NEW DEBATE

Oocyte donation for stem cell research

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The future success of stem cell research by means of somatic cell nuclear transfer (SCNT) depends on a sufficient supply of human oocytes. However, oocyte donation presents certain risks for the donor, and concerns for women’s welfare are rightly vocalized. At the same time, these risks are comparable with the risks faced by other healthy research subjects. Thus, research donation can withstand ethical scrutiny if it fulfils the same conditions as other research involving healthy human subjects. Specifically, this means that the benefits of the research project need to outweigh the harms, that risks must be minimized, that informed consent has to be guaranteed by averting undue inducement and the recruitment of vulnerable women and that donors can and should be reimbursed for their research participation.

Key words: ethics/oocyte donation/research subject/stem cell research/undue inducement

Introduction

In the wake of the Hwang scandal (Cyranoski, 2006), it has become clear that the future success of developing patient-specific stem cell lines by somatic cell nuclear transfer (SCNT) will depend largely on a sufficient supply of human oocytes. However, oocyte donation after ovulation induction presents certain risks for the donor, and concerns for women’s welfare are rightly vocalized. Some interest groups try to reinforce the idea that in this context, science and women’s welfare are conflicting to the extent that they seem incompatible, thus creating the impression that regulators’ choices are limited to either supporting the exploitation of women or hampering scientific progress. This representation stands in sharp contrast to the way other types of research involving healthy human subjects are treated. This type of research is widely accepted, but safeguards are installed to protect research subjects. Specifically, researchers need to ensure that risks are minimal, that participants are sufficiently informed about the risks and discomforts of the procedure and that they freely consent to participate. Although great care is taken to avert undue inducement and the recruitment of vulnerable populations, this does not necessarily rule out reimbursement for research participation.

In this article, we start from the premise that oocyte donors for stem cell research ought to be treated as any other healthy research subject. Next, we focus on ways to optimize the risk–benefit balance by reducing risks and maximizing benefits. The final part will counter arguments that payment of oocyte donors turns oocytes into commodities, jeopardizes informed consent and leads to the exploitation of economically disadvantaged women.

Research donors

An oocyte donor for stem cell research is subjected to the same treatment as an oocyte donor in the reproductive setting, but the aim of the donation is to advance medical knowledge rather than to establish a pregnancy. This objective puts them in the same category as other healthy research subjects, although the protocols to which an oocyte donor is subjected differ somewhat from those of other research subjects. Research subjects are usually subjected to experimental drugs or procedures, and body tissues are not necessarily obtained. Therefore, oocyte donors may be regarded as a special category in between research subjects and oocyte donors for infertility treatments, namely ‘research donors’ (Magnus and Cho, 2005). However, their special status does not mean that there are new ethical issues to be considered in the case of research donation compared with other types of research participation. Both domains involve concerns with regard to risks, informed consent, therapeutic misconceptions and so on. Comparisons with oocyte donation for infertility treatments may be useful in some instances, for example, when considering methods of risk reduction. However, the set of ethical principles involved in infertility treatment—with direct benefits for concrete patients—differs substantially from those involved in research. In our analysis of the ethical issues surrounding oocyte donation for stem cell research, we will therefore rely on the framework of guidelines that is already in place for healthy research subjects rather than on guidelines for other types of donations. This will mainly have repercussions in the discussion surrounding the appropriateness of financial incentives, as there is generally
less restraint to pay research subjects than there is to pay the donors of human tissues—such as blood, bone marrow or organs—for therapy.

Locating research donation in the broader research setting, rather than treating it as an unprecedented challenge, makes it easier to formulate conditions to reconcile a vital subfield of embryonic stem cell research and the well-being of the oocyte donors. These conditions are based on the principle of proportionality, which requires that a risk–benefit calculus is made to assure that the benefits for society obtained by the oocyte donation justify the risks for the donors. A similar calculus should be made in case of oocyte donation for infertility treatments, but in these cases, the benefits are of a different nature because the receiving couple is directly and significantly benefitting from the donation, and in cases of donation by friends or family, the donors themselves share this direct benefit.

