

ESHRE Task Force on Ethics and Law 12: Oocyte donation for non-reproductive purposes

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The present paper focuses on oocyte donation for non-reproductive purposes, i.e. research and future therapy. The general principles of research ethics apply to these interventions. The proportionality principle demands that any possible harms to the oocyte donors should be proportionate to the possible benefits for society. The non-maleficence principle states that every reasonable effort should be made to minimize risks for donors. The position is adopted that, *mutatis mutandis*, women who donate oocytes for research should be treated similarly to research participants in clinical trials. This implies, among other things, that oocyte donors for research should receive reimbursement for all costs of the procedure and should get compensation for the time lost and inconvenience suffered during the treatment. In order to avoid malpractice and exploitation of poor women, a number of measures are proposed such as a ban on the import of oocytes.

Key words: oocyte donation/proportionality/reimbursement/research participants/safety

Introduction

The usual aim of oocyte donation is to assist the reproduction of infertile women or women with a genetic problem. Oocyte donation may, however, also have non-reproductive purposes, i.e. research and future therapy. There is no general agreement as to whether this is morally justified and if so, on what conditions. The donation of oocytes to create embryos for non-reproductive purposes is controversial because of the moral status of the embryo. In view of the limited moral value of the embryo (ESHRE Task Force on Ethics and Law I), however, this is not a categorical objection. A second moral issue, which will be the main concern of the present paper, regards the position and interests of candidate oocyte donors.

Scientific background

Oocyte donation for non-reproductive purposes

Examples of research include:

- (i) preclinical safety studies to assess possible risks of new technologies for medically assisted reproduction (e.g. oocyte cryopreservation, *in vitro* maturation);
- (ii) research aiming at the development of cell therapy, more specifically nuclear transfer for autologous cell therapy, often termed 'therapeutic cloning';
- (iii) developing models to study specific genetic diseases;

- (iv) fundamental research in order to study basic biological mechanisms of, for instance, early embryo development.

Examples of future therapeutic aims include:

- (i) autologous cell therapy by means of nuclear transfer,
- (ii) allogenic cell therapy for a relative, using human embryonic stem cells from preimplantation embryos matched by means of PGD/HLA-typing.

Types of oocyte donors

Various types of oocyte donors may be identified. At present, only competent adult women are considered as a source of oocytes: (i) IVF patients who are asked to donate some of their oocytes; (ii) women applying for specific gynaecological interventions like sterilization; (iii) donors who spontaneously present themselves and (iv) women applying for an experimental reproductive technology for their own benefit, like nuclear transfer to avoid mitochondrial disease. The latter can be invited to donate oocytes for preclinical feasibility and/or safety studies. Women of all aforementioned categories may be willing to provide oocytes for altruistic, financial or self-benefiting reasons. In case of donation for future therapy, the reasons may also be mixed, in that contributing to therapy for a child, relative or friend may meet both the interests of the recipient and the donor.

Medical risks for oocyte donors

Medical risks regard both the hormonal stimulation and the aspiration of the oocytes. Hormone injections are uncomfortable and have side effects. The major risk is ovarian hyperstimulation syndrome (OHSS), which can be of early onset [due to the injected human chorionic gonadotrophin (hCG)] or of late onset (due to hCG produced by early pregnancy). Two clinically relevant types can be distinguished: severe and moderate OHSS. Severe OHSS is characterized by an increased risk for thromboembolism, circulatory failure, breathing difficulties, multi-organ failure and in very rare cases death. Moderate OHSS is recognized by the following symptoms: bloating, abdominal discomfort and nausea and includes abdominal distention and weight gain. The risk percentages for IVF patients cannot be extrapolated to oocyte donors since they (with the exception of oocyte sharers) do not become pregnant after the stimulation. The incidence of moderate OHSS in IVF patients is ~6%. The incidence of severe cases of OHSS, which require hospitalization, is 1% for early onset and 1% for late pregnancy-related onset. This incidence may be decreased further by the investigation of predisposition factors, the use of milder stimulation protocols and the use of GnRH agonist to trigger ovulation instead of hCG. The risk of severe OHSS in oocyte donors, if the precautionary measures are applied, can be reduced far below 1%.

According to large studies, there is no evidence that the hormonal stimulation increases women's risk of cancer later in life. The major risk of oocyte aspiration (by means of the insertion of a needle through the vagina) is an infection, which may result in infertility of the donor. This risk of iatrogenic infertility is estimated to be very low. Many women report that the aspiration is painful. Pain can be reduced by preferential local anesthesia, which carries extremely small risk and discomfort, although usually general anesthesia is used to avoid pain, which, however, carries higher risks. The risk of intra-abdominal bleeding is estimated to be between 0.1% and 1.3%.

