Proposed oocyte donation guidelines for stem cell research

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To expand the availability of stem cell lines suitable for basic research and clinical application, somatic cell nuclear transfer has been proposed and will require human oocyte donation. The recommendations made by the California Institute of Regenerative Medicine advisory committee on oocyte donation are based on peer-reviewed, best practices, and best clinical judgment and are intended to assist researchers in design and Institutional Review Board (IRB) evaluation of research protocols for oocytes donated exclusively for research purposes. (Fertil Steril® 2010;94:2503–6. ©2010 by American Society for Reproductive Medicine.)

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Stem cell research has the potential to discover and advance treatments for chronic disease and injury (1). To realize this potential, researchers are pursuing a number of promising avenues of research to expand the availability of cell lines suitable for basic research and clinical application.

To date, human embryonic stem cells (ESCs) have typically been derived from human blastocysts originally created for reproductive purposes by IVF. The quality and diversity of lines derived from embryonic sources (human ESC lines) has increased in recent years. For example, blastocysts screened through preimplantation genetic diagnosis have been used to develop specific human ESC lines, thus enabling the study of specific diseases. The National Institutes of Health recently promulgated guidelines enabling of human ESC from surplus IVF embryos, suggesting a further expansion of this research (2).

The IVF procedures may also be used to create blastocysts for nonreproductive purposes. Blastocysts may be created for fundamental research to study basic biological mechanisms of early embryo development. Parthenogenetic lines, derived from embryos of a fertilized egg cell, have also been developed for research purposes. Research aimed at developing cell therapies may use oocytes for nuclear transfer experiments. Nuclear transfer involves inserting the nucleus from a somatic cell (for example, a skin cell) into an oocyte from which the nucleus has been removed. At present, nuclear transfer experiments have been performed successfully in non-human animals and primates (3). Stem cells derived from the resulting blastocysts are copies or "clones" of the original somatic cell because their nuclear DNA matches that of the donor cell. Therapeutic cloning through nuclear transfer and parthenogenesis has been proposed as a means of developing human cellular therapies immunologically matched for the recipient. Alternatively, cloning cells from diseased individuals can be used to establish models to study the etiology of those diseases (4).

Since 2008 researchers have been able to induce somatic cells to demonstrate human ESC properties. These induced pluripotent stem cells (iPSC) have enabled the development of patient-specific lines that hold promise for the development of cellular therapies. In addition, because of their somatic cell source, iPSC avoid the social controversy associated with lines derived from embryonic sources.

Evidence suggests that a cell line's source correlates with differences in gene expression. Recent studies associate these expression patterns with epigenetic differences between human ESCs and iPSCs (5). Given these demonstrated differences in existing lines, researchers believe that it is important to also pursue nuclear transfer experiments. The development of safe and effective cell therapies will benefit from research involving cell lines derived from all potential sources.

ETHICAL CONSIDERATIONS

Using IVF procedures to create research blastocysts, demonstrating the feasibility of nuclear transfer in humans, and making operational such methodologies will require the donation of human oocytes. Investigators will need to secure oocytes from women consenting to donation exclusively for research use. Such donation has raised

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TABLE 1

Preinduction screening exclusion criteria.

Medical history
1. Single ovary
2. Previous history of OHSS
3. History of thrombosis / bleeding diathesis / familial thrombophilia
4. Uncontrolled hypertension / diabetes
5. ASA III anesthetic risk
6. History of estrogen sensitive cancers
7. History of ovarian tumors of low malignant potential (LMP or borderline) or malignancies
8. History of PID requiring hospitalization

Exclusionary diagnostics
9. BMI <20 and >30
10. Advanced maternal age (Elevated day 2 or 3 FSH or E_2; elevated or diminished AMH. The existing literature does not allow researchers to define universal cutoffs for AMH due to limited experience using this marker of ovarian reserve clinically).
11. Antral follicle (2–10 mm diameter) count >20
12. Endometrioma or stage III-IV endometriosis
13. Any abnormal tubo-ovarian morphology (hydrosalpinx) or uterine morphology (fibroids) that impacts access on ultrasound for retrieval
14. Inability to tolerate ultrasound or pelvic examination
15. High vaginal pH (>4.5), This exclusion could be lifted if treatment of bacterial vaginosis results in a follow-up pH <4.5
16. History of infertility
17. Hyperprolactinemia
18. Use of an IUD

Note: OHSS = ovarian hyperstimulation syndrome; ASA = American Society of Anesthesiologists; PID = pelvic inflammatory disease; BMI = body mass index; AMH = anti-Müllerian hormone; IUD = intrauterine device.

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ethical concerns as oocyte retrieval involves potential acute and long-term risk to the donor (6). Although oocyte donation has been performed for decades in the context of fertility treatments, donation for research will neither achieve pregnancy nor create direct therapeutic benefits to the donor or potential patients at this time (7).

