

Development and Investigation of a Free and Informed Choice Process for Embryo Donation to Stem Cell Research in Canada

Jeff Nisker, MD, PhD, FRCSC,¹ Angela White, MA,² Francis Tekpetey, PhD,¹

Valter Feyles, MD, PhD, FRCSC¹

¹Department of Obstetrics and Gynaecology, Schulich School of Medicine & Dentistry, University of Western Ontario, London ON

²CIHR Strategic Training Initiative in Research in Reproductive Health Sciences (STIRRHS), University of Western Ontario, London ON

Abstract

Objectives: To develop and investigate a consent process that satisfies the Assisted Human Reproduction (AHR) Act and the Canadian Institutes of Health Research (CIHR) Stem Cell Guidelines, furthers free and informed choice, and fosters embryo donation to human embryonic stem cell (hESC) research.

Methods: Consultations were undertaken with an hESC scientist, in vitro fertilization (IVF) team members, and the ethicist-author of the CIHR Guidelines to review the AHR Act, the CIHR Stem Cell Guidelines, the established consent process for embryo donation at University Hospital, London Health Sciences Centre, the characteristics of patients appropriate for contact, and strategies for sensitive recruitment. Invitation-to-participate packages were sent to patients.

Results: Patients deemed appropriate for contact had indicated their intent to donate embryos to research, had embryos that had been cryopreserved for more than five years, had not received donor gametes, and had publicly listed addresses, with no suggestion of separation of the parties. Strategies developed to promote anonymity, confidentiality, and informed choice included a "firewall" between clinical and research teams and documents reiterating that, if embryos were donated, the woman would have to undergo additional IVF treatment to have a child. Of 40 couples contacted, only 22 agreed to donate embryos to the hESC study. One couple no longer wished to donate embryos to research, one package was returned as undeliverable, and no response was received from 16 couples.

Conclusions: The consent requirements of the AHR Act and the CIHR Stem Cell Guidelines should be met. Consider delaying the request for final consent until a significant time after IVF treatment to ensure that patients no longer want their embryos for reproductive purposes and are free from perceptions of coercion. A consent process promoting free and informed choice, sensitive recruitment, and donation of embryos for hESC research should be developed by the Canadian professional bodies.

Résumé

Objectifs : Mettre au point et à l'étude un processus de consentement qui répond aux critères de la *Loi sur la procréation*

Key Words: Human embryonic stem cell, consent, ethics

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assistée (LPA) et des lignes directrices sur les cellules souches des Instituts de recherche en santé du Canada (IRSC), facilite l'obtention d'un consentement libre et éclairé, et favorise le don d'embryons aux fins de la recherche sur les cellules souches embryonnaires humaines (CSEh).

Méthodes : Des consultations ont été menées auprès d'un chercheur sur les CSEh, de membres d'une équipe de fécondation *in vitro* (FIV) et de l'éthicien-auteur des lignes directrices des IRSC afin d'étudier la LPA, les lignes directrices sur les cellules souches des IRSC, le processus établi de consentement au don d'embryons au *University Hospital du London Health Sciences Centre*, les caractéristiques des patientes avec lesquelles il s'avère approprié de communiquer, ainsi que les stratégies visant un recrutement à l'écoute des besoins. Des trousseaux de sollicitation à la participation ont été expédiés aux patientes.

Résultats : Les patientes avec lesquelles il semblait approprié de communiquer avaient indiqué leur intention de faire un don d'embryons aux fins de la recherche, comptaient des embryons qui étaient cryoconservés depuis plus de cinq ans, n'avaient pas bénéficié de gamètes de la part d'un donneur et comptaient des adresses publiques, sans indication d'une séparation des parties. Les stratégies élaborées pour promouvoir l'anonymat, la confidentialité et le choix éclairé comptaient un « coupe-feu » entre les équipes et les documents cliniques et de recherche réitérant que, lorsque des embryons faisaient l'objet d'un don, la patiente aurait à se soumettre à un autre traitement de FIV pour avoir un enfant. Des 40 couples approchés, seuls 22 ont consenti à donner des embryons aux fins de la recherche sur les CSEh. Un couple s'est rétracté après avoir changé d'avis quant au don d'embryons aux fins de la recherche; un envoi a dû être retourné puisqu'il s'avérait non distribuable; et 16 couples n'ont offert aucune réponse à notre demande.

