

Oocyte Donation – Clinical and Scientific Aspects

This paper has been prepared for the Bioethics Advisory Committee as background information on oocyte donation for research.

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Introduction

Oocytes for fertility treatment

Oocytes (eggs) can be donated for the treatment of infertility or for research. The donation of oocytes for the treatment of infertility is an established method of assisted reproduction and has been used in patients with ovarian failure, increased risk of serious genetic disorders, or multiple failed *in vitro* fertilization (IVF) attempts. Older women are more often recipients of donated oocytes for fertility treatment as they are more likely to suffer conditions for which such treatment is needed. Those who donate oocytes for the treatment of infertility may be women undergoing infertility treatment and who are willing to share their oocytes with another infertile woman; or they may be healthy women who donate their oocytes altruistically.

Oocytes for research

Oocytes for research may come from a wider range of sources:

- (a) Women undergoing infertility treatment. Oocytes from such women could be surplus to their fertility treatment, or they could be immature oocytes that are unsuitable for fertilisation or have failed to fertilise following IVF;
- (b) Women undergoing medical procedures such as the removal of ovaries. These procedures may yield immature oocytes that can be used for research;
- (c) Women not undergoing any form of medical treatment i.e. healthy women who undergo ovarian stimulation in order to provide oocytes specifically for research;
- (d) Cadavers and aborted foetuses, which may provide immature oocytes for research; and

- (e) Oocytes created from stem cells. It has been shown that it is possible to create mouse oocytes from mouse embryonic stem cells. If this could be achieved using human embryonic stem cells, these created human oocytes could then be used for research. A team of researchers in the UK have demonstrated that human embryonic stem cells display a capacity to generate immature gametes. However, research on creating human oocytes from human embryonic stem cells are in the preliminary stages.

Recently, the demand for human oocytes for research purposes has led to concerns regarding the risks of the procedures involved in obtaining the oocytes. To understand these concerns, one has to understand how oocytes are normally produced, the hormone therapy that a woman has to undergo to produce the additional oocytes required for infertility treatment or for research, and the procedures involved in the retrieval of these oocytes.

How Oocytes are Normally Produced

Oocytes are produced in the ovaries. The number of oocytes in a woman's ovaries is fixed before birth and diminishes with age. At birth, a baby girl has approximately one to two million oocytes. At puberty, the number has reduced to 300,000 to 400,000, of which usually one will fully mature each month and about 1000 will die at various stages of maturity. This continues till menopause, when the number of functional oocytes will have been exhausted.

Before puberty, the oocytes are in the resting stage and each of them is surrounded by cells that protect it and support its development, forming structures called primordial follicles. Each month, about 10-20 primordial follicles mature and can be detected by ultrasound scans. These follicles will compete for growth-inducing follicle-stimulating hormone (FSH) resulting usually in the development of only one follicle, termed the dominant follicle. Under the influence of luteinising hormone (LH), the dominant follicle will release a mature oocyte at ovulation (a term used for the time mid-way in the menstrual cycle when the mature oocyte is released).

Ovarian Stimulation and Retrieval of Oocytes

Normally only one follicle will fully mature and release an oocyte in each monthly cycle. However, in the presence of sufficient FSH, or other drugs with a similar action, more follicles can mature. In assisted reproduction, FSH is used to stimulate these follicles so that more oocytes would be available for use. In the standard therapy, the hormone is given daily for 10-12 days by injections. To prevent premature release of the oocytes, injections of another hormone are also given.

During ovarian stimulation, the physician will closely monitor the patient for signs and symptoms of adverse effects of the drugs used, as well as the maturation of the follicles through serial ultrasound scans and blood tests. When the ultrasound scans show that the follicles have reached the appropriate stage of maturity, another hormone, human

Chorionic Gonadotrophin, is given by injection to induce the release of oocytes at 36-40 hours. However, in practice, the oocytes are collected before they are released, via a special needle attached to an ultrasound vaginal probe and with the woman under anaesthesia. Figure 1 shows how oocytes are produced via normal ovulation and via ovarian stimulation.