Given ethical concerns related to the use of human oocytes, the research community has engaged in a number of initiatives designed to advance donor safety. The National Academies of Sciences have published guidelines that include provisions addressing donor safety. These guidelines have been adopted by states sponsoring stem cell research. In 2006, the California Institute for Regenerative Medicine commissioned the Institute of Medicine to convene a workshop titled "Assessing Risks of Oocyte Donation for Stem Cell Research" (7). The workshop report concluded that there are opportunities for minimizing medical risks in donors who provide oocytes exclusively for research.

CURRENT COMMITTEE CHARGE

Building on the Institute of Medicine workshop and report, the California Institute for Regenerative Medicine convened an advisory committee comprised of six experts with clinical experience in reproductive medicine, public policy, and ethics. The committee was charged with developing specific recommendations for reducing the risk of ovarian hyperstimulation syndrome (OHSS) and other acute complications that may occur after oocyte donation. The recommendations are based on published evidence in peer-reviewed literature, best practices, and best clinical judgment. A draft of the guidelines was posted for public comments and circulated to experts in the field for review. Comments obtained from this public/expert review process have been incorporated into the final recommendations. The guidelines are intended to assist researchers in the design, and Institutional Review Boards (IRB) in the evaluation, of research protocols involving the donation of oocytes exclusively for research.

STATEMENT OF PRINCIPLE

The Institute of Medicine workshop and report discussed the unique ethical context in which oocyte donation for research exists—women incur some medical risk without direct benefit to themselves or others. Because of this risk-to-benefit ratio the Institute of Medicine committee advocated a "conservative" or cautious approach to research donation when otherwise healthy donors are involved. Our committee concurs with the Institute of Medicine that potential research donors should be evaluated in a conservative manner. Central to this approach is the identification of risk factors associated with a greater likelihood that a donor will develop OHSS or other complication. In practice, the identification of any clinically evidenced risk factor should be considered grounds for exclusion. This approach is more stringent than published guidelines for assisted reproduction, where specific risk factors may be deemed acceptable in a woman undergoing IVF for her own reproductive benefit or that of another woman or couple.

These guidelines draw on peer-reviewed literature, best practices, and the clinical judgment of the investigators to identify individual characteristics that would result simultaneously in a high chance of successful donation and a low probability of adverse health events. The committee recognizes that such recommendations should be flexible and dynamic, and that it is appropriate to reevaluate specific recommendations in light of new evidence.

Furthermore, the committee recognizes that developments in stem cell science may shift the risk-to-benefit ratio, thus altering the ethical context of research donation. For example, if the clinical utility of nuclear transfer is demonstrated in humans, there may be circumstances where donors incur more direct benefit, such as access to potent new therapies for themselves, their family members, or others. Alternatively, new developments using iPSC may provide approaches to generate new lines for cellular therapy that obviate the need for embryo-derived lines. Similar consideration should be given to potential donors with diseases that may be the subject of study as a result of oocyte donation. Under such circumstances, ethically appropriate proposals may evolve from these current recommendations. The IRB should evaluate the rationale for such deviation and judge accordingly consistent with their duty to determine whether risks are reasonable and consistent in relation to anticipated benefits (8).

FRAMEWORK FOR OHSS AND ACUTE OUTCOME RISK REDUCTION

The goal of these guidelines is to identify donor characteristics that, in the committee's judgment, would result in a high chance of successful donation and a low probability of adverse health events. Toward these ends, the committee recommends the application of a four-point framework designed to coincide with clinical

TABLE 2

Early ovulation induction monitoring.

Days	Recommendations
Days 1–7	
Dosing	Starting dose up to 150 IU if age $<$ 34 y 225 IU gonadotropins if age $\geq$ 34 y Maintain starting dose for at least first 5 d of stimulation
Days 2–3	Elevated FSH and E_2 levels may predict poor response
Days 7–10	
Indicators for stopping (hyper-response)	$>$ 1,000 pg/mL E_2 or $>$20 12-mm follicles on day 6 of stimulation $E_2 > 3{,}500$ pg/mL on day of hCG administration
Indicators for stopping (hypo-response)	Consider canceling if less than three active growing follicles

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opportunities for donor screening and evaluation. Specific guidelines for exclusion are contained in the corresponding tables (9–14).

