Human Eggs: The Need, the Risks, the Politics

By Ann A. Kiessling, Bedford Stem Cell Research Foundation

The tasks of eggs include remodeling gene expression to a state of pluripotency and supporting the first few cleavage divisions with stockpiled biomolecules. The enormous size of mammalian eggs, including human, may play a key role in these tasks. The fully grown human egg, with a diameter of 110 to 120 microns and a volume of approximately 900,000 cubic microns, is nearly 250 times larger than a white blood cell, and nearly 4,000 times larger than a sperm head.[1]

The nucleus of the egg, termed the germinal vesicle, is also huge. With a diameter on the order of 50 microns, the volume of the germinal vesicle is approximately 65,000 cubic microns, more than ten times the volume of a white blood cell. This huge nucleus provides ample open scaffolding for chromatin, a characteristic that may play an important role in gene expression.

The Need for Human Eggs

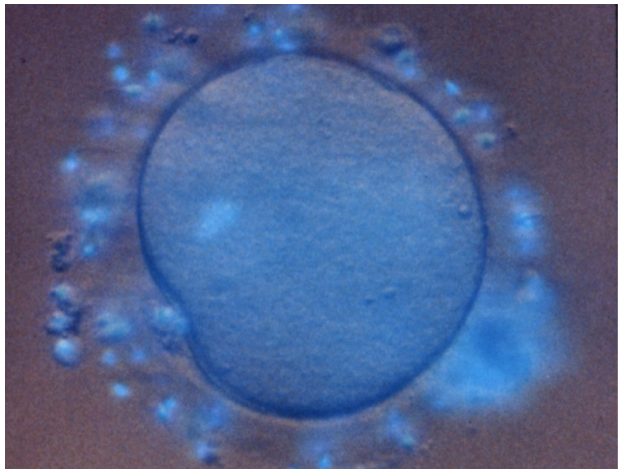
The egg also has an unusual and unique cell cycle. Oocytes are arrested within the ovary in late G2 of the cell cycle for at least one, and in most cases, several decades. As such, they represent not only the largest, but one of the most quiescent, long-lasting human cells. This is a highly unusual cell cycle arrest point, and the strategy behind this arrest is not known with certainty. In this state, they have twice the normal amount of DNA (tetraploid) and are said to be in the prophase of meiosis. This is the stage at which they stockpile biomolecules for future use and in which chromosome crossover can occur, a process that leads to new combinations of genetic information on each chromosome, giving rise to the genetic uniqueness of each egg.[1]

When the egg is mature, protein and nucleic acid synthesis cease. The huge germinal vesicle migrates to the edge of the oocyte and forms the first metaphase plate adjacent to the plasma membrane, rather than in the center of the cell as in somatic cells. Almost as soon as the metaphase plate is formed, a unique, unequal cell division occurs, which results in the production of the polar body, approximately the size of a somatic cell, which contains a complete set of chromosomes. This is meiosis I. Following the unequal cell division, in contrast to all other cell cycles, the nuclear membrane does not reform around the remaining chromosomes. They immediately undergo a rearrangement, which results in a second metaphase plate. Then the second meiotic arrest occurs [See Figure 1]. The huge cell arrested at metaphase II is very fragile. If not activated within one to two days, the egg will perish.

Several lines of investigation have shown that factors outside the nucleus, in the cell cytoplasm, control the egg's cell cycle. The transfer of cytoplasm from metaphase II eggs into germinal vesicle-stage eggs initiates meiosis. Molecular characterization of the egg meiosis promoting factor (MPF) revealed it is composed of two cell cycle proteins, Cdc2 and cyclin B [See Figure 2], known cell cycle regulators in somatic cells.