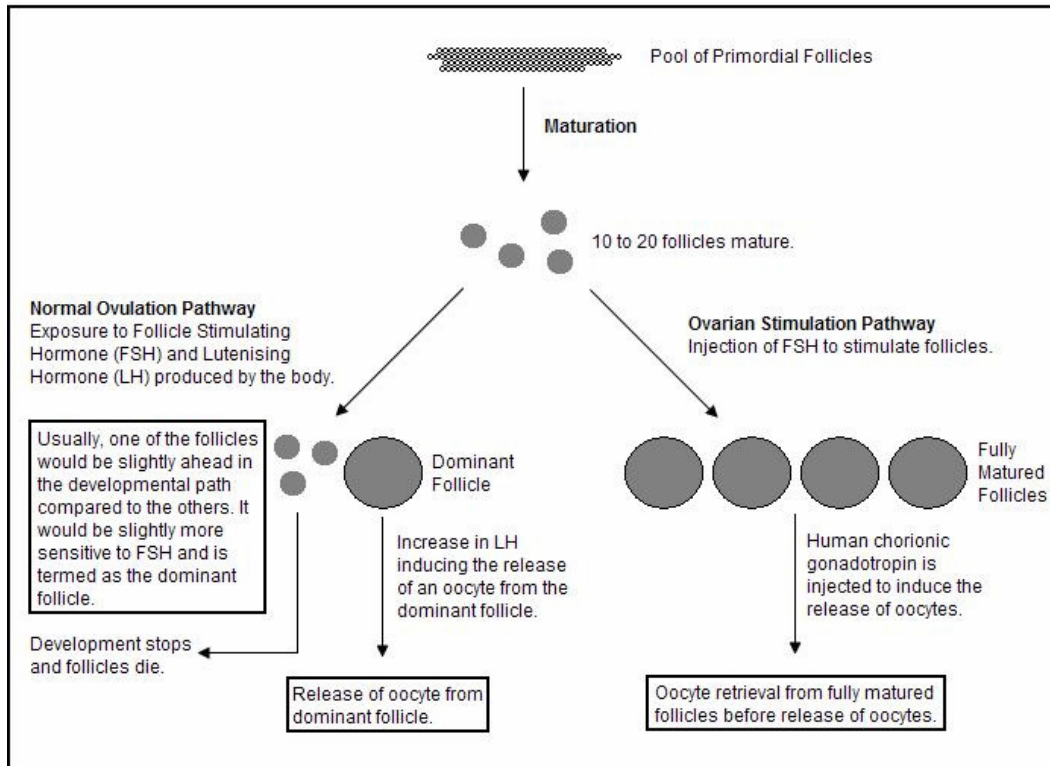


Figure 1: How oocytes are produced in the ovaries

Medical Risks of Ovarian Stimulation and the Retrieval of Oocytes

Ovarian stimulation may give rise to ovarian hyperstimulation syndrome (OHSS), in which there is accumulation of fluids in the abdominal cavity. The symptoms of OHSS are nausea, vomiting, diarrhoea, lower abdominal discomfort or distension, usually occurring soon (less than 10 days) after ovulation or oocyte retrieval and resolving spontaneously within several days. These symptoms are caused primarily by an increased permeability of blood vessels. Clinical experience suggests symptoms of mild OHSS are a common side effect in up to 20-30% of patients undergoing assisted reproductive technology (ART) procedures. The moderate form of OHSS is of greater concern and occurs in 1-10% of such patients. It can be minimised with careful use of FSH in the ovarian stimulation.

Severe OHSS occurs in less than 1% of IVF patients, usually when large numbers of oocytes (more than 30) are produced as a result of high sensitivity to the standard dose of FSH. The symptoms usually appear after seven days of oocyte collection and include hypotension and decreased urine output, reflecting gross accumulation of fluid in various parts of the body, such as the abdominal and lung cavities. Life-threatening complications include kidney failure, respiratory failure, bleeding from ovarian rupture and thromboembolism (obstructive blood clots). OHSS is more often seen in patients who become pregnant. OHSS can be avoided by the judicious use of hormones and careful pre-treatment assessment and monitoring of the patients. Women less than 30 years old and those with polycystic ovaries are at increased risk. For oocyte donors, careful use of low doses of FSH prevents OHSS.

As oocyte retrieval involves a minor surgical procedure, done under mild anaesthesia, there is a risk, although very low, of haemorrhage and infection and adverse effects of the anaesthesia.

It is not known if there are adverse long-term consequences of ovarian stimulation. The possibility of the potential risk of cancers of the breast, ovary and uterus, which are hormone related, has been investigated. The results so far have suggested at worst some low risk of ovarian cancer, but more research over a longer time span is required to determine if there are definite undesirable long-term or very long-term effects of ovarian stimulation. Although there are no clearly documented proofs of adverse long term effects of ovarian stimulation, the American Society for Reproductive Medicine's view is that "it would be prudent to consider limiting the number of stimulated cycles for a given oocyte donor to approximately six" because of the possible health risks.

Oocytes for Research

Oocytes donated for research can be used in many experimental situations. They can be fertilised to create embryos, from which stem cells can be derived or they can be used as they are, without being fertilised, for example in preclinical safety or feasibility studies of new technologies. Examples would be oocyte preservation or *in vitro* maturation, or somatic cell nuclear transfer (SCNT), also known as therapeutic cloning. Oocytes can also be activated to produce an entity called a 'parthenote', from which stem cells could be derived. Human oocytes are particularly required for studies of nuclear re-programming.

