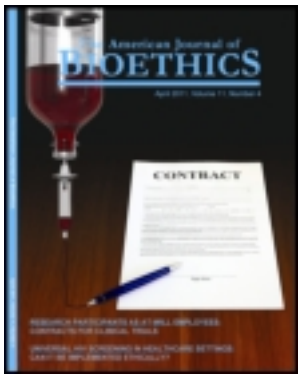

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Ethical Concerns Eliminated: Safer Stimulation Protocols and Egg Banking

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Ethical Concerns Eliminated: Safer Stimulation Protocols and Egg Banking

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The health risk for research donors—in this case women donating oocytes for somatic cell nuclear transfer (SCNT)—has indeed been one of the major indirect arguments against embryonic stem cell research via SCNT. In accordance with Ellison and Meliker (2011), we already argued some years ago that ovarian hyperstimulation syndrome (OHSS) incidence rates in an IVF population cannot be transferred to oocyte donors (Mertes and Pennings 2007). Moreover, the field of assisted reproduction is constantly evolving and new developments may well defuse this argument completely.

There are two elements that we would like to contribute to the discussion. First, new stimulation protocols can reduce the risk of OHSS to an even greater extent than Ellison and Meliker suggest. Second, just as "spare" in vitro fertilization (IVF) embryos are now being donated for human embryonic stem cell research, it is only a matter of time until "spare" human oocytes will also become available so that there will no longer be a need to stimulate women solely for research purposes.

The first development consists of banning human chorionic gonadotrophin (hCG) from the ovarian stimulation protocol. OHSS is directly related to hCG, which is administered to trigger final egg maturation and ovulation. However, in a gonadotropin-releasing hormone (GnRH) antagonist protocol, final egg maturation can be triggered with GnRH agonist instead of hCG (Kol and Dor 2009). Several studies have reported a total absence of OHSS with this protocol (Melo et al. 2009). However, one study in a cohort of patients who were specifically at risk of developing OHSS reported one early-onset case (out of 51 patients) of severe OHSS in a patient with a polycystic ovary (Griesinger et al. 2011). Therefore, it is still recommended to select donor candidates carefully (avoid women with PCOS etc.), even when using this "safe" protocol, in order to eliminate the occurrence of OHSS in oocyte donors.

While the development of OHSS-free protocols offers an instant solution to the specific problem of the OHSS risk for research donors, a second development is—in the long run—likely to solve the more general problem of submitting healthy young women to a medical procedure (and the discomforts attached to it) exclusively for research purposes. Oocyte freezing has long been very inefficient, but, thanks to the introduction of vitrification (ultrarapid freezing) and improvements to slow freezing methods, freezing oocytes is now as efficient as freezing embryos. Oocytes are currently frozen for a variety of reasons: for female cancer patients

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who want to preserve their reproductive chances in the face of aggressive treatment methods (that may deplete their ovarian reserve), for women with diseases that commonly lead to premature ovarian failure (like Turner syndrome), and for women who fear infertility if they postpone childbearing too long. With the introduction of the OHSS-safe protocol (mentioned earlier), a large number of IVF patients can be added to this list. The reason is that higher ongoing pregnancy rates are observed when embryos are transferred in an unstimulated cycle (due to a more receptive endometrium), which means that all retrieved oocytes or embryos should be cryopreserved for the duration of at least one cycle (Devroey and Adriaensen 2011). If oocytes rather than embryos are frozen, this will avoid ethical problems for persons (patients and policymakers) who attribute a high moral value to the embryo and want to avoid their destruction if possible. Since a very limited number of embryos will be created for each cycle, few (if any) will become supernumerary. Moreover, this scheme would avoid the notorious conflicts regarding embryo disposition between the gamete donors when the partners divorce, one of them dies or becomes incompetent, etc., as the woman will remain the sole decision maker regarding her oocytes (Pennings 2000). The relevance of this new IVF strategy for the availability of human oocytes for stem cell research is that instead of embryos (as is the case now), oocytes will become supernumerary after treatment is completed. When women have to decide about their fate, they will choose between the standard options: destruction, donation for science, or donation for reproduction. Since donation for science has fewer ethical and psychological ramifications than donation for reproduction, a large proportion of the women is expected to direct oocytes to this option.

If segmented IVF (as the new protocol is called by Devroey and Adriaensen) becomes common practice, this will likely provide the largest "pool" of research oocytes. In addition to this, it is also expected that improved egg freezing techniques and the reduced risk of developing OHSS will lead to an increase in so-called "social freezing," that is, oocyte banking for women who fear being infertile by the time they are ready to reproduce. The utilization rate of these frozen oocytes will not be 100%. Some women who have not found a partner by the time they reach the age limit, will eventually decide not to reproduce. It is impossible to predict now how high the rate will be, but again some of these women will donate for science, thus reducing the shortage of oocytes. Finally, also a number of so-called "medical freezers" (who fear infertility caused by disease or treatment) will not return to use their frozen oocytes and may decide to donate them to research.