One aspect simplifying this calculus in the case of research donation is that whereas in most clinical trials both short-term and long-term risks are unknown, the situation in oocyte donation for research is different. Ovarian stimulation and oocyte retrieval are common procedures in infertility treatment, and thus, accurate data are available on the immediate health risks for women. Moreover, because most factors determining those risks are known, it is possible to lower the risks without jeopardizing the procedure. Research into the long-term risks of ovarian stimulation is still underway, and many of the existing studies present conflicting data. However, there are at least some indications about the possible long-term effects—which is not always the case for many other research subjects—that help candidate donors make an informed decision.

**Minimizing risks for donors**

The most important risk that oocyte donors are subjected to is the chance of developing ovarian hyperstimulation syndrome (OHSS). Other risks and discomforts include infections, bleeding and possible currently unknown long-term effects. However, a number of measures can be taken to minimize these risks.

**OHSS: screening donors for predisposing factors, reconsidering ovulation induction regimens and monitoring donors**

OHSS is the most prominent side effect of ovarian stimulation and one of the main reasons for concern in both IVF patients and oocyte donors. It is important to stress that the percentages of OHSS in IVF patients cannot simply be transferred to oocyte donors. The development of severe OHSS is much lower in donors because pregnancy does not usually follow an altruistic donation (apart from donors in an egg-sharing programme), and thus, there is no second wave of hCG (Sauer et al., 1996). Papanikolaou et al. (2005) observed that late OHSS cases are more likely to be severe than early OHSS cases and that almost all late OHSS cases in their study of >4000 IVF/ICSI cycles occurred in a pregnancy cycle (96.7%). These figures thus predict a much smaller risk for donors than for IVF patients. Nevertheless, OHSS does occur even in donors. A number of predisposing factors can be identified such as young age and the presence of polycystic ovaries (Whelan and Vlahos, 2000). These factors constitute reasons for individualized medication regimens and close monitoring in both IVF treatments and research donation. In the latter case, researchers may opt to exclude certain candidate donors altogether when they present high-risk factors. After all, these women receive no direct benefit following their donation, and the oocytes can be obtained from a different donor without any major drawbacks, whereas this is obviously not the case when a woman is stimulated for her own reproduction. Ovulation induction regimens can also be adjusted according to a donor’s response to previous ovarian stimulation cycles. If she experienced an OHSS previously, she is likely to react in a similar way in subsequent stimulation cycles (Sauer et al., 1996) and should thus be refused as a donor or receive a safer level of stimulation.

Besides adjusting regimens on an individual basis, there should be a general trend towards moderation in ovulation induction regimens to diminish the occurrence of OHSS. The wish to obtain as many oocytes (and embryos) as possible to increase the success rate of IVF has led to a preference for high-dose gonadotrophin regimens to obtain a maximum number of oocytes. This caused the prevalence of OHSS to increase at a faster pace than the increase in IVF cycles during the 1990s (Abramov et al., 1999). There have been calls to abandon protocols leading to a maximal ovarian response in infertility treatment (Roest, 1999). This recommendation certainly applies to oocyte donation for research because research donors—in contrast to IVF patients—do not benefit from a maximal number of retrieved oocytes and are unlikely to consent to the same degree of health risks as an IVF patient. Following the same reasoning, if moderate regimens still lead to a strong response in candidate donors, the protocol should be abandoned faster than in IVF patients. Careful monitoring is required to ensure that the protocol is adjusted or cancelled whenever necessary.