The transfer of cytoplasm from metaphase II eggs into cleaving embryos arrests embryo cleavage at the M phase of the cell cycle. This indicates that metaphase II arrest is also controlled by cytoplasmic factors, termed cytostatic factor (CSF). A serine/threonine kinase, cMos, is an important component of CSF. As shown in Figure 2, cyclin B is synthesized during S phase and complexes

FIGURE 1

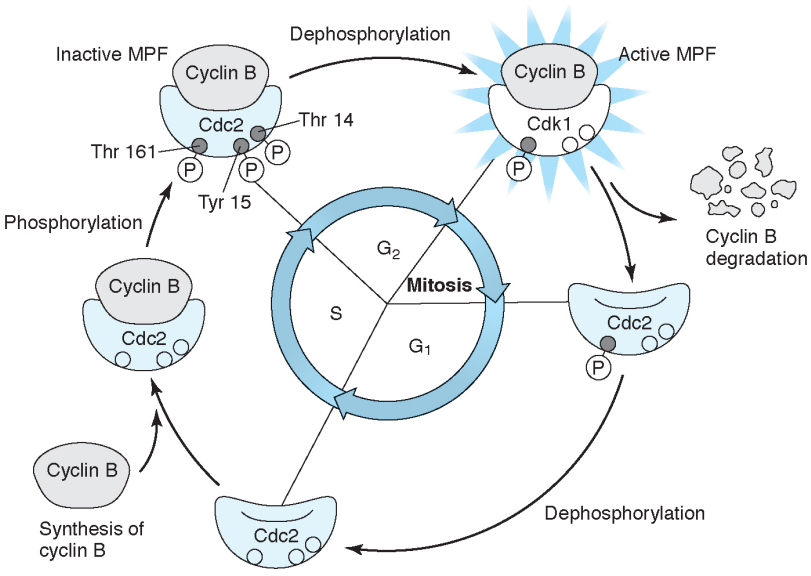


with Cdc2. The activation of the complex by Cdc25 leads to kinase activity with a broad spectrum of targets, including other enzymes and structural proteins. Importantly, one of MPF's targets for phosphorylation early in the M phase is the degradation machinery for cyclin B, which normally occurs after the metaphase plate is fully formed, allowing reformation of the nucleus after cell division in somatic cells.

Thus, meiosis I requires activation of the cyclin B/Cdc2 complex, and metaphase II arrest requires blocking the degradation of cyclin B. This is the function of cMos. It phosphorylates mitogen-activated protein (MAP kinase) which plays a central role in maintaining chromosomes in metaphase after the extrusion of the first polar body. Therefore, a fundamentally important aspect of releasing the egg from metaphase arrest is the elimination of cMos activity. Although not fully identified, the factors that eliminate cMos activity and allow the destruction of cyclin B must be stockpiled within the egg's cytoplasm, awaiting recruitment.[1]

These profound cytoplasmic controls on the egg cell cycle serve to emphasize the importance of cytoplasmic stockpiles to the success of critical egg functions. By pausing at interphase, the nuclear factors essential to remodeling chromatin remain available in the cytoplasm. It stands to reason that some chromatin-remodeling components target egg chromatin and others target the sperm nucleus, although this is not known with certainty. Sperm chromatin is highly specific, rich in sperm-specific proteins which pack the DNA tightly into the tiny sperm nucleus which must be dissolved in order to remodel the chromatin into an embryonic state. Presumably, once metaphase arrest is overcome and a nuclear membrane forms around the egg chromatin, it may be more readily remodeled into an embryonic state. The exact nature of the egg cytoplasm factors responsible for remodeling somatic cell nuclei transplanted into the egg are not known with certainty, but are presumably the same as those involved in egg and sperm chromatin remodeling. Given the low efficiency (approximately two percent) of successful offspring development following nuclear transplantation ("cloning"), some aspects of somatic cell nuclear remodeling may be inadequate to re-establish a developmentally competent embryonic state. Nonetheless, the remodeling activities may be competent to generate lines of pluripotent stem cells at a higher efficiency than embryonic development.

FIGURE 2



The zygote phase of human development, the time from fertilization to the first cleavage, is approximately 24 hours. During this interval, not only does chromatin remodeling take place, but also silencing of the factors maintaining meiotic arrest, one complete round of DNA replication, chromatin condensation into chromosomes, and the first mitotic cell cycle. The activation of human eggs without removal of the egg's chromosomes (parthenogenesis) or with the removal of the egg's chromosomes followed by transplantation of somatic cell chromosomes (somatic cell nuclear transfer; SCNT) were reported in 2001.[2] Although a high percentage of the human eggs responded to activation stimuli, and initiated cleavage, and many of the parthenotes reached the blastocyst stage, no stem cell lines were derived. More recent attempts to derive pluripotent stem cells from human parthenotes were successful, however, with a reported efficiency of 6 cell lines from 46 activated eggs.[3]

This is an exciting development that promises a new source of pluripotent stem cells for therapies, especially for pre-menopausal women who could have stem cells derived from their own eggs for their own treatment.[4] Once research has revealed all the components of this extraordinary series of cellular events, eggs may no longer be needed to re-program somatic cells, but they will remain the only source of parthenogenetic stem cells.