Conclusions : Les critères quant au consentement que contiennent la LPA et les lignes directrices sur les cellules souches des IRSC devraient être respectés. Il faudrait envisager de repousser la demande d'un consentement final jusqu'à ce qu'un délai significatif se soit écoulé depuis le traitement de FIV, et ce, pour s'assurer que les patientes ne souhaitent plus avoir recours à leurs embryons à des fins de reproduction et qu'elles n'aient pas l'impression de faire l'objet de coercition. Un processus de consentement favorisant un choix libre et éclairé, un recrutement à l'écoute des besoins et le don d'embryons aux fins de la recherche sur les CSEh devrait être élaboré par les ordres professionnels du Canada.

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INTRODUCTION

Human embryonic stem cell (hESC) research has become an important focus for Canadians living with chronic illness and their families, and for clinicians, scientists, scholars, and policy makers.¹⁻⁵ However, there is a scarcity of embryos available for hESC research in Canada because of the prohibition in Canada's Assisted Human Reproduction (AHR) Act of creating human embryos for research purposes.⁶ In addition, there are relatively few cryopreserved embryos that are "eligible"³ for hESC research in Canada. The reasons for the limited number of cryopreserved embryos that could be used for research include the lack of public funding for in vitro fertilization (IVF) treatment^{7,8} and the lack of "project-specific consent to embryo research from the embryo providers at the time of research use" as mandated by the AHR Act and the CIHR Guidelines.³

The purpose of this study was to develop a process by which clinicians can offer patients the opportunity to donate embryos that are no longer required for reproductive purposes to hESC research in a manner that satisfies the requirements of the AHR Act⁶ and the CIHR Stem Cell Guidelines^{9,10} but also promotes free and informed choice and fosters hESC research in Canada.

METHODS

Consultation Process

A consultation process was undertaken with a stem cell scientist who had sought access to human embryos designated as "donated to research," with IVF clinicians (nurses, psychologists, social worker, physicians), with laboratory scientists working at University Hospital, London Health Sciences Centre, and with the ethicist who was an author of the Canadian Institutes of Health Research (CIHR) Pluripotent Stem Cell Guidelines.⁹ In addition, the established informed choice process for donation of embryos to research at University Hospital was explored in order to learn how couples with cryopreserved embryos at University Hospital were offered the option of donating for research embryos that remained after family completion. Discussion also focused on (1) the characteristics of patients that would suggest they were appropriate for participation in this study, (2) strategies to avoid harm (such as emotional distress) to patients from re-contacting them for this study, (3) methods of concealing the identity of patients from the research team, and (4) strategies to offer patients free and informed choice to consider donation of their embryos to the hESC study.

Process by Which Embryos Had Been Designated as "Donate to Research"

All patients who had been referred to University Hospital for consideration of IVF had received, prior to their first consultation, an information package that outlined potential courses of treatment and the associated physical and psychological risks. Although consent forms were included, the patients were asked not to sign these until after discussions with a nurse, counsellor (psychologist or social worker), and physician. At the time of embryo cryopreservation, patients gave written consent for embryos to be donated to research or to another couple or to be discarded when no longer required for their reproductive purposes; patients gave this consent with the understanding that they would be contacted again for their final decision and consent when they were sure they no longer required their embryos for reproductive purposes. It was indicated on the consent form that "it is not possible to provide couples with a detailed description" of the research for which they may be asked to donate embryos when re-contacted, as "different research projects might be ongoing" when the patients decide they no longer require their embryos for reproduction.

Examples of potential research projects were given, but stem cell research was not one of the research areas cited. From 1999 onwards, patients were mailed an annual invoice for \$120 for continued cryopreservation of their embryos, and this invoice was accompanied by a form asking patients to consider confirming or changing their last recorded intention regarding the disposition of their embryos.

Patients Determined Most Appropriate for Recruitment

The patients deemed to be most appropriate for participation in this study as a result of our discussions were those who (1) had initially indicated their intent to donate their embryos to research when no longer required for their reproductive purposes, (2) had embryos cryopreserved for more than five years without indicating that they intended to use them for reproductive purposes, (3) had not received donor gametes, and (4) had publicly listed addresses that corresponded to the addresses on file at the hospital, with no suggestion that the parties had separated. A list of such patients was compiled from laboratory and clinical files by the medical director and the IVF laboratory director.

RESULTS

Developing and Implementing the Informed Choice Process for the hESC Study

The invitation for patients to participate in this study included a cover letter from the medical director reminding patients of their options: to continue to store their embryos

for their future reproductive purposes, to donate their embryos to others, to discard them, or to donate them to a research project in the future. The letter assured patients that their relationship with clinical team members would not be affected by their choice. The medical director did not have a professional relationship with any of the patients being contacted.

A research envelope was prepared for later insertion into this package. The research envelope contained a letter from the hESC scientist, describing his study and reminding potential participants that if they chose to donate their embryos but later changed their minds about having a child through IVF, the woman would again have to undergo ovarian stimulation and oocyte retrieval. Potential participants were given contact information for the hESC researcher, the IVF medical director, and the research ethics board (REB) director. Consent forms to participate in the hESC study were also included.