**Long-term effects of drugs and procedures**

Despite the frequent use of ovarian stimulation and oocyte retrieval in IVF cycles, there are still a great number of uncertainties surrounding the effects of the used drugs and procedures. Potential donors should be informed about these uncertainties, and long-term follow-up is needed to assess the possible dangers involved. More specifically, heightened chances of developing cancer should receive the necessary attention (Practice Committee of the American Society for Reproductive Medicine, 2004). Several studies have been conducted on this subject, but the results are largely inconclusive, although some consistency is reported on the data that relate to nulligravid women (Ness et al., 2002; Brinton et al., 2005). As more women who were subjected to fertility drugs reach the age at which hormonally related cancers are common and as data on more recent treatment methods become available, further research is certainly warranted. In particular, studies focusing on fertile oocyte donors would be welcome because infertility may itself be a factor influencing cancer susceptibility that is difficult to correct in research based on IVF treatments. Data on adverse effects of the procedure should by preference be collected by an independent physician.
Again, because the donors do not benefit directly from their donation, it is important to err on the safe side. Therefore, as long as long-term effects are unclear, it is advisable to avoid repeated donations by the same woman.

Follow-up care
In accordance with international guidelines on research involving human subjects, research subjects are entitled to free medical treatment for injuries resulting from research participation and should be compensated for any resulting impairment, disability or handicap (CIOMS, 2002). Whether oocyte donors fall under these guidelines at present is debatable, but in keeping with the prerequisite to maximally reduce risks, it is evident that this requirement ought to apply to oocyte donors. This is an important issue because their personal health insurance may not want to cover medical expenses resulting from a procedure that was carried out without medical indications or necessity. Thus, research centres should guarantee free follow-up care for their research subjects, in this case oocyte donors, by ensuring insurance coverage.

Limiting donors to IVF patients
Although health risks for altruistic donors can be minimized by following these recommendations, they cannot be completely removed. Another possibility then is to limit donors to a group of women already subjected to the perils of ovarian stimulation and oocyte retrieval. IVF patients can be asked to either donate oocytes that have failed to fertilize or share their fresh oocytes. Some countries, such as Israel, only allow IVF patients to donate oocytes for reproductive purposes by egg sharing (Rabinerson et al., 2002). Elsewhere, programmes exist in which IVF patients are asked to donate excessive oocytes for research (Heng, 2005; Dennis, 2006; Randerson, 2006).

Because IVF patients are a vulnerable category, a strict separation needs to be respected between the doctors involved in the patient’s treatment and the research team requesting oocytes. Otherwise patients may feel pressurized to donate, and concerns would surface that the patients’ ovaries may be stimulated more than needed for their own treatment, leading to additional health risks. Moreover, to minimize the possible reduction in success rate for the patients themselves, egg sharing should only be allowed when a large number of oocytes are collected. This specifically applies when egg sharers do not receive substantial compensation (discussed later).

Obviously, the number of research oocytes that can be retrieved from IVF patients is limited. Moreover, the use of oocytes that have failed to fertilize during IVF treatment results in poorly developing embryos (Lavoir et al., 2005). Refinement of techniques such as oocyte freezing and especially in vitro maturation (IVM), however, may make more good quality oocytes available (Jaroudi et al., 1999; Trounson et al., 2001). IVM of oocytes would allow a number of retrieved—immature—eggs to be used that are currently considered as inadequate for both fertility treatment and therapeutic cloning. An important proof of principle was delivered by the creation of an embryo by nuclear transfer using an IVM oocyte (Heindryckx et al., 2005). Optimizing the oocyte freezing technique to the level of embryo freezing may in turn result in a preference by IVF patients—and especially women undergoing medical procedures that will jeopardize their future fertility—to freeze oocytes instead of embryos. This will lead to ‘spare oocytes’ instead of ‘spare embryos’. Although these oocytes may be damaged by cryopreservation, they are likely to be of better quality than oocytes that have, for example, failed to fertilize during IVF treatment.

Alternative sources of oocytes
A final possibility to limit the risks involved in oocyte donation is to reduce the number of donors by exploring alternative sources of oocytes. Human oocytes could be obtained from cadavers, aborted female fetuses or surgically removed ovaries. These oocytes would, however, need to be matured in vitro, a procedure that has shown positive results but that requires further investigation (Biron-Shental et al., 2004). Alternatively, single oocytes can be donated during abdominal surgery such as tubal ligation. Sterilization patients have previously been asked to donate oocytes after mild stimulation (Braude et al., 1984; Messinis et al., 1986).