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Although a Korean team reported the creation of several lines of pluripotent human stem cells following nuclear transplantation into human eggs, the reports were false, and as of this writing, there have been no reports of the creation of pluripotent human stem cells by SCNT.

Important progress in elucidating the cellular factors necessary to reprogram mouse fibroblasts into pluripotent stem cells without SCNT were recently reported.[5 6] Of 24 factors known to be expressed in pluripotent mouse ES cells in culture, a combination of 4 factors expressed simultaneously from constructs introduced into the fibroblasts were sufficient to induce pluripotency: Oct3/4, Sox2, c-Myc and Klf4. This elegant work provides valuable clues about egg functions involved in remodeling, but the genetic manipulation methods used are not applicable to human fibroblasts designed to provide therapeutic stem cells, partly because of the risk of cMyc-induced tumors. For the time being, oocytes, either before or after fertilization[7] are still needed to re-program human somatic cell chromosomes. Identification of these essential transcription factors provides important guidelines to establish reproducible egg-activation procedures that lead to the expression of these factors by both parthenotes and nuclear transplants.

Many aspects of egg development remain mysterious because unlike other cells, laboratory methods have not been developed to support the life cycle of eggs in culture. This fundamentally important roadblock is the largest hurdle faced by nuclear transplant stem cell scientists. A report of the production of mouse eggs from mouse embryonic stem cells in culture generated much excitement that mammalian egg biology could be studied in greater detail in the laboratory,[8] but the findings have been difficult to repeat and have not been reported by other laboratories. In the absence of a laboratory culture system to generate oocytes, the sole source of human eggs at the time of this writing is surgical recovery from the ovaries of pre-menopausal women.

The Risks of Egg Donation

The supply of eggs in the ovaries of women is established early in fetal development. Oogonia stop dividing in the fetal ovary during the second trimester of fetal development and become primary oocytes, surrounded by a single layer of granulose cells. Infant girls are born with on the order of one million primary oocytes. By the time she is approximately 50 years of age, the oocytes are all gone. This means that on the order of 20,000 eggs die each year, including the dozen or so which are ovulated.

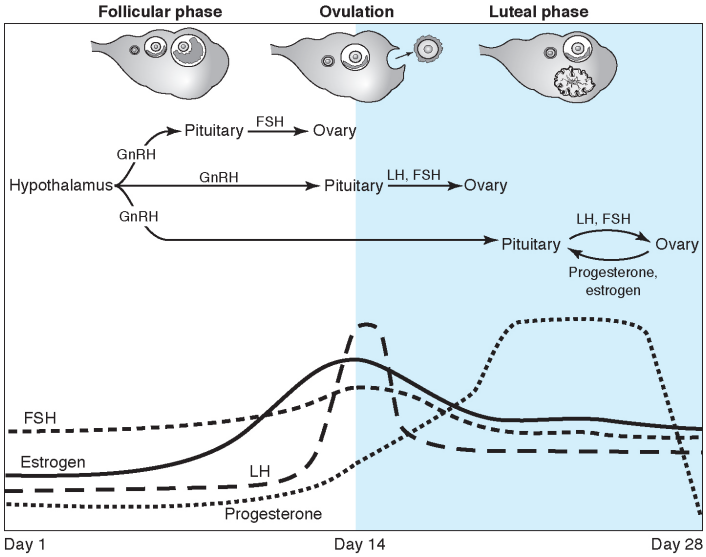
Whether or not the eggs recruited for ovulation are selected from the remaining healthy cohort, rather than from the cohort that has entered the death pathway, is not known with certainty. Several lines of evidence have shown that many more human eggs can be fertilized and initiate development than actually give rise to offspring. Moreover, the failure of fertilized eggs to develop into offspring is not due to failure to develop into multiple types of cells, but failure to develop functioning organs, such as the heart. This suggests that many more eggs may have the potential to remodel nuclei and give rise to stem cells following nuclear transplant than have the potential to give rise to babies. The human and medical value of being able to distinguish between cleaving eggs with the full potential to give rise to offspring and those with limited potential cannot be overstated. Research in this area has been essentially eliminated by the 1996 ruling of the U.S. Congress that"… such research is valuable, but will not be funded by taxpayer dollars."[9]

