproductive medicine among many in society.

Why Are We Still Debating Compensation to Donors?

Oocyte donation, like many ARTs, developed outside the traditional experimental process of most new therapies. In many fields, new technologies go through an extended experimental period that has some measure of oversight. If oocyte donation research had been funded by the National Institutes of Health (NIH) or was developed in a research facility that accepted federal funds, the protocols would have been reviewed by an institutional review board (IRB). Frequently, health participants in research protocols are compensated for their time, inconvenience, and the risk of participation. The practice of oocyte donation developed in a much different environment. When consent forms were used, there was evidence that the risks to oocyte donors were minimized when compared to the risks listed for the same process with fertility patients [11]. Rather than recruiting oocyte donors directly, many fertility centers relied on third parties to recruit, screen, pay, and *inform* oocyte donors. Donors described feeling less like patients and more like guinea pigs when they went in for the clinic visits [42].

As donors became more experienced and networked through the growth of online social networking, many of them realized that they could set the terms of their donation. Women began marketing themselves directly to infertile couples, and couples and brokers began recruiting primarily through college newspaper classified ads. Donors with particular phenotypic characteristics were in higher demand, and the market was all that controlled the compensation to donors. Offers of compensation as high as $100,000 made headlines [43]. Eventually, attempts were made to put limits on the compensation provided to oocyte donors. The ASRM issued an ethics committee statement that

compensation should be approximately $5,000 and making the claim that there is no justification for compensation of $10,000 [44], but demand to recruit the limited number of potential donors in certain communities like New York City drove these compensation rates to $10,000 and higher.

Much has been written about how selecting gametes based on the phenotype of the donor (along with a number of social traits such as education) is a step too far toward commodifying children. The concern is that there is still a great deal of uncertainty in the creation of a child, but when you put a dollar value on one, you begin to expect a certain quality for your investment [45, 46]. There are no guarantees with human reproduction. Much can happen when DNA from gametes combines, which is unpredictable.

Had oocyte donation developed within the same regulatory framework as research, with compensation amounts reviewed and approved by an IRB that were deemed to be fair but not coercive, it is unlikely that we would still be debating payment to donors almost three decades after the first birth from an oocyte donation. It is the complicity of the medical community with this market-based system of compensation that most critics object to. Additionally, if we pay a donor who is tall, with blonde hair and blue eyes, and a high IQ much more than we would pay a woman of color, this implies that babies with these characteristics are more valuable.

Other countries have taken a very different approach to compensating oocyte donors. In the UK, oocyte donor compensation is permitted only for donor expenses, though the HFEA recently increased the amount donors may be compensated [47]. The ESHRE ethics committee stated in its 2002 ethics guidelines that compensation for reproductive material is unethical [48]. Compensation for the donor's time and effort is acceptable; however, the compensation could not be high enough where it would be perceived as a profit or entice people who otherwise would not donate or cause them to withhold information that might be important for the safety of the donation. The committee argued that excessive compensation would undermine "the very notion of informed consent by the donor" [48].

An alternative model of compensation has developed particularly in the UK, where payments are limited, but also in the USA. Women undergoing IVF for their own infertility treatment are offered a reduction in treatment costs in exchange for donating some of their oocytes. These oocyte-sharing arrangements have garnered both praise and criticism [49–51]. The oocyte donor is not subjected to invasive medical treatments where there is no benefit to her as traditional oocyte donors are asked to do, fertility patients often produce more oocytes than are needed, and this arrangement appears to benefit both parties. Others have argued that this arrangement takes advantage of women who could not otherwise afford IVF because each donated oocyte potentially reduces her changes of obtaining a pregnancy. This may be less true today as success rates using fewer embryos per transfer are resulting in better success rates than a decade ago.