Because embryonic stem cell research is still in an early phase of development, a number of investigations can probably be performed with animal oocytes instead of human oocytes. Although this raises concerns about the creation of hybrids with human cellular nuclei but animal mitochondria, clear guidelines on issues such as the length of time these embryos should be allowed to develop and the oversight of the proposed experiments by an external institution should be able to respond to these concerns.

Oocytes might also be derived from embryonic stem cells. Oocytes have been obtained from mouse embryonic stem cells in vitro, but no live births have been reported so far, and the research has not been extended to humans (Hübner et al., 2003). Further exploration of this possibility to produce human oocytes in the lab should certainly be encouraged because it could represent a ‘renewable’ source of oocytes, eventually eliminating the need for donors.

Maximizing benefits of research
Besides reducing the risks for the donors, the risk–benefit ratio can be optimized by maximizing the benefits that can result from oocyte donation. The benefits of personalized stem cell treatment are for the time being merely a possibility in the distant future, and it remains uncertain whether this treatment will ever be widely available. In an attempt to maximize benefits and respond to concerns over distributive justice, research into, for example, the development of genetic diseases deserves priority over research aimed specifically at expensive tailor-made stem cell therapies, because those may only benefit a limited portion of society. If donated oocytes are used for stem cell banking, an effort should be made to include tissue matches for the donor in an attempt to expand the benefits for the donor and to ensure distributive justice (Greene, 2006). On a technical level, a minimum requirement for the acceptance of a research project could be that the other necessary steps of the process in which the oocytes are used are mastered. It would, for example,
make little sense to create embryos by SCNT for therapy, if a researcher does not yet have the skills to derive stem cells from an embryo. More studies on animals and supernumerary embryos should be done first to ensure that human oocytes are not wasted on preliminary research that can be done with alternative resources (Cobbe, 2006). Finally, coordination and collaboration rather than competitiveness between researchers are to be encouraged to prevent unnecessary duplication of research. A higher efficiency can be reached by sharing knowledge and exchanging stem cell lines.

Financial incentives
Another much debated issue concerns the financial remuneration for research donors. Payments are said to lead to commodification of human material, undue inducement and exploitation.

Commodification of human body material
The term ‘commodification’ refers to the assignment of a monetary value to something that was previously located outside the economic realm. The negative undertone of this phenomenon results from the idea that the value of certain things cannot or should not be expressed in terms of money. The human body is incontestably one of those things. For that reason, most countries that allow oocyte donation for infertility treatment do not allow payment for oocytes. However, the concern for commodification does not justify a complete ban on financial remunerations for oocyte donors. As oocyte donation is a very lengthy and uncomfortable procedure, justice requires that donors are compensated for their time and effort. In the case of oocyte donation for infertility treatment—which often involves known donors—it may be argued that a donation should be entirely motivated by altruism and that payments may vulgarize a donor’s noble intentions or exploit a desperate infertility patient. However, the symbolic meaning of oocyte donation in the context of reproduction differs completely from that in the context of research. As long as other research subjects are not expected to participate in research for purely altruistic reasons, neither should research donors (Hyun, 2006). Thus, although they should not be paid for their oocytes as such—because that would amount to the commodification of oocytes—they are entitled to receive compensation for their time and effort. As a consequence, a distinction should be made between donors undergoing ovarian stimulation for the sole purpose of donating and women donating oocytes without being submitted to extra burdens, as is the case, for example, when donating while having abdominal surgery or when undergoing IVF (Steinbock, 2004). In the latter case, substantial payments are hard to justify, although a small amount is probably justified as an incentive. Another consequence of adopting this model for payment is that payment should be prorated and should not depend on the actual delivery of oocytes or on the number of eggs retrieved. If a procedure needs to be interrupted for medical reasons but the donor has already invested significant amounts of time and effort, she should still be reimbursed.