Maturation of a primary oocyte in preparation for ovulation is the result of wonderfully orchestrated communications between the ovary and two glands in the brain, the hypothalamus and the pituitary [See Figure 3]. The hypothalamus produces protein hormones whose target is the pituitary. The pituitary gland responds by releasing more protein hormones whose target is the ovary. The pituitary hormones are termed gonadotropins and the hypothalamic hormones are gonadotroping-releasing hormones.

One of the gonadotropins is follicle-stimulating hormone (FSH), which stimulates the granulosa cells surrounding the primary oocyte to divide and secrete estrogen. Estrogen in turn stimulates increased expression of receptors for FSH on the surface of the granulosa cells, thus capturing more FSH each time it is released into the bloodstream by the pituitary. In response, the oocyte resumes growth and expression of oocyte-specific proteins.

The cyclic recruitment of a primary oocyte to undergo maturation for ovulation that month begins within a day or two of the onset of menstruation, which signals that no pregnancy has occurred. In the absence of pregnancy, the granulosa cells in the ovary essentially cease synthesis of the steroid hormones, estrogen and progesterone. The drop in steroid hormones stimulates

FIGURE 3. HORMONAL COMMUNICATION BETWEEN THE BRAIN AND THE OVARY.



the hypothalamus and pituitary to resume their hormone synthesis. Approximately 10 days following the onset of menstruation, FSH release has stimulated the development of a fluid-filled, estrogen-rich sac termed an ovarian follicle.[1]

Within the hormone- and nutrient-rich environment of the follicle, the oocyte cytoplasm stockpiles biomolecules. Estrogen produced by the granulosa cells not only acts locally to stimulate the egg and other cells in the growing follicle, but also enters the bloodstream and stimulates the pituitary to decrease production of FSH and stimulate release of another gonadotropin, leutinizing hormone (LH). By approximately day 13 of the menstrual cycle, LH pulses reach the same height as FSH pulses, which begin to decline [See Figure 3]. This circumstance initiates a dramatic cascade of responses in the follicle, including the transformation of the granulose cells from producing estrogen to producing progesterone, which ultimately leads to release of an egg arrested at metaphase II [See Figure 1].

Egg donation for research involves the hormonal treatments employed for assisted reproductive technologies developed during the past two decades, but with increased medical monitoring.[10, 11] The availability of pharmacologic doses of gonadotropins provided the opportunity to treat women whose infertility resulted from their own hormone imbalances. It also provided the opportunity to increase the levels of gonadotropins in hormonally normal women to stimulate more than one egg to resume maturation each month, thus increasing the number of eggs available for fertilization in laboratories. Such in vitro fertilization (IVF) procedures have become the standard of care for a variety of infertility conditions.

Approximately 100,000 women go through egg collection each year in the United States, some for their own reproductive needs, others to donate eggs for fertility treatments. The goal is to stimulate final maturation of 10 to 20 oocytes in concert. This allows several eggs to be fertilized and begin development. The most normal-appearing embryos are then selected for transfer to the woman's uterus for possible gestation.

To help ensure that the eggs are all at the same stage of maturation at the time of collection, hormones are administered to block the pituitary stimulation of the ovary. A common approach is a drug that actually stimulates an outpouring of GnRH from the hypothalamus. Such drugs are termed GnRH agonists, and an example is Lupron. After two or three days, the over-stimulated hypothalamus actually shuts down its release of GnRH, a circumstance termed "down-regulation." This leads to no FSH production by the pituitary, and after several days, the ovary is quiet.