If reproductive oocyte donors are well compensated, equity would assume that donors for research purposes would also be well compensated. Similarly, couples who have stored embryos left over from fertility treatment might be expected to be able to recoup some of their investment by selling embryos to researchers. Oddly, in the USA, this is not the case. The committee that wrote the NRC-IOM report [30] recommended that individuals who donate gametes for research purposes not be compensated. Similarly, the ASRM ethics committee has recommended that fertility patients being offered the chance to donate embryos to research not be compensated [52]. Other prominent ethics advisory committees have come to the conclusion that donors ought to be compensated just like individuals who participate in research that has no therapeutic benefit [53–55]. Payment for gametes and embryos for research purposes has become a contentious issue [56–60]. On the one hand, there are those who argue that embryonic stem-cell research will be unable to proceed unless we are able to pay donors because there simply are not enough women who will go through all that is involved to donate altruistically [58]. On the other hand, there are great concerns that because the phenotype of the donor is no

longer important, women in other countries where the regulations and laws are less stringent will be coerced into donating for little compensation, contributing to a research agenda they and members of their community will never benefit from [56, 57].

Mitochondrial DNA from Donor Oocytes

There are two potential purposes for developing a technology that can combine the DNA of one woman's oocyte with the mitochondrial DNA of another woman's oocyte. The first is that it can permit a woman at risk of transmitting a mitochondrial DNA disorder to have a potentially healthy, genetically related child. The second purpose is that the technology might allow women of advanced maternal age to have genetically related children with the assistance of donor cytoplasm. There are three scientific procedures under study, and donor oocytes are required for all three.

The first technique is *cytoplasmic or ooplasmic transfer (CT)*. Researchers remove a fraction of the cytoplasm from the donor oocyte and inject it into the recipient's oocyte prior to or at the same time as fertilization.

The second technique is called *pronuclear transfer (PNT)*. IVF is performed using the intended parent's sperm and oocyte. Once the oocyte is fertilized, it contains the separate genetic material of the sperm and that of the oocyte cell each enclosed in a membrane. These are called the male and female pronuclei. The embryo also contains the mother's mitochondria, which originates from the cytoplasm in her oocyte. When the embryo is still a single undivided cell, the two pronuclei are removed from the single-celled zygote. A donor oocyte is then fertilized. At the same state of development, the two pronuclei within the donor's zygote are removed and discarded. The parent's pronuclei are then placed into the enucleated zygote. The reconstructed embryo cell now contains the pronuclear DNA from the intended parents and the mitochondria from the donor's oocyte.

The third technique is called *maternal spindle transfer (MST)*. Maternal spindle transfer (also known as "metaphase II spindle transfer") is a transfer technique that works on a similar principle to PNT. The main difference between the two techniques is that MST uses two unfertilized eggs to reconstruct an egg with healthy mitochondria that can then be fertilized.

The birth of the first baby using CT was announced in a letter to the editor of the Lancet by a US-based fertility clinic [61]. A year later, another clinic in the USA reported a live twin birth following CT from frozen donor oocytes [62]. In addition, a Chinese team of researchers reported live births (five healthy infants and three ongoing pregnancies in nine patients) after the injection of sperm and the cytoplasm of tripronucleate zygotes into metaphase II oocytes of patients with repeated implantation failure [63]. In 2001, the original US-based fertility clinic reported on 28 cases of CT. They claimed 12 clinical pregnancies and that there had been 30 live births worldwide following CT [64]. Later that year, the clinic admitted that, in addition to the 15 healthy live births, there were two additional fetuses with Turners Syndrome (one miscarried and the other was aborted) and one case of Pervasive Developmental Disorder [65]. Some of the children born after CT had mtDNA from both oocytes. This heteroplasmy of different variants of mitochondria has prompted safety concerns [64, 66]. Italian researchers report in 2001 the birth of healthy twins following CT [67].

In July of 2001, the US Food and Drug Administration (FDA) sent a letter to sponsors and researchers stating that they need an IND before continuing research into CT. The two primary US-based research institutes that are developing this technology continue conducting research on animal models and claim to be working with the FDA to establish an IND, so the research can continue. CT is not legal in the UK under the HFE Act because it alters an egg before it is transferred to a woman. There were media reports of US couples traveling abroad to seek CT after the ban, however, including the parents of a child who had been born following CT [68]. Indeed, at present, CT is offered with IVF in

many countries. For example, in 2011, reports from Chennai, India, noted the births of healthy twins after CT, which were reportedly the "first in Asia" [69], although this may not be the case. In 2012, commercial websites have listed clinics offering CT in India, North Cyprus, Ukraine, Armenia, Georgia, Israel, Turkey, Thailand, Singapore, Germany, and Austria [70].