Nuclear reprogramming is the process whereby a mature somatic cell is transformed into one that has the characteristics of an embryonic cell, which may be totipotent (able to develop into all types of tissues) or pluripotent (able to develop into all types of tissues except the placenta). Various strategies have been used to induce the pluripotent embryonic state, such as SCNT, cellular fusion, the use of cell extracts and culture-induced reprogramming.

Currently, nuclear reprogramming is not well understood. Much more research is required in this area, which could be applied in the treatment of many presently

incurable diseases. There is the possibility of deriving patient-specific stem cells, which could prevent tissue rejection, deriving disease-specific stem cell lines to study the cause, progression, diagnoses and treatment of diseases as well as the possibility of generating tissues and organs to replace diseased ones.

The oocytes presently available for research are mainly those that have failed to fertilise following IVF. However, fresh oocytes are preferred to oocytes that have failed to fertilise following IVF, as they are believed to improve the efficiency of SCNT. Oocytes that have failed to fertilise after IVF are less effective as they have been shown to have limited developmental potential. Scientists have indicated that increased availability of suitable oocytes would enhance stem cell research. Hence, such oocytes are in considerable demand for research.

Oocyte Sharing

Oocytes from a woman undergoing infertility treatment can be “shared” with other patients or with a research programme. In return the woman receives help to bear the cost of the infertility treatment. The advantage for research is that the oocytes will be fresh and mature, and thus the chance of successful nuclear reprogramming will be higher than with oocytes that are matured in-vitro. The disadvantage is the possibility that women may be induced to “share” and inducement is considered undesirable. Heng et al. have suggested that compensated oocyte sharing is the best means of securing oocytes for therapeutic cloning research.

Current Guidelines on Oocyte Donation for Research in Singapore

In Singapore, all research involving human oocytes must be approved by a research ethics committee or an institutional review board (IRB) as well as the Ministry of Health (MOH).

Explicit consent must be obtained from the oocyte donor and there must be no inducement, coercion or any undue influence. Potential oocyte donors, who are not part of an ART programme, must be interviewed by a special panel, which has to be satisfied that the prospective donor is of sound mind, has fully understood the procedures and implications of the donation and that she has given her consent voluntarily.

In cases where the potential donor is a patient undergoing infertility treatment, the principal physician and embryologist in charge of the patient’s treatment should not be the principal investigator of the research team using this patient’s oocytes.

Specific Issues in Oocyte Donation

There are a number of ethical issues raised in oocyte donation and the use of oocytes for research, which overlap with, but are not the same as, the issues raised in infertility treatment. The essential difference is that in infertility treatment, a child will hopefully

result from the process, and the interests of the child add a further dimension to consideration of ethical issues. In research, on the other hand, there is no child and no direct benefit to the donor, and the ethical considerations primarily relate to the need for consent, the risks to the donors and the avoidance of coercion and exploitation.

Ethical issues are not covered in detail in this paper, but a number of special considerations are considered below:

- a) **Beneficence**: It is a basic principle of medicine that benefits should outweigh risks/harm, and the proportionality principle should apply, i.e. higher risks must be minimised and where unavoidable, justified by greater benefits (Pennings et al, 2007; Mertes & Pennings, 2007). In the case where oocytes are to be used in research, the benefits are general, not specific to the donor, and the obligation is for careful selection of promising experiments likely to yield useful research findings with minimal risk to the oocyte donor.
- b) **Payment**: In general one can distinguish three positions with respect to payment for oocytes – re-imburement of reasonable expenses only, limited payments for time, trouble and effort, and outright sale regulated by supply and demand. The [Human Cloning and Other Prohibited Practices Act](#) 2004, Singapore, (HCOPP Act) states that reasonable expenses incurred by oocyte donation are allowed. The intention is to avoid commodification of oocytes and to maintain oocyte donation as an altruistic act done without inducement. There has been some debate on whether that should be relaxed. Heng et al., for example, proposed that subsidy be made to compensate patients undergoing IVF in exchange for oocytes donated for research (Heng et al., 2006). Mertes & Pennings (2007) suggested that any payment be based on effort and discomfort rather than on the number of oocytes retrieved, that there should be limits on payments, and that they should be made directly to the donor and not through middlemen or clinics.
- c) **Import & export of oocytes**: For a number of countries such as Australia and the UK, the import and export of oocytes are regulated because of the concern that women, especially those who are financially vulnerable, may be exploited. Ethical concerns arising from the import or export of oocytes should be seriously considered.
- d) **Compensation for complications**: Complications during ovarian stimulation and oocyte retrieval may occur; the risk of OHSS is higher when there are more follicles developing. This is an accepted risk during infertility treatment. However, for volunteers who donate oocytes, the question of compensation has to be addressed. In clinical drug trials the principle is accepted that healthy volunteers need to be insured by the institution against possible adverse consequences arising from their participation. Whether a similar requirement could be required in research involving the donation of oocytes is open to doubt, as insurance companies do not as a rule offer such policies and research grant agencies are also not likely to allow

such costs to be built in. A lack of insurance cover might, however, be a major disincentive to healthy volunteers.

