Human Egg Donor Program for Stem Cell Research

Ann A. Kiessling, Lisa Smith, Maureen Kearnan, Jose Cibelli, Margaret Wray, Susan Moss, Hui-Zhong Yin, Paul Winig, Robert Kaufmann
Bedford Stem Cell Research Foundation, Somerville, MA, United States of America

ABSTRACT

Program development began in 1998 and has three phases: Intake, Cycle of Egg Collection (CEC), Exit.

Intake has 12 steps: initial inquiry, information session, consent form review, two written tests (Minnesota Multiphasic Personality Index, SCL-90), personal history questionnaire, interview with psychologist, hormone and infectious disease testing, gynecologic exam, written assessment of understanding, interview with study monitor. The information session reviews the research, the consent form, physical risks, time commitment, and places the prospective donors in charge of arranging each successive step of Intake. The study monitor is independent of the medical and research teams and assesses the prospective donor's understanding of the research, the risks, and her independence in participation. Intake exclusion criteria: no children; severe depression, schizophrenia, psychoses; major personal conflicts, including prior relationship with research team or criminal record; infection; abnormal physical findings; evidence of inability to comprehend or comply with program steps, 3 or more CECs.

CEC has 5 steps: medication training, 10-12 days of hormone injections, serum hormone measurements, ultra-sound examinations of ovary, egg collection. CEC cancellation criteria: acute illness or donor anxiety, under-response to hormone treatment (fewer than 3 eggs anticipated), over-response to hormone treatment (blood serum estrogen value greater than 300 pg/ml on day 4 of hormones, or greater than 3500 pg/ml on final day of hormone injections), new medical findings. The medical team is separate from the research team and donor identity is blinded to the research team.

Exit has 4 steps: recovery from egg collection, follow-up visit to gynecologist two-weeks post procedure, exit questionnaire, exit interview with psychologist.

Donor recruitment began in September, 2000, with a Boston Globe ad: "Research team seeks women aged 21 to 35 with at least one child to donate eggs for stem cell research; compensation for time, travel and child care expenses." Newspaper ads were placed in 2000 to 2003, but have been discontinued because prospective donors self refer to Bedford Research Foundation. 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, 23 (6%) completed 37 CECs: 3 women completed 3CECs, 8 women completed 2 CECs, 12 women completed 1 CEC. No donors experienced ovarian hyperstimulation syndrome, excessive bleeding or infection.

Donor reimbursement ranged from $560 to $4,004 depending on expenses and steps completed. Eggs collected per cycle ranged from 0 to 21, average 7.4± 3, total 274. Program cost per completed cycle: $27,200; cost per egg $3,673.

BACKGROUND

When activated, eggs have the extraordinary capacity to reprogram gene expression by their own chromosomes, and those of a fertilizing sperm, to a state of pluripotency. Moreover, eggs from many animal species can similarly reprogram gene expression in somatic cell chromosomes, making it possible to derive lines of pluripotent stem cells genetically identical to the somatic donor cell. Several lines of evidence indicate that such genetically identical pluripotent stem cells may replace dead or defective cells in incurable diseases, such as heart failure, spinal cord injury, diabetes, Parkinson's disease and AIDS.

The capacity to reprogram somatic cell chromosomes has not been demonstrated for human eggs, limiting the possibility of the derivation of genetically identical pluripotent stem cells for research and therapeutic purposes. Once the process of reprogramming is understood, it may be possible to reprogram somatic cells to pluripotent stem cells without the need for eggs. To carry out the necessary research, human eggs are needed.

Human ovaries are populated with about one million immature eggs, which die at the rate of approximately 20,000 per year. Since only one or two dozen eggs are ovulated each year, there is a large reservoir of human eggs not used for reproduction. Although it may be possible to develop methods to mature human eggs in laboratory culture, such methods are not now available. For this reason, the only source of mature human eggs for reprogramming experiments are from the ovaries of ovulating women who have undergone hormone treatments to stimulate the simultaneous maturation of several eggs, the process used for assisted reproduction.

The monthly process of egg maturation is the result of a highly coordinated communication between hormones elaborated by the hypothalamus and pituitary glands in the brain, and the ovary, termed the hypothalamic-pituitary-ovarian-axis. To stimulate the coordinated maturation of several eggs, instead of one or two, this axis must be interrupted and replaced with an augmented one.

The hypothalamus secretes gonadotropin releasing hormone (GnRH) to stimulate the pituitary to produce follicle stimulating hormone (FSH) to activate receptors in the ovary. In response, cells in the ovary produce estrogen, which feeds back to the hypothalamus-pituitary pathway, decreasing the production of FSH by the pituitary and stimulating the pituitary to produce luteinizing hormone (LH) to bring about the final stages of egg maturation as well as convert estrogen-producing cells to progesterone-producing cells. The net result: one or two eggs mature (figure on the left).