Since the 1990s, experiments using PNT in mice have shown that reconstructed embryos continue to develop after pronuclear transfer. These experiments show promise that PNT might be an effective means of preventing mtDNA disorders. There are no reported live human births following PNT; however, at the 2003 meeting of the American Society for Reproductive Medicine, Dr. Jamie Grifo from New York University and his colleagues at Sun Yat-Sen University in Guangzhou, China, announced a triplet pregnancy following PNT [71]. The multiple gestation pregnancy was selectively reduced to twins. Unfortunately, some months later, the pregnancy ended in a miscarriage. PNT and MST research using animal [72] and human gametes that were not transferred to the uterus has continued in the UK [73]. CT is illegal in the UK because it is considered to be genetic modification.

The guiding principle for governance of all these technologies to date has been safety, a difficult bar to say the least. The Nuffield Council, an ethics board in the UK, declared PNT and MST to be ethical for the purpose of mitochondrial disease prevention if the technologies prove to be safe and effective [74]. It must be noted that the Nuffield Council is funded by the Wellcome Trust which also funds the Wellcome Centre for Mitochondrial Research at the University of Newcastle. The Human Fertilisation and Embryology Authority (HFEA) report recommended that before PNT and MST could be used in treatment, specific safety must first be established [75].

Safety of these technologies is also the principle focus of the US FDA and the UK HFEA, two organizations that have taken essentially opposite approaches to governance of new reproductive technologies to date. Both maintain that if these technologies can be developed to the point where safety and efficacy can be established, the next ethical question is whether these technologies may amount to germ-line genetic modification [76]. The media has focused on the notion that the child born from these technologies will have "three genetic parents" [77]. While this technically may be true, it will only express the DNA of two parents. The third would only contribute mtDNA which does not influence the phenotype of the child. But, what are the implications of intervening with mtDNA both physically and psychologically? Physicians engaged in this research ought to keep databases of these children so that long-term follow-up studies can be conducted. Finally, like oocyte donation for research, the phenotype of the donor does not matter with these technologies. Unlike reproductive donors who are carefully selected for characteristics and traits that tend to make the women less likely to be exploited (presumable college-aged women can read and comprehend a consent form, have the financial means to support themselves, and access to the Internet where they can research and talk to other former oocyte donors), the DNA of oocyte donors for CT, PNT, or MST does not matter. It would be very easy to outsource, obtaining this commodity to India in much the same way we see happening currently with gestational carrier surrogates [78].

Physicians engaged in oocyte and embryo donation must bear a measure of responsibility for what is taking place in their own clinics and also for knowledge of and ability to relay to patients the current national and international trends. The physician/nurse-patient relationship is grounded in trust. Just as laboratory procedures that are anything but meticulous can lead to lifelong heartache, caregivers must rigorously study those guidelines provided by the ASRM and ESHRE and identify best practices for recruiting, counseling, and informing potential oocyte and embryo donors in order to minimize potential harm. Values that govern medical practice must also be extended to women who are willing to donate oocytes. Although there is an inherent conflict of interest in the doctor/nurse-donor relationship [79], it is incumbent upon the physician to treat patients who merely act as donors

with as much care and respect as physicians would give the patients for whom their goal is to cure. This includes providing adequate follow-up care and even engaging in follow-up research to determine the long-term risks of oocyte donation and also means being aware of trends in society that could lead to the exploitation of economically disadvantaged donors [80]. Physicians will likely be held responsible for their participation in the use, for example, of gametes and embryos obtained from banks or international organizations, that is, to ensure that they are reputable organizations in full compliance with standards designed to protect both the donors and recipients of genetic material.

Editor's Commentary

Public debate over the ethics of assisted reproduction occurred long before the birth of Louise Brown, and it continues to draw interest. Of course this is not surprising, as it is deserving of such attention. After all, our field of medicine abuts with religion, law, and ethics, and we deal with the most primal elements of life. There will never be a unanimous decision reached on the majority of our basic tenets, but that does not mean that we cannot reach a reasonable consensus opinion on many, if not most, of our challenging issues.