1. Preinduction screening exclusion criteria (Table 1)
    - Medical history
    - Targeted diagnostics to identify potential risk factors
2. Early ovulation induction monitoring (days 1–7, Table 2)
    - Dosing recommendations
    - Day 2–3 indicators
    - Indicators of hyper-response
    - Indicators of hypo-response
3. Oocyte aspiration (Table 3)
    - Method and certification
    - Recommended protocols
4. Surveillance after aspiration (Table 3)
    - Short term
    - Menses check

We recommend that the quantified criteria for inclusion, exclusion, and management be considered guidelines. Clinical judgment should be used to individualize care for each patient. It might be appropriate in selected circumstances to include or exclude individuals or to modify treatment based on considerations that deviate slightly from the stated criteria. However, it is recognized that safety for the patient is the paramount consideration in patient participation and clinical management.

The tables identify exclusionary criteria to be considered in donor screening and monitoring protocols. For certain indicators, where there is sufficient support in the literature, quantitative criteria are recommended. For some criteria it is not possible to recommend quantitative criteria at this time. For such criteria, it is incumbent on the practitioners to develop procedures and policies based on their own clinical experience. These guidelines attempt to provide sufficient specificity to assist researchers in the design and IRBs in the evaluation of research protocols.

Specifically normal range values for anti-Müllerian hormone, FSH, E_2, and antral follicle count may vary among programs and therefore it is imprudent to provide value guidelines recognizing that assay performance can vary and absolute risk is dependent on multiple factors. The committee also refrained from providing a recommendation regarding polycystic ovary syndrome (PCOS). Some reports have suggested that OHSS risk is highest in women with PCOS-like characteristics (15). The committee believes that the strength and consistency of a possible association is insufficient to warrant a specific recommendation. Furthermore, much could be learned potentially from cell lines derived from women with PCOS. As with all women undergoing an IVF cycle, the baseline ultrasound scan and antral follicle count should be combined with an appropriately dosed stimulation protocol to ensure safety.

Comment on Infectious Disease Screening

There is uncertainty regarding the relationship between specific infectious diseases and adverse medical outcomes from retrieval. Rarely *Chlamydia*, gonococcus, or bacterial vaginosis affect risk for upper tract infection in donors. High vaginal pH (>4.5) is an indicator of bacterial vaginosis. Bacterial vaginosis can be transmitted to the upper tract and may confer an increased risk of pelvic infection during ovary puncture (11, 16). Any infectious diseases identified should be treated before a potential donor is reconsidered.

TABLE 3

Retrieval and postretrieval monitoring.

Oocyte aspiration	
Method and qualification	1. Retrieval by experienced IVF physician; conscious sedation recommended under the care of a board-certified anesthesiologist.
Recommended protocols	2. Consider avoiding aspirin-containing medications for 2 weeks before retrieval.
Postaspiration surveillance	
Short term	1. If patient calls because of symptoms, she must be seen within 24 hours.
Menses check	2. Call with menses; if no menses 2 weeks after retrieval, then pregnancy test.

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The Food and Drug Administration has its own requirements for donor screening and specimen testing regarding infectious diseases (17). Thus, screening is important for the protection of laboratory personnel who handle biological samples as well as for potential recipients of human ESC therapies. Screening requires a review of relevant medical records, including a donor medical history, interview, and physical examination. The screening for donors of reproductive cells or tissues should specifically address risk factors for, and evidence of:

1. HIV
2. Hepatitis B
3. Hepatitis C
4. Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob
5. *Treponema pallidum*
6. Communicable disease risks associated with xenotransplantation
7. *Chlamydia trachomatis* and *Neisseria gonorrhea*

Although none of the agents identified in these screening tests are risk factors for acute outcomes in oocyte donation, these guidelines seem prudent to avoid contamination of human ESC lines. Another consideration discussed by the panel was the relative contraindication of donors with a history of chronic pelvic pain. In some circumstances women with such a history should be allowed to participate in oocyte donation, but clinical judgment should be cautious as exacerbation of chronic pelvic pain could be misconstrued as an acute procedure-related complication. Treatment of *Chlamydia*, gonorrhea, or syphilis, with evidence of resolution for 1 year and negative repeat testing, should be established before a donor is reconsidered.

Comment on Registries and Long-Term Donor Tracking

The committee concurs with the observation in the Institute of Medicine report that the absence of registries to track the health of oocyte donors represents a limitation for evaluating any long-term effects. There is a need for additional data that would be applicable to the population in question—ostensibly healthy donors who are not intending to undergo IVF at the time of donation. Evidence suggests that oocyte donation that is performed exclusively for research is rare presently, thus raising questions about our ability to compile data with sufficient statistical power to draw valid inference. As stem cell research advances there may be opportunities to compile additional data; however, in all likelihood such a registry system would require coordination of multiple centers.

Need for Ongoing Evaluation

These guidelines support a precautionary approach to oocyte donation exclusively for research. Specific recommendations are based on published evidence, best practices, and the committee's best judgment at the time of publication. The committee expects that ongoing developments in the field of reproductive medicine may produce evidence that warrants a reevaluation of specific recommendations.

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