Ethical considerations

Balancing benefits and harm

The ultimate aim of medical research is to increase knowledge for the prevention and treatment of disease. More specifically, research using donated oocytes and embryos may contribute to the improvement of reproductive medicine (ART, fertility control, prevention of genetic disease, recurrent spontaneous abortion, and so on), increased knowledge of the pathophysiology of serious disease (e.g. cystic fibrosis and so on) and regenerative medicine (e.g. cell therapy). The expected benefits from research in this area are substantial.

Critics, however, consider the burdens and risks of oocyte donation for non-reproductive purposes to be *a priori* disproportional. This view is debatable as the risks, even though real and significant, are not unreasonably high. Furthermore, in order to put these risks in perspective, two analogies should be kept in mind. First, the participation of healthy persons in medical research with no medical benefit for themselves is universally accepted—even though participation may carry significant, and not always predictable, risks for research

subjects. In the case of oocyte donation, on the contrary, the risks for women are known because the procedures for ovarian stimulation and oocyte pick-up are routinely used for IVF patients. A second analogy, which becomes especially relevant if/when oocytes are used in the future for (cell) therapy, is cell/tissue/organ donation by living donors. In these cases, a much higher risk level is accepted.

General principles of research ethics apply also to this field. First, the principle of proportionality, which requires that the risks for research subjects are in proportion to the expected benefits for science and society. Research and ethics committees should make this principle operational when evaluating individual research projects. The ethics committees should in particular scrutinize whether the expected benefits of research using donated oocytes are realistic, imminent or speculative and furthermore, how many oocytes are needed. If thousands of oocytes are needed for a study with a highly uncertain benefit or chance of success, the total risk for oocyte donors may be disproportional.

The second principle of research ethics is that researchers make every reasonable effort to minimize risks for the research subjects. When the scarcity of oocytes intensifies (and this will be the case if somatic cell nuclear transfer becomes possible without good alternative treatment), there is a serious risk that respect for ethical principles will dwindle. Women may be put under pressure, doctors may modify the stimulation regime in order to obtain more oocytes, the trend towards commercialization of oocyte donation could be reinforced, and finally, there may be an even greater temptation to recruit donors among vulnerable women in countries that have less adequate protective regulations.

In this context, the responsibility to minimize risks includes close monitoring of the cycle; use of mild and/or safer stimulation protocols (even though this may decrease the number of oocytes obtained); limitation of the number of cycles per donor in order to reduce her individual risk and identification and exclusion of women with a higher risk of OHSS. It may be argued that both nulliparous women and women who have not completed their family should be excluded as well, considering the possible risk of infertility caused by the intervention. However, this proposal is considered too restrictive, as available data indicate that this risk is extremely low. It has been argued similarly that IVF patients should be excluded because donating some of their oocytes may diminish their chance of having a child. However, this risk can be adequately minimized by imposing conditions such as setting a minimum number of retrieved oocytes for the patient and by taking into account the fertilization rate in a previous cycle.

Respect for autonomy

Respect for autonomy should be a core principle in the context of oocyte donation. Hence, adult competent informed women are able to decide for themselves whether they can accept the risks involved in the research project. Critics argue that oocyte donation for research and therapy is problematic, or even unacceptable because of the pressure put on women. However, some kind of pressure may also exist in the context of women donating oocytes for reproductive purposes.

A crucial safeguard is the provision of counselling by an independent counsellor. The same measure should be adopted in the context of oocyte donation for non-reproductive purposes. Counselling should be obligatory for all donors. An additional safeguard is the exclusion as donors of women who are involved in the research project or who work in the same department.

Respect for autonomy is expressed in the informed consent, more particularly voluntary consent based on adequate information. There is concern that some oocyte donors involved in research projects have not been adequately informed about the goals, the procedure and/or the risks. There is an ongoing debate about the standards for informed consent and the precise information to be given. The information given in order to obtain proper consent should include elements of both the clinical and research protocol. Clinical information regards the possible risks and inconvenience for the donor related to ovarian stimulation, monitoring and oocyte pick-up. This information is similar to the information given to regular IVF patients. Research related information regards the purpose(s) of the research to be undertaken and the contribution of the donation to this purpose. Specific information to be given to donors whose oocytes will be used in embryonic stem cell research includes (see ESHRE Task Force on Ethics and Law IV) that embryos will be created that will be used to isolate human embryonic stem cells and, if and when appropriate, that these cells may be used for therapy (see ESHRE Task Force on Ethics and Law IV).

Donors may have unrealistic hopes and beliefs about their contribution and/or about the development of the techniques. Misconceptions should be avoided as much as possible by clear language understandable to the candidate donor, by providing written material and by imposing a mandatory waiting time for donors to reflect on their decision. These demands require the exclusion of illiterate women. It is important to check the understanding by the candidate donors of the information provided.