Drs. Kalfoglou and McGee focus on contemporary issues that have been spotlighted in the media. This chapter serves as a nice companion piece to the earlier commentary on ethics written for the 1st edition of the book. Some of the newer controversies have been generated as a result of the natural evolution of egg and embryo donation over time. For instance, it was questionably ethical to pay egg donors $250 to participate in "research" in 1984 at UCLA; it is certainly more reasonable to question the payment at today's rate of $8,000 per cycle. Egg banking, a technique which will likely revolutionize the manner in which we store and utilize donor eggs in the future, ushers in a whole new set of circumstantial dilemmas, including posthumous use of stored gametes. Extending services to single menopausal women, gay men using gestational carriers, or other less than traditional recipients has become increasingly commonplace and yet far from accepted standard of practice, at least in many parts of the world.

I believe that we need to be particularly aware of the general public's social sensitivities. As a field of medicine, we have come very far, very fast. Our general charge is to enhance the quality of a woman's life by making her a mother, and yet our techniques, including those developed using egg donation, may now produce children who by design will never know their genetic parents. Certainly there exists a chorus of voices opposed to such actions, and therefore we need to be methodically focused on assuring ourselves, and the public, that the actions we take "do no harm." Harm in this case means not only to the individual but to society at large.

References

1. Blyth E. Information on genetic origins in donor-assisted conception: is knowing who you are a human rights issue? Hum Fertil (Camb). 2002;5(4):185–92. Provides a full analysis on knowing your genetic origins as a human right.
2. Lorbach C. Experiences of donor conception: parents, offspring and donors through the years. Philadelphia: Jessica Kingsley Publishers Inc.; 2009.
3. Kenney NJ, McGowan ML. Looking back: egg donors' retrospective evaluations of their motivations, expectations, and experiences during their first donation cycle. Fertil Steril. 2010;93(2):455–66.
4. Lindheim S, Porat N, Jaeger A. Survey report of gamete donors' and recipients' preferences regarding disclosure of third party reproduction outcomes and genetic risk information. J Obstet Gynaecol Res. 2011;37(4):292–9.
5. Center for Disease Control and Prevention (CDC). Assisted reproductive technology (ART) report: national summary report. 2010. http://apps.nccd.cdc.gov/art/Apps/NationalSummaryReport.aspx. Accessed 20 June 2012.