It is unclear whether the recent decision of the UK’s Human Fertilisation and Embryology Authority (HFEA) to allow discounted infertility treatments for research donors follows this model of only paying for time and effort (Newcastle University Press Office, 2006). If one starts from the perspective that these women are undergoing ovarian stimulation primarily for their own treatment, the reimbursement they receive—in the form of a discount—can hardly be regarded as compensation for time and effort, but is in fact a payment for their oocytes, which then become commodities. Alternatively, one could argue that in this egg-sharing scheme, both the patient and the researchers requesting the oocytes pay their part of the ovarian stimulation and oocyte retrieval procedures. In this representation, there is no payment to the donor but a participation in the cost of the procurement and thus no commodification of oocytes.

Undue inducement
A second important argument against financial incentives for oocyte donors is that it would be a source of undue inducement. This assertion is based on research showing that payment is a significant motivating factor for most oocyte donors (Lindheim et al., 2001; Pennings and Devroey, 2006). However, although this indicates that money works as an inducement, it does not imply undue inducement per se (Shamoo and Resnik, 2006). Undue inducement results from two conditions: the presence of a high risk and high payments aimed at convincing people to accept these risks against their better judgement. Emanuel (2005) has argued that payment can thus only be undue if high risks are present, which should never be the case in research projects. Thus, undue inducement should primarily be avoided on the level of risk reduction rather than payment reduction. Nevertheless, high payments—especially in the form of completion bonuses—may encourage the donor to withhold risk information from researchers or to insist on proceeding with the procedures even though certain risk factors arise. To avoid this, payments should be capped.

Besides limiting payments, other steps can be taken to increase informed consent and thus lower the risk of undue inducement by monetary compensation. One could provide a leaflet or brochure specifically designed for candidate donors to make sure that all relevant information is provided and to allow them to read it over at home. Secondly, one could demand at least secondary school education to ensure that they can understand the information about the medical procedure and possess the general level of knowledge to understand how science works. Both steps are part of the generally recognized rule in recruitment for research trials that one should not disproportionately focus on members of vulnerable groups such as poor, uneducated women. Also, potential donors should be able to repeat the hazards that are involved in their donation and should have enough time to think these risks through and to discuss them with an independent counsellor. A so-called cooling-off period might be installed after a potential donor is informed and before consent is asked (HFEA, 2006).

Another concern over undue inducement is that donors may be recruited in developing countries and/or that oocytes may be imported. If regulatory and health care standards in the countries of origin are not up to par with those of the countries using the oocytes in research, donors may be subjected to greater
risks and are less likely to benefit from the research to which they donate. Also, it is a lot more difficult for the researcher to ascertain that these donors were sufficiently informed and have a clear understanding of both the risks and the goal of the research to which they are contributing. Therefore, this kind of importation should be banned or strictly regulated. When ovarian stimulation is part of the research protocol, the ethical committees that need to approve research involving human subjects can incorporate the requirement that stimulation should not take place abroad (leaving room for motivated exceptions for collaboration between countries that handle comparable standards regarding research donation). Alternatively, the refusal to use oocytes that are harvested in developing countries could be adopted as a code of good practice rather than a legal requirement and could, for example, be supported by organizations such as the International Stem Cell Forum or the International Society for Stem Cell Research.