Once the ovary is quiet, recruitment of several oocytes may be accomplished by administration of relatively high doses of FSH. This clinical treatment is termed controlled ovarian hyperstimulation (COH) and is accomplished by daily injections of pharmacologic doses of gonadotropins. The artificial stimulation of the ovary brings about maturation of several oocytes in concert and the simultaneous division of the granulosa cells to several million per egg. Collectively, they produce estrogen at levels at least an order of magnitude higher than a natural cycle.

In order for the fertility clinic to plan the oocyte collection before spontaneous ovulation occurs, the mid-cycle surge of LH by the pituitary must also be blocked. Agonists such as Lupron do not inhibit COH, so it may be continued throughout the period of hormone injections. Alternatively, some drugs inhibit, rather than stimulate, hormone production by the hypothalamus. Termed antagonists, such drugs can be administered after the COH is begun specifically to inhibit spontaneous LH release by the pituitary. Importantly, despite the pharmacologic intervention, the eggs recruited do not necessarily comprise a synchronous cohort and the

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growing follicles may have a range of sizes. The COH is continued for 10 to 12 days, approximately the same number of days of stimulation as occurs during a natural menstrual cycle. When the developing follicles have grown to approximately 2 cm in diameter, and appear to be producing sufficient estrogen, an artificial surge of LH is administered by a single injection of a high concentration of gonadotropin. Nearly all eggs that have responded to the COH will resume meiosis in response to that single injection (as seen in Figure 3). In this regard, it is important to note that the capacity to resume meiosis II may precede full maturation of oocyte cytoplasm.

Approximately 34 hours after administration of the artificial LH surge, eggs are collected directly from the ovarian follicles with the aid of ultrasound-guided needle aspiration, a procedure requiring anesthesia and taking about 30 minutes. There are several health risks associated with COH. One is an unusual over-response by the ovary to the artificial gonadotropin stimulation which results in abnormally high levels of estrogen production, swelling of the entire ovary to several times normal size, and accumulation of fluid in the abdomen. This serious complication, known as ovarian hyperstimulation syndrome (OHS), is the reason that all women undergoing COH should be monitored closely for estrogen production in response to gonadotropin injections. Women going through IVF who become pregnant are at greater risk for OHS because the pregnancy hormone adds to the stimulation of the ovary, increasing its response. Women donating eggs for research can be protected from OHS by establishing conservative screening criteria for the possibility of underlying endocrine disorders which would lead to a heightened response to hormone treatment, and discontinuing the gonadotropin injections as early in the cycle as indicated to avoid OHS.

A second risk of egg collection is hemorrhage due to trauma to a blood vessel during the egg collection. This can be avoided by careful ultrasound examination by a skilled physician experienced in ultrasound-guided egg collection. A third risk of egg collection is infection, which can be avoided by prophylactic antibiotic treatment and aseptic surgical procedures. A fourth risk of egg collection is ovarian torsion, a condition brought about by the ovary rotating in such a way that it compromises its blood supply. The risk of this is greater if the donor experiences OHS. A fifth risk of egg collection is the anesthesia itself; although exceedingly rare, unusual reactions to anesthetic agents can result in death.

During a workshop sponsored by the National Institute of Medicine in 2006, the expert discussions indicated that all of the medical risks associated with egg donation could be nearly eliminated by good medical history taking (e.g. hormone profile, responses to prior pregnancies and anesthesia) and good medical management, except one, the long-term consequences of such high levels of hormonal stimulation. Since hormone stimulation for fertility treatment has only been standard of care for fewer than two decades, the long term consequences will not be known with certainty for another two or three decades. Prospective egg donors should be well informed of this, and the total number of cycles of egg donation they undergo should be limited.[10, 11]

Twenty three women undergoing 37 cycles of egg collection for stem cell research between 2000 and 2005 did not experience OHS, bleeding, problems with anesthesia, ovarian torsion, or infection.[11] Donors responded to newspaper ads: "Research team seeks women aged 21 to 34 with at least one child to donate eggs for stem cell research; compensation for time, travel and child care expenses." Intake into the research project involved 11 steps [See Table 1], cycles of egg collection five steps [See Table 2], and exit from the cycle four steps [See Table 3]. The guidelines for the egg donor program were developed by an ethics committee chaired by Ron Green at Dartmouth College.[10] The physicians caring for the donors were not involved in the research.