6. Center for Disease Control and Prevention (CDC). 2009 Assisted reproductive technology (ART) report: section 4: ART cycles using donor eggs. http://www.cdc.gov/art/ART2009/section4.htm. Accessed 20 June 2012.
7. Walker J. Genetic parents win custody of baby: California judge also denies surrogate mother visitation rights. The Washington Post. Tuesday, 23 Oct 1990;A4.
8. Hoffman DI, Zellman GL, Fair CC, Mayer JF, Zeitz, JG, Gibbons WE, Turner TG. Cryopreserved embryos in the United States and their availability for research. Fertil Steril. 2003;79(5):1063–9. http://www.rand.org/pubs/research_briefs/RB9038/index1.html. Accessed 23 June 2012.
9. Lyerly AD, Steinhauser K, Voils C, et al. Fertility patients' views about frozen embryo disposition: results of a multi-institutional U.S. survey. Fertil Steril. 2010;93(2):499–509.
10. Provoost V, Pennings G, De Sutter P, Van de Velde A, Dhont M. Trends in embryo disposition decisions: patients' responses to a 15-year mailing program. Hum Reprod. 2012;27(2):506–14.
11. New York State Task Force on Life and the Law. Assisted reproductive technology: analysis and recommendations for public policy. 1998. Executive summary available at: http://www.health.ny.gov/regulations/task_force/reports_publications/execsum.htm. Accessed 23 June 2012.
12. Kalfoglou AL, Geller G. A follow-up study with oocyte donors exploring their experiences, knowledge, and attitudes about the use of their oocytes and the outcome of the donation. Fertil Steril. 2000;74(4):660–7.
13. New York State Task Force on Life and the Law. Thinking of becoming an egg donor? Get the facts before you decide! 2002. Available at: http://www.health.ny.gov/publications/1127/. Accessed 23 June 2012.
14. Examples of oocyte banks advertising on the Internet. https://www.donoreggbankusa.com/, http://www.myeggbank.com/donor-eggs/index.php, http://www.fairfaxeggbank.com/, https://www.nwcryobank.com/. Accessed 20 June 2012.
15. Johnson M. (U.K. Parliamentary Under-Secretary of State, Department of Health). The Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 20042004 No. 1511. http://www.legislation.gov.uk/2004/1511. Accessed 20 Dec 2012.
16. Kalfoglou AL, Sauer MV. A precautionary approach to oocyte donation for stem cell nuclear transplantation. Am J Bioeth. 2011;11(9):31–3.
17. Extend FertilityTM. Female egg banking services. http://www.extendfertility.com/female-egg-banking.htm. Accessed 20 June 2012.
18. Frozen Egg Bank, Inc. Frozen donor eggs reverse the biologic clock. http://www.eggfreezing.com/. Accessed 20 June 2012.
19. Dondorp W, De Wert G. Fertility preservation for healthy women: ethical aspects. Hum Reprod. 2009;24(8):1779–85.
20. Dondorp W, de Wert G, Pennings G, et al. Oocyte cryopreservation for age-related fertility loss. Hum Reprod. 2012;27(5):1231–7.
21. The Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril. 2005;83(6):1622–8.
22. ESHRE Task Force on Ethics and the Law. Taskforce 7: ethical considerations for the cryopreservation of gametes and reproductive tissues for self use. Hum Reprod. 2004;19(2):460–2.
23. The Practice Committee of the Society for Assisted Reproductive Technology and the American Society of Reproductive Medicine. Essential elements of informed consent for elective oocyte cryopreservation: a practice committee opinion. Fertil Steril. 2008;90:S134–5.
24. Bahadur G, Morrison M, Machin L. Beyond the 'embryo question': human embryonic stem cell ethics in the context of biomaterial donation in the UK. Reprod Biomed Online. 2010;21(7):868–74.
25. de Lacey S. Decisions for the fate of frozen embryos: fresh insights into patients' thinking and their rationales for donating or discarding embryos. Hum Reprod. 2007;22(6):1751–8.
26. McMahon CA, Saunders DM. Attitudes of couples with stored frozen embryos toward conditional embryo donation. Fertil Steril. 2009;91(1):140–7.
27. Lyerly A, Steinhauser K, Namey E, et al. Factors that affect infertility patients' decisions about disposition of frozen embryos. Fertil Steril. 2006;85(6):1623–30.
28. Ehrich K, Farsides B, Williams C, Scott R. Constructing an ethical framework for embryo donation to research: is it time for a restricted consent policy? Hum Fertil. 2011;14(2):115–21.
29. Sehnert B, Chetkowski RJ. Secondary donation of frozen embryos is more common after pregnancy initiation with donated eggs than after in vitro fertilization-embryo transfer and gamete intrafallopian transfer. Fertil Steril. 1998;69(2):350–2.
30. National Research Council and Institute of Medicine. Final Report of The National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to The National Academies'. Guidelines for human embryonic stem cell research. National Academy Press: Washington. 2010. http://www.nap.edu/catalog.php?record_id=12923#toc. Accessed 22 July 2012.
31. Stein R. 'Embryo bank' stirs ethics fears. The Washington Post Saturday. 6 Jan 2007. http://www.washingtonpost.com/wpdyn/content/article/2007/01/05/AR2007010501953.html. Accessed 20 June 2012.
32. Kolata G. Clinics selling embryos made for 'adoption'. NY Times. 23 Nov 1997. http://www.nytimes.com/1997/11/23/us/clinics-selling-embryos-made-