Compensation: exploitation or fairness?

General comments

There is a fairly wide consensus that payment of gamete donors is morally unacceptable (see ESHRE Task Force on Ethics and Law III). Many countries prohibit this practice. Some commentators, however, consider it to be unfair not to pay gamete donors. One argument is that the purpose of donation makes a difference from an ethical point of view. Payment is most controversial when the gametes are destined for infertility treatment, as this would amount to the commercialization of reproduction. This objection, however, is irrelevant in the context of donation for non-reproductive purposes. Nevertheless, payment in this context is controversial as well, mainly because it could constitute undue inducement, undermining the autonomy of, especially poor, donors. A possible way to avoid recruitment among poor women would be to demand adequate schooling since low educational levels are associated with low income.

It is generally acknowledged that expenses of the donor can be reimbursed. This may include the time invested in

collaboration. Oocyte donors spend a considerable number of hours in the medical setting, undergoing interviews, counselling and medical procedures related to the process. Moreover, in addition to these inconveniences, compensation can be offered for physical discomfort like nausea, blood takings etc. In fact, such compensation for healthy subjects participating in research and clinical trials is widely accepted. If this analogy is considered valid, it would be justified to compensate oocyte donors for the inconvenience and discomfort and at the same time to stick to the view that large sums of money are inappropriate as these may well function as undue inducement. Moreover, in order to avoid the commodification of human body material, the compensation should be given irrespective of the number and the quality of the oocytes retrieved and should depend solely on the efforts made by the donor.

Oocyte sharing

In some countries, a compensation in kind is offered for oocytes. In the case of oocyte sharing, this compensation consists mostly of a reduction in the cost of her IVF cycle. In view of the principle that the money is compensation for discomfort and inconvenience suffered during the process, the compensation should be very modest in the case of oocyte sharing as these disadvantages were primarily accepted by the patient for her own treatment. If substantial payment is given, this in fact comes down to payment for the oocytes. Other in kind compensations, like free surgical intervention such as sterilization, are not necessarily excluded.

Internationalization and supervision

Given the growing internationalization of scientific research in general and stem cell research in particular, human body material will move between countries. In order to facilitate the possibility of control and supervision, the origin of oocytes and the conditions under which they were obtained should be traceable. At all times, the researchers should be able to show that the oocytes used in the protocol were obtained according to the ethical standards. However, strong scepticism about the effectiveness of the control exercised on the practice in clinics in some countries makes this a highly unrealistic rule. Unless appropriate control by independent authorities can be guaranteed, the most effective way to avoid malpractices and trade in oocytes is not to import human oocytes. Simultaneously, no oocytes for research should be collected from women coming from abroad.

Future developments

The use of mature oocytes from adult women may be a temporary solution. The evaluation of their use will depend on the development of new techniques to obtain oocytes like *in vitro* maturation, oocytes derived from stem cells etc. Research to find female-friendly alternatives should be stimulated.

Recommendations

Risk reduction

Oocyte donation for research should be a primarily altruistic act motivated by the wish to contribute to the advancement

of science and medicine. Society has the responsibility to structure scientific research in a procedure that guarantees respect for ethical principles.

This implies that

- (i) serious efforts should be made to minimize the risks for the donor;
- (ii) careful selection of candidates should eliminate women with a specific risk factor;
- (iii) stimulation protocols should be softer in order to decrease the risks of OHSS.

Simultaneously, research projects should be carefully selected and screened to avoid wastage of oocytes. This also implies sharing of research data in order to avoid unnecessary duplication of experiments.

Informed consent

Donors must have given free and voluntary consent. In order to enable them to decide, they should be provided with all the relevant information both regarding the procedure (risks, time, discomfort, and so on) and regarding the expected benefits of the research to which they contribute. To allow candidates to think through their decision, a brochure should be distributed. Counselling by an independent counsellor not involved in the research project is necessary.

Compensation

Oocyte donors should receive reimbursement for all direct and indirect costs of the procedure and should receive a compensation for the time lost and inconvenience suffered during the treatment. The compensation should be fair and in proportion to the amounts currently paid to research subjects. To prevent undue inducement and disproportional recruitment among vulnerable groups, illiterate and poor women should be excluded as donors. For reasons of control, this implies a prohibition or at least a very cautious attitude towards import of oocytes. The center that finally uses the oocytes in research shares responsibility and should verify whether the oocytes are obtained according to ethical standards. No candidate donors coming from abroad should be accepted.

Alternatives

Increased research in less burdensome alternative sources of oocytes or strategies to do without the use of donors in the long run should be conducted.

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