Besides the obvious practical advantages of stem cell researchers having frozen eggs readily available, there is also an ethical advantage in using these "leftover" eggs rather than fresh eggs specifically harvested for research purposes. Medical freezers, social freezers, and IVF patients who ultimately decide to donate their oocytes to research have endured the discomfort of the stimulation cycles (with the minimal risks of OHSS) for their own treatment (either now or in the future). One could speak of a two-phased donation cycle: The collection (stimulation and pickup) phase is separated from the donation phase, as the collection was not performed *because of* the donation. This is similar to supernumerary embryo donation by IVF patients and to blood donation by hemochromatosis patients where patients have a phlebotomy for their treatment and afterward decide to donate their blood to others (Pennings 2005). The ethically relevant point here is that one cannot claim that donors have been lured into taking unnecessary risks for a study with uncertain benefits.

For researchers who need oocytes at this very moment, reliance on spare banked oocytes is not an option, as it will take another couple of years until the oocytes that are banked today become available for research. For that reason, we briefly refer to yet another option that might provide a temporary solution to the "oocyte shortage," namely, an egg-sharing program whereby social freezers donate some of their oocytes at the time of retrieval—rather than after relinquishing their child wish—in exchange for a participation in the costs related to egg retrieval. This scheme in itself does not reduce the risk of OHSS (although it could be envisaged that the use of the safest protocol is made mandatory in this case), but the risk—if any—would be taken by the donor with a clear benefit for herself in mind, namely, that of enlarging her reproductive options. Obviously, this option would require a fair deal of counseling and is likely to be received as controversial, although we would argue that it is less controversial than egg sharing for (immediate) reproductive purposes (on either side of the equation).

In conclusion, we agree with the main message of Ellison and Meliker that the risk of OHSS has been overstated in the context of research donors, but even small risks should be further minimized or eradicated whenever possible. This can be done by adopting an hCG-free stimulation protocol for all oocyte donors and by reliance on spare banked oocytes as soon as they become available. ■

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The Conundrum of Oocyte Donation, Human Research, OHSS, and Ethics

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> Not long after Henrietta's death, planning began for the HeLa factory—a massive operation that would grow to produce trillions of HeLa cells each week. . . . [Twenty-five years later] Hopkins had part of Henrietta alive and scientists everywhere were doing research on her and the family had no idea. (Skloot 2010, 93, 180)

Oocyte donation is a critical foundation in human embryonic stem cell research (hESC). Oocyte (i.e., egg) donation is a complex procedure with little or no oversight by a federal regulatory agency. These donations encounter complex clinical and multifaceted ethical dilemmas. Among the most concerning are dubious donor recruitment practices, poor informed consent, risks with stimulation protocols and the in vitro fertilization (IVF) procedure, and lack of long-term follow-up.

TERMS AND MEANINGS

It is important that standard terminology be maintained to avoid confusion among people with different backgrounds: researchers, patients, donors, media, politicians, clinicians, the public, and the world community. To start, the International Society for Stem Cell Research (ISSCR) has provided a "Glossary of Stem-Cell Related Terms," which could be acknowledged as the accepted definitions for use in publications, media, consents, education, and legislation (http://www.isscr.org/Glossary_of_Stem_Cell_Related_Terms, accessed May 2, 2011).

Relevant examples for this discussion from the ISSCR Glossary include:

> **Cloning:** In biology, the process in which an organism produces one or more genetically identical copies of itself by asexual means. . . .
>
> **Nuclear transfer:** A technique in which an egg has its original nucleus removed and exchanged for the nucleus of a donor cell . . . .Nuclear transfer is also referred to as somatic cell nuclear transfer (**SCNT**). . . .
>
> **Reproductive cloning:** The transfer into the uterus of an embryo derived by nuclear transfer with the intent to establish a pregnancy. . . .
>
> **Stem cells:** Cells that have both the capacity to self-renew (make more stem cells by cell division) as well as to differentiate into mature, specialized cells. . . .
>
> **Therapeutic Cloning:** The generation of embryonic stem cells from an embryo derived by nuclear transfer for therapeutic purposes. The resultant cell line would be genetically identical to the donor of the transferred nucleus. In humans, the therapeutic potential includes research using patient- or disease-specific human embryonic stem cells to study the basis of disease or advance towards tissue replacement.

OOCYTE DONOR RECRUITMENT

Provocative tactics are often employed to recruit and promote reproductive egg donors; independent agencies use recruitment techniques that are entrepreneurial and highly unregulated. For example, recruitment advertisements for egg donors fail to follow guidelines promulgated by the Society of Assisted Reproductive Technology (SART) and American Society of Reproductive Medicine (ASRM) (Practice Committees, SART and ASRM 2004; Levine 2010). Women aged 18 to 30 years are solicited for their oocytes at universities across the country and on the Internet, for up to $100,000. Simply browse a college newspaper or Google "egg donor" (e.g., www.elitedonors.com). By donating a few good eggs, young women may pay for their medical care, living expenses, car, or education. However, the long-term consequences for these young women, such as the impact on their reproductive health or cancer risks, are unknown. No one monitors how many times the women donate or what medications they use, or follows up on their

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