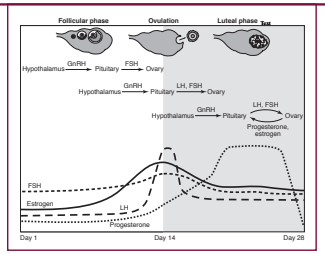
www.bedfordresearch.org

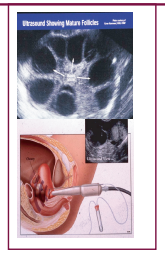
BACKGROUND (cont'd)

A central element of assisted reproduction technology is hormonal treatment regimen that stimulate the synchronous maturation of 10 to 20 eggs instead of one or two. This is accomplished by suppressing the hypothalamus-pituitary pathway and administering pharmacologic doses of exogenous FSH and LH. Several hormone regimen are now available to accomplish this and tens of thousands of women undergo assisted reproduction annually all over the world. Once multiple eggs mature in the ovary, they are collected with an ultra-sound guided needle through the wall of the vagina (Figure below, right). The tip of the needle penetrates the ovarian sac containing the egg, which is then collected by gentle vacuum into a tube for transport to an incubator in the laboratory. Although the egg collection procedure carries the risk of infection and damage to the ovary, such side effects are rare, and many women seeking to achieve a pregnancy go through multiple cycles of hormone stimulation and egg collection. A potentially serious side effect is an unanticipated over-response of the ovary to the pharmacologic doses of FSH and LH that can result in a life-threatening condition termed ovarian hyperstimulation syndrome. Other less serious, but uncomfortable side effects include the mood swings brought about by suppression of the hypothalamus-pituitary pathway and the ten-fold higher levels of estrogestn and progesterone that result from the increased doses of FSH and LH.

The complexity of the egg collection regimen has led to concern about the use of human eggs for research rather than reproduction. Some groups feel that only women undergoing egg collection for fertility treatment should be asked to donate eggs for research; other groups feel that women undergoing fertility treatment should never be asked to donate eggs for research because of emotional conflict with their own family building goals.

In the fall of 1999, an Ethics Advisory Board was convened to design a program of egg donation for stem cell research that would serve as the Gold Standard (*R. Green, et al. Hasting Center Report, 2002*) The first ad was placed in the Boston Globe in September, 2000: "Research team seeks women between the ages of 21 and 35 with at least one child to donate eggs for stem cell research." In 2003 the Egg Donor Program was reviewed by the Board of Trustees and the Ethics Advisory Board for the Bedford Research Foundation, followed by review of the Intake process by the Western Institutional Review board in 2004, the California Instutes of Regenerative medicine Standards Working Group in 2005, and by a newly convened Institutional Review Board in compliance with Massachusetts law in 2006. In summary, the Bedford Stem Cell Research Research Foundation' Egg Donor Program has been reviewed by more than 60 ethicists, physicians, scientists and patient advocates.





SUMMARY

- Through 2005, 391 requested information, 290 (74%) returned the initial inquiry, 202 (52% attended information sessions, 143 (37% returned consent forms104 (27%) completed the psychological screening, 51 (13%) completed the physical screening.
- 28 women (7%) initiated 44 CECs, 23 (6%) completed 37 CECs: 3 women completed 3 CECs, 8 women completed 2 CECs, 12 women completed 1 CEC.
- No women experienced ovarian hyperstimulation syndrome, excessive bleeding, or infection.
- Donor reimbursement ranged from $560 to $4004 depending on expenses and steps completed
- Eggs collected ranged from 0 to 21, average 7.4 ± 3, total 274
- Program costs per completed cycle, $27,200; per egg, $3,673

INTAKE

Step 1 Initial inquiry. Prospective egg donors requesting information fill out a brief questionnaire outlining age, general health, number of children, current address and employment status.

Steps 2, 3 Information session. A detailed explanation of the science, the process, the risks and the time line for participation. Interested women participate in a follow-up review and explanation of the consent form. Prospective donors are informed they are personally responsible for scheduling each step of their Intake.

Steps 4, 5 The Minnesota Multiphasic Personality Index and the SCL-90. Scored multiple-choice tests measuring mental status and life stress.

Step 6 Personal History questionnaire. Six page questionnaire detailing ethnic background, medical and personal history.

Step 7 Psychological Interview. In depth nterview with a psychiatrist or PhD psychologist skilled in recruiting study subjects for biomedical research. Medical team meeting to determine if donor should proceed.

Steps 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 test counseling is provided.

Step 10 Gynecologic exam. Complete gyn examination including Pap smear. Medical team meeting to discuss all findings.

Step 11 Written assessment of understanding. Ten questions to assess basic understanding of research and the egg collection process, including risk factors.

Step 12 Interview with study monitor. pInterview with a knowledgeable individual not part of the medical or research team to ensure the donor understands the process, the risks and is not being coerced by anyone to participate.

Exclusion criteria at Intake: no children; severe depression, schizophrenia, psychoses; major personal conflicts, including relationship with research team or serious criminal record; infection; abnormal physical findings; evidence of inability to comprehend or comply with program steps, 3 or more prior cycles of egg collection.

CYCLE OF EGG COLLECTION

Step 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.

Steps 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 of serum estradiol is detected, hormone injections are stopped and her cycle is 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.

Step 5 Egg collection. Ultra-sound guided egg collection, standard for assisted reproduction, is performed by a medical team separate from the research team.

Cancellation criteria. Over-response to hormone injections, under-response to hormones (fewer than 3 eggs maturing), new medical findings, acute illness or donor anxiety.

EXIT

Steps 1 Recovery from egg collection. Donors are encouraged to limit activities the day following the egg collection. detailed

Step 2 Follow-up visit to the gynecologist. Two weeks following the egg collection, a repeat gyn exam with ultrasound measurement of the ovaries is performed to ensure donor recovery.

Steps 3,4 Exit questionnaire and exit interview with psychologist. Series of questions to assess donors level of discomfort, concerns about the process, recovery from the CE.

info@bedfordresearch.org