- e) ***Collection only in licensed ART centres:*** As the process of obtaining oocytes involves careful monitoring and specialised procedures, it should be conducted by suitably qualified physicians and in licensed ART centres. In Singapore, research using oocytes can be carried out only in ART laboratories which are licensed by the MOH.

Guidelines for the Procurement of Oocytes for Research

Subsequent to the news of unethical procurement of human oocytes by South Korean stem cell researchers, there is an increasing interest on this subject. Several ethics and professional bodies worldwide have issued new guidelines or revised their existing guidelines on obtaining oocytes for research.

International Society for Stem Cell Research (ISSCR)

In December 2006, the ISSCR finalised its Guidelines for the Conduct of Human Embryonic Stem Cell Research. Section 11 deals with the provision of oocytes for research. The guidelines include recommendations along the following lines:

1. Monitoring of recruitment practices should be done to ensure that women from vulnerable populations are not exploited;
2. When reimbursement is allowed, the research proposal should be reviewed rigorously so that any reimbursement or financial compensation does not constitute undue inducement;
3. No payment should be made based on the number or quality of the oocytes;
4. Oocyte procurement be done by experienced physicians, and the ovarian stimulation protocol used should be such that the risk of OHSS is reduced;
5. There should be a limited number of cycles of ovarian stimulation that a woman is allowed to be exposed to (for both research and for treatment); the number to be determined by an oversight committee based on review of latest available scientific information;
6. The cost for medical care required “as a direct and proximate result of the woman’s provision of oocytes for research” should be provided;
7. “Researchers may not request that members of the infertility treatment team generate more oocytes than necessary for the optimal chance of reproductive success” (paragraph 11.5a); and

8. “An infertility clinic or other third party responsible for obtaining consent or collecting materials should not be paid specifically for the material obtained, but rather for specifically defined cost-based reimbursements and payments for professional services” (paragraph 11.5.b.vii).

European Society for Human Reproduction and Embryology (ESHRE)

In 2007, the ESHRE Task Force on Ethics and Law published its recommendations on Oocyte Donation for non-reproductive purposes (Pennings et al, 2007). It adopted the position that “women who donate oocytes for research should be treated similarly to research participants in clinical trials” (page 1210) and that the donation should primarily be altruistic, and thus recommended along the following lines:

1. Minimising the risks for the donor by ensuring that the research is based on ethical principles and that the ovarian stimulation protocols are such that the risk of OHSS is reduced;
2. Careful selection of research projects to avoid wastage of oocytes;
3. Sharing of research data in order to avoid unnecessary duplication of experiments;
4. Oocyte donors must give free and voluntary consent. They should be counselled, provided with relevant information and given time to think the matter through before making the decision;
5. Oocyte donors should be reimbursed for the cost of all procedures, whether direct or indirect, as well as be compensated for the time lost and inconvenience suffered during the treatment;
6. To prevent undue inducement and disproportional recruitment among vulnerable groups, illiterate and poor women should be excluded as donors;
7. Prohibition or at least a very cautious attitude towards import of oocytes;
8. Research centres are responsible for obtaining oocytes ethically;
9. Donors from abroad should not be accepted; and
10. Encourage more research using alternatives sources of oocytes.

UK Human Fertilisation and Embryology Authority (HFEA)

In 2006, the Human Fertilisation and Embryology Authority (HFEA), UK, carried out a public consultation on donation of oocytes for research. In February 2007, it issued a statement allowing women to donate oocytes either specifically for research or in

conjunction with their infertility treatment, provided “there are strong safeguards in place to ensure the women are properly informed of the risks of the procedure and are properly protected from coercion.” In addition, the HFEA launched its new 7th Edition of the Code of Practice in May 2007, which includes detailed guidelines for the procurement, storage and use of oocytes for research.

Conclusion

Oocytes are important for the progress of basic science research as well as stem cell and ART research. The donation of oocytes is associated with medical risks and donors have to be fully informed of the procedures and risks, and given sufficient time and information before making the decision to donate. It is also important that there are safeguards to protect oocyte donors and ensure that there is no coercion or undue influence on their decision to donate.

As science and technology advances, there may be a possibility that human oocytes may not be required for research and alternatives such as cybrids and stem-cell derived oocytes may be used instead. Generally there appears to be a consensus world-wide on the need for oocytes for research, and that donors should be compensated for the risk and the time involved.

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