for-adoption.html?pagewanted=all&src=pm. Accessed 20 June 2012.
33. Ryan J. Press release: Abraham Center for Life no longer in embryo business. 30 May 2007. http://www.eworldwire.com/pressrelease/17092. Accessed 20 June 2012.
34. NBC Connecticut. Fertility center fined for giving patient wrong embryos, Monday, 28 June 2010. http://www.nbcconnecticut.com/news/local/Fertility-Center-Fined-for-Giving-Patient-Wrong-Embryos-97267539.html. Accessed 21 June 2012.
35. BBC News. Embryo mix up couple to speak out. Monday, 15 June 2009. http://news.bbc.co.uk/2/hi/8098553.stm Accessed 21 June 2012.
36. Randhaws K. Top IVF clinic gives woman wrong embryos. London Evening Standard, 18 July 2011. http://www.standard.co.uk/news/top-ivf-clinic-gives-woman-wrong-embryos-6423018.html. Accessed 21 June 2012.
37. Saletan W. Scrambled eggs: aborting a fetus because it's not yours. Slade. Wednesday, 18 March 2009. http://www.slate.com/articles/health_and_science/human_nature/2009/03/scrambled_eggs.html. Accessed 21 June 2012.
38. Celizic M. She was implanted with the wrong embryo: plans to say 'hello, and goodbye' when she delivers the baby soon. NBC News. 21 September 2009. http://today.msnbc.msn.com/id/32950836/ns/today-today_health/t/she-was-implanted-wrong-embryo/#.UNPD67apZIZ. Accessed 21 June 2012.
39. Ethics Committee of the American Society for Reproductive Medicine (ASRM). Disclosure of medical errors involving gametes and embryos. Fertil Steril. 2011;96:1312–4.
40. Snyder RS. Reproductive technology and stolen ova: who is the mother? Law Inequal. 1998;16(1):289–334.
41. Yoshino K. UCI settles dozens of fertility suits. Los Angeles Times. 11 Sept 2009. http://articles.latimes.com/2009/sep/11/local/me-uci-fertility11. Accessed 22 June 2012.
42. Kalfoglou AL, Gittelsohn J. A qualitative follow-up study of women's experiences with oocyte donation. Hum Reprod. 2000;15(4):798–805.
43. Alfonsi S. Inside egg donation: more money for blondes? ABC News. 11 May 2010. http://abcnews.go.com/WN/egg-donation-agencies-paid-money-favored-attributes/story?id=10614326. Accessed 23 June 2012.
44. Ethics Committee of the American Society for Reproductive Medicine (ASRM). Financial compensation of oocyte donors. Fertil Steril. 2007;88:304–9.
45. Fox D. Paying for particulars in people-to-be: commercialisation, commodification and commensurability in human reproduction. J Med Ethics. 2008;34(3):162–6.
46. Macklin R. What is wrong with commodification? In: Cohen CB, editor. New ways of making babies: the case of egg donation. Bloomington: Indiana University Press; 1996.
47. Hughes J, Gallagher J. Egg donor compensation is to triple under new HFEA guidelines. BBC News. 19 Oct 2011.
48. ESHRE Task Force on Ethics and Law. Task Force III: gamete and embryo donation. Hum Reprod. 2002;17(5):1407–8.
49. Blyth E. Subsidized IVF: the development of 'egg sharing' in the United Kingdom. Hum Reprod. 2002;17(12):3254–9.
50. Strathen M. Reflections on gamete donation. BioNews No. 630 24 October 2011. http://www.bionews.org.uk/page_110416.asp. Accessed 26 June 2012.
51. Gürtin ZB, Ahuja KK, Golombok S. Egg-sharing, consent and exploitation: examining donors' and recipients' circumstances and retrospective reflections. Reprod Biomed Online. 2012;24(7):698–708.
52. American Society for Reproductive Medicine (ASRM) Ethics Committee. Donating spare embryos for stem cell research. Fertil Steril. 2009;91(3):667–70.
53. Carson S, Eschenbach D, Lomax G, Rice V, Sauer M, Taylor R. Proposed oocyte donation guidelines for stem cell research. Fertil Steril. 2010;94(7):2503–6.
54. Statement on the compensation of oocyte donors. New York State Stem Cell Science [online]. 2009. http://www.stemcell.ny.gov/docs/ESSCB_Statement_on_Compensation_of_Oocyte_Donors.pdf.
55. http://www.bionews.org.uk/page_110416.asp. Accessed 26 June 2012.
56. Batzer F, Daar J. Harmony and compensation for oocyte providers. Am J Bioeth. 2011;11(9):39–41.
57. Dickenson D. The threatened trade in human ova. Nat Rev Genet. 2004;5(3):167.
58. Dickenson D. Good science and good ethics: why we should discourage payment for eggs for stem cell research. Nat Rev Genet. 2009;10(11):743.
59. Klitzman R, Sauer M. Payment of egg donors in stem cell research in the USA. Reprod Biomed Online. 2009;18(5):603–8.
60. Ramsey J. Donating eggs for research – should the HFEA reconsider its policy on payments to egg donors? Reprod Biomed Online. 2007;15:25–33.
61. Cohen J, Scott R, Schimmel T, Levron J, Willadsen S. Birth of infant after transfer of anucleate donor oocyte cytoplasm into recipient eggs. Lancet. 1997;350(9072):186–7.
62. Lanzendorf SE, Mayer JF, Toner J, Oehninger S, Saffan DS, Muasher S. Pregnancy following transfer of ooplasm from cryopreserved-thawed donor oocytes into recipient oocytes. Fertil Steril. 1999;71(3):575–7.
63. Huang CC, Cheng TC, Chang HH, et al. Birth after the injection of sperm and the cytoplasm of tripronucleate zygotes into metaphase II oocytes in patients with repeated implantation failure after assisted fertilization procedures. Fertil Steril. 1999;72(4):702–6.
64. Barritt JA, Brenner CA, Malter HE, Cohen J. Mitochondria in human offspring derived from