Through 2005, 391 women requested information, 290 (74%) returned the initial inquiry, 202 (52%) attended information sessions, 143 (37%) returned consent forms, 104 (27%) completed the psychological screening, 51 (13%) completed the physical screening, 28 (7%) initiated 44 CECs, 12 women completed one CEC, eight women completed two CECs, and three women completed three CECs. Eggs collected per cycle ranged from 0 to 21, with an average of 7.4 ± 3 and a total of 274. Almost all the women had never and did not plan to donate their eggs to fertility clinics. Program cost per completed cycle was $27,200. Egg donor compensation ranged from zero for those not returning consent forms, to $560 to $4,004, depending on expenses and steps completed. The scheme for donor compensation was essentially the "wage-payment" model advocated by Dickert and Grady in 1999.[12]

The Politics of Human Egg Donation

Remarkably, egg donation for stem cell research has

been debated worldwide, as if standard guidelines for human research subjects were not sufficient to inform and protect research egg donors. Particularly difficult to understand is the logic behind the contention that the best way to protect egg donors is to not reimburse them for their time and effort.[13, 14] Standard practice worldwide is to compensate healthy human research subjects for time and effort, whether it be for donation of blood samples, semen specimens, sleep studies, dietary questionnaires, drug trials, etc. The risks and benefits of the research are evaluated by committees of professionals charged with the responsibility of assuring that the research may yield information worth the risks the human subjects will assume, that the human

TABLE 1. INTAKE PROCESS FOR PROSPECTIVE EGG DONORS FOR STEM CELL RESEARCH

STEP	ACTIVITY	DESCRIPTION
1	Initial inquiry	Prospective donors return questionnaire with age, general health, number of children, address and employment status
2	First information session	Detailed explanation of the science, the process, the risks and the time line for participation
3	Second information session	A follow-up information session covering the consent form and the responsibility of the donor to schedule all intake steps
4	Minnesota Multiphasic Personality Index	Scored multiple-choice test measuring overall mental status; scored by MMPI
5	SCL-90	Scored multiple-choice test measuring acute life stresses; scored by psychologist/psychiatrist.
6	Personal History	QuestionnaireSix page questionnaire detailing ethnic background, medical and personal history
7	Psychological Interview	In depth interview with psychiatrist/psychologist skilled in recruiting study subjects for biomedical research. *Medical team meeting to determine if donor should proceed*
8, 9	Hormone Profile and Infectious Disease testing	Blood tests to measure baseline hormone levels and detect antibodies against HIV, hepatitis, STDs, CMV and EBV. HIV counseling provided.
10	Gynecologic exam	Complete gynecologic examination including Pap smear and ultrasound examination of ovaries Medical team meeting to determine if donor should proceed
11	Interview with Study Monitor	Private interview with knowledgeable individual not part of medical or research team to ensure the donor understands the process, the risks, the time commitment and is not being coerced by anyone to participate. *Medical team meeting to determine if donor should proceed*

TABLE 2. CYCLE OF EGG COLLECTION

STEP	ACTIVITY	DESCRIPTION
1	Medication Training	Donors are instructed in subcutaneous injections of hormones and provided a calendar with the details of medications to be taken and required blood tests and ultrasound exams.
2, 3, 4	Hormone injections, serum hormone measurements, ultra-sound examinations of ovary	On Day 4 of hormone injections, blood estradiol levels are measured to ensure the donor's ovary is not over-responding to the hormone stimulation. If estrogen levels are less than 300 pg/ml, the cycle is continued; if greater than 300 pg/ml, hormone injections are stopped and her cycle cancelled. Estradiol measurements and ultra-sound examinations are scheduled for Days 6, 8 and daily thereafter. 5,000 units of human chorionic gonadotropin are administered 34 hours before egg collection, unless serum estradiol levels reach 3500 pg/ml before the leading egg follicle reaches 18 mm in diameter, in which case the cycle is cancelled.
5	Egg Collection	Ultra-sound guided egg collection, standard for assisted reproduction, is performed by a medical team separate from the research team