One way of making this possible on a practical level is to make sure that the origin of oocytes is traceable at all stages of the research project. The instalment of relevant authorities abroad (similar to the HFEA in the UK) could provide a legal framework to ensure the intended traceability. They could, for example, scrutinize centres that obtain oocytes for research and issue, or retract, operation licenses based on their findings. When the oocytes that are retrieved in one of these centres are used by an external researcher, a paper trail should be created, confirming the provenance of the concerning oocytes through some sort of ‘certificate of origin’. This way, a researcher—and whichever authority needs to approve the research—can be sure that the oocytes were obtained in a trustworthy centre. Of course, because many countries do not yet have authorities that oversee stem cell research, installing a similar procedure will be harder in some countries than in others. Another foreseeable problem is that authorities can be deceived, which was illustrated by the Hwang scandal, in which everything looked good on paper, whereas in reality, the procedure was not followed (Hyun and Jung, 2005). It is simply practically unfeasible to send an international team around to check on this, and thus, a chance will always remain that some abuses will slip through the cracks. Thus, the system that would be most watertight would probably be a complete ban of import (from any country, not only developing countries) on penalty of licences being revoked, loss of funding or other sanctions, whereby exceptions can be made when specific treaties are established between the responsible authorities of different countries that hold similar standards of research ethics.

Exploitation

Concerns about exploitation are somewhat paradoxical. On the job market, there is a common understanding that when people are asked to perform risky or unpleasant tasks, remunerations should be sufficiently high to avoid exploitation. It is not clear why the opposite should be true in the case of payments to research donors. One could argue that to avert exploitation, payments to oocyte donors should be higher, not lower (Fost, 2005). However, this does not mean that there are no legitimate concerns for exploitation surrounding oocyte donation.

Kalfoglou and Gittelsohn (2000) have reported on malpractices ranging from denying a promised anaesthesia during oocyte retrieval and denying follow-up care to intimidation by physicians and the absence of informed consent. The protection of oocyte donors against exploitation should therefore focus on issues such as informed consent, conflicts of interest, due medical treatment and follow-up care rather than on whether the donor receives any payment.

Conclusions

The ethical problems surrounding oocyte donation for stem cell research are plentiful but not insurmountable. Using existing practices in the field of research involving healthy research subjects as a starting point, many recommendations can be formulated regarding oocyte donation for stem cell research.

First and foremost, risks and benefits of oocyte donation for stem cell research need to be balanced. Scientists should document the possible benefits of their research to society on the one hand and their efforts in risk reduction on the other hand. Possible efforts in risk reduction include (i) decreasing the number of required oocytes by performing preliminary research without oocytes, with oocytes from alternative sources (such as animal oocytes, in vitro matured oocytes, stem cell-derived oocytes, etc.) or with oocytes obtained through less invasive procedures (such as excess oocytes from IVF treatments, single oocyte donations during a surgical procedure, etc.); (ii) screening of candidate donors; (iii) setting up individualized regimens and (iv) careful monitoring and follow-up care. In addition, scientists can be asked to co-operate in long-term follow-up projects by gathering information on possible adverse effects.

Second, payments to oocyte donors do not automatically lead to commodification of human gametes, undue inducement or exploitation of women. Denying oocyte donors a fair compensation will not avoid any of these problems from occurring. However, in a regulatory vacuum, there is an undeniable chance that abuses will take place. Therefore, it is recommended that payments are limited and are based on the efforts and discomforts of the donor. Also, undue inducement and exploitation should be averted by focusing on guaranteeing informed consent, avoiding conflicts of interest and providing sufficient medical care for the donors (Vogel, 2006). To prevent abuses, importation of oocytes (especially from developing countries) and hormonal stimulation of foreign women solely for the purposes of donating oocytes for research should be prohibited. Furthermore, to assure informed consent, adequate school education of donors should be a condition.

Oocyte donation for stem cell research should be approached with the same set of principles one currently applies to other types of research presenting risks for healthy research participants. The health problems that could arise as a consequence of an oocyte donation procedure call for the necessary restraint and oversight in the recruitment of oocyte donors for stem cell research. The acceptability of a research project will need to be judged on a case-by-case basis, and in many instances, the possible benefits may not outweigh the risks or alternative approaches may deserve preference. However,
promising research projects backed up by the necessary efforts in risk reduction, in averting undue inducement and in securing informed consent can withstand ethical scrutiny.

References