ooplasmic transplantation: brief communication. Hum Reprod. 2001;16:513–6.
65. Barritt JA, Brenner CA, Malter HE, Cohen J. Rebuttal: interooplasmic transfers in humans. Reprod Biomed Online. 2001;3(1):47–8.
66. Brenner C, Barritt J, Willadsen S, Cohen J. Mitochondrial DNA heteroplasmy after human ooplasmic transplantation. Fertil Steril. 2000;74:573–8.
67. Dale B, Wilding M, Botta G, et al. Pregnancy after cytoplasmic transfer in a couple suffering from idiopathic infertility: case report. Hum Reprod. 2001;16(7):1469–72.
68. How far will couples go to conceive? CNN.com. 17 June 2004. Available at: http://edition.cnn.com/2004/HEALTH/03/12/infertility.treatment/index.html. Accessed 26 June 2012.
69. WebIndia123. Woman conceives through cytoplasmic transfer technology. 21 November 2011. http://news.webindia123.com/news/articles/India/20111121/1876130.html. Accessed 20 Dec 2012.
70. Medical Tourism India. Cytoplasmic transfer. Wednesday, 31 Aug 2011. http://www.medicaltourism.in/medical-tourism-procedures/ayurvedic-therapies/gynecology-ivf-treatment-female-reproductive-system-and-pregnancy/cytoplasmic-transfer/cytoplasmic-transfer.html. Accessed 26 June 2012. HealthTourism.com. Cytoplasmic transfer abroad – medical tourism guide. Details of leading clinics and hospitals performing cytoplasmic transfer to foreign patients. http://www.health-tourism.com/cytoplasmic-transfer/. Accessed 26 June 2012.
71. BBC News Online. Foetus with three parents created. 14Oct2003.http://news.bbc.co.uk/1/hi/health/3189718.stm. Accessed 26 June 2012.
72. Tachibana M, Sparman M, Sritanaudomchai H, et al. Mitochondrial gene replacement in primate offspring and embryonic stem cells. Nature. 2009;461:367–72.
73. Craven L, Tuppen HA, Greggains GD, et al. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature. 2010;465:82–5.
74. Nuffield Council on Bioethics. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review. 2012. http://www.nuffieldbioethics.org//mitochondrial-dna-disorders. Accessed 26 June 2012.
75. Human Fertilisation and Embryology Authority. Review of scientific methods to avoid mitochondrial disease 2011. 2012. Available at: http://www.hfea.gov.uk/6372.html. Accessed 26 June 2012.
76. Bredenoord AL, Pennings G, de Wert G. Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues. Hum Reprod Update. 2008;14(6):669–78.
77. Sample I. 'Three parent babies' cure for illness raises ethical fears. The Guardian. 5 June 2012. http://www.guardian.co.uk/science/2012/jun/05/mitochondrial-genetic-disease-ethical-doubts. Accessed 26 June 2012.
78. Medical Tourism Corporation. India gestational surrogacy success rate. 7 Jan 2009. http://www.medicaltourismco.com/medical-tourism/india-gestational-surrogacy-success-rate/. Accessed 26 June 2012.
79. Kalfoglou AL, Geller G. Navigating conflict of interest in oocyte donation: an analysis of donors' experiences. Womens Health Issues. 2000;10(5):226–39.
80. Kalbian A. Considering the risks to economically disadvantaged egg donors. Am J Bioeth. 2011;11(9):44–5.