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TABLE 3. CYCLE EXIT

STEP	ACTIVITY	DESCRIPTION
1	Recovery from Egg Collection	Donors are encouraged to limit activities the day following the egg collection.
2	Follow-up Visit to Gynecologist	Two weeks following the egg collection, a complete gynecologic exam with ultrasound measurement of the ovaries is performed to insure donor recovery
3, 4	Exit Questionnaire and Exit Interview with Psychologist	A series of questions to assess donor's level of discomfort, concerns about the process, her recovery from the CEC, any concerns about her future well being.

subjects are fully informed of all the risks and the benefits, that they are participating of their own free will, and are reasonably compensated for their time and effort devoted to the research. Most human subjects review boards (commonly termed institutional review boards, IRBs) are convened by research hospitals and universities and follow guidelines established by the National Institutes of Health for human subjects research (ohsr.od.nih.gov/guidelines/index.html). They are made up of physicians, scientists, ethicists, laypersons, and attorneys. The NIH guidelines are based on the Belmont Report (ohsr.od.nih.gov/guidelines/belmont.html), "a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects."

Compensation for research subjects is generally decided by IRBs on a case-by-case basis. The goal is to guarantee that the study subject is not being coerced by financial reward, but is also not being exploited by lack of compensation for expenses, time and effort to participate in the research. Not compensating research subjects at all is not generally viewed as providing protection against subjects putting themselves at risk.

Egg donation for stem cell research has become caught up in issues of equity, feminism and the lack of regulations guiding the fertility treatment industry.[14, 15] Very few existing IRBs have had an opportunity to consider and debate a research protocol involving human egg donation. The debates have gone on, instead, in legislative bodies designing laws governing stem cell research, and in the public press.

Particularly outspoken critics include Judy Norsigian, executive director of Our Bodies, Ourselves.[15] Her concerns center on the risks of multiple egg extractions, particularly the side effects from the medications used, which she contends are not adequately explained to women undergoing COH for egg collections. She cites many negative and serious side effects of the drug Lupron, most of which are associated with its long-term use to treat conditions such as uterine fibroids, not the relatively short-term use for COH. In fact, Lupron was not used for the cycles of egg collection for the egg donors described in the previous section. She also cites the risks of OHS, described above, which can, in fact, be nearly eliminated by careful, early monitoring of the response to the gonadotropin injections.

Other outspoken critics are Marcy Darnovsky of the Center for Genetics and Society, who has advocated the importance of protecting poor minority women from exposing themselves to cycles of egg collection for financial compensation. Women in California donating eggs for research can be reimbursed only for "direct" expenses, probably not for time and effort, thus bypassing the "wage-payment" guidelines advocated in 1999.[12] Similar financial constraints were put into the stem cell legislation passed in Massachusetts in 2005.

It is not clear how time and effort compensation for the research egg donor would jeopardize her safety. Discussions of limiting compensation to the medical team informing her of her risks and caring for her during the CEC, which might be more relevant, are lacking. The cost of the hormones alone for a CEC exceed "wage-payment" guidelines, and the reimbursement guidelines considered reasonable by most IRBs. In the end, the medical team, the pharmaceutical companies, the ultrasound equipment companies, and the researchers themselves will all be compensated for the egg donor's efforts—but not the donor herself.

Many bioethicists who have studied research egg donor issues, such as Professor Bonnie Steinbock, believe egg donors should be compensated: "Any time we ask people to do things that impose significant burdens

and some degree of risk, fairness may require that they be adequately compensated. At the same time, there's a general consensus that it would be improper to offer enormous sums of money to egg donors that could sway their judgment."[15] Kathy Hudson of the Johns Hopkins University Genetics and Policy Institute in Washington, D.C. agrees.[12]

The hope of all stem cell scientists is that the ability to remodel cells without human eggs is just around the corner. But until that corner is turned, eggs are needed. Generous women willing to undergo egg collection for research purposes deserve the same considerations as all other volunteers for biomedical research. It is time to return the human subjects concerns surrounding egg donation back to the committees of professionals experienced in processes of informed consent and appropriate, non-coercive levels of compensation. Or, as recently advocated by Professor Dan Wikler and colleagues, perhaps all women volunteering for egg donation should be compensated, whether or not they actually participate.[16]

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FOOTNOTES

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