The anonymity of the patients was protected by not affixing any identifying information on the invitation-to-participate packages until after the hESC scientist and research administrator had completed the tasks necessary for the preparation of the research envelope. Because of the possibility that patients may not have told family or friends that they had pursued IVF, the packages did not have the name of the hospital or the IVF program visible on the outside of the envelope.

Approval was sought from the Office of Research Ethics, University of Western Ontario. The director, however, deemed REB approval unnecessary, as all potential participants were patients whose embryos had been cryopreserved for more than five years, and thus had to be contacted in a non-research capacity to either confirm their intent to continue to cryopreserve their embryos or to designate their final disposition to research, to another couple, or to be discarded.

Couples' Responses to Being Mailed the Invitation-to-Participate Package

Of the 40 packages mailed, 23 were mailed back and one was returned as undeliverable (Figure). No response was received from 16 couples. The information letter indicated that both partners must sign the consent form if the couple chose to donate their embryos. All but one of the couples who responded chose to donate their embryos to hESC research; the couple who refused indicated that one partner was no longer willing to donate their embryos to any research endeavour. Twenty-two responses, including the negative response, were received within one month of the mailing, and one was received nine months later.

Transfer of Embryos to the Stem Cell Laboratory

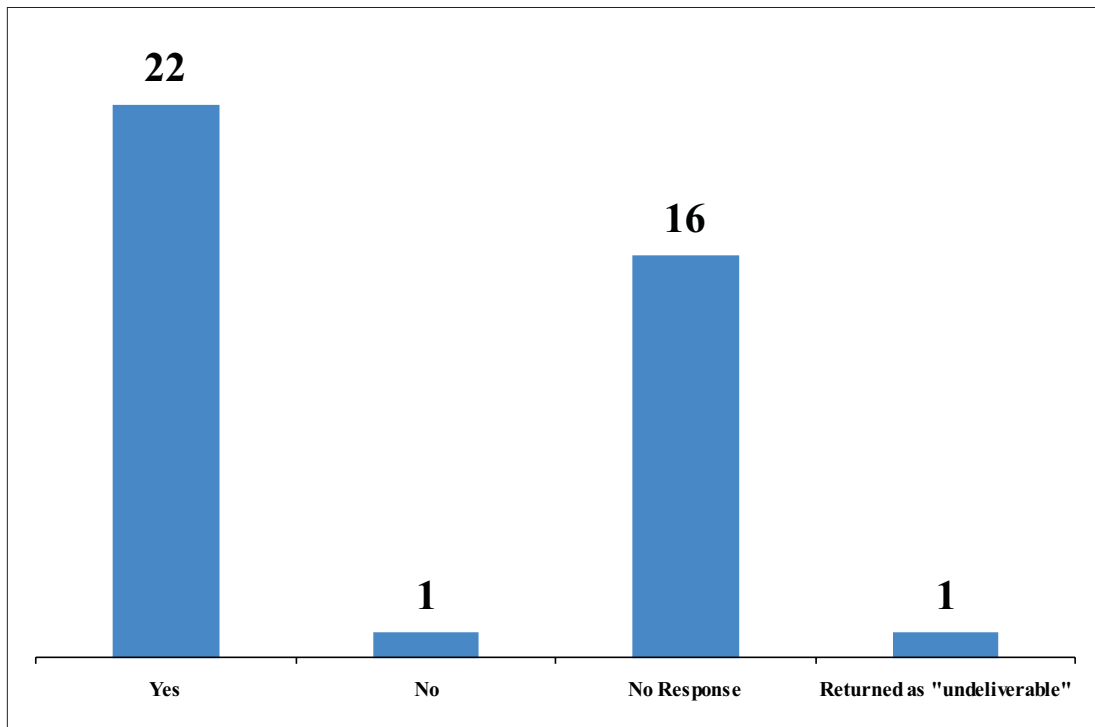
The clinical assistant recorded the patients' decisions opposite their names on the recruitment list, secured in the medical director's office. The medical director took a copy of each consent form to the IVF laboratory director, who generated an anonymous identification code for each donor, along with information on the number and quality of embryos that were donated. The codes were recorded in a secure binder. On the day of each hESC experiment, the 2 mm diameter cryopreservation straws containing the donated embryos were taken from the liquid nitrogen tank designated "donation to research" and transferred into a portable cryotank. This cryotank was carried by the hESC research assistant to the stem cell laboratory, where the straws were immediately thawed and the embryos removed. Patients' names had been placed on the straws at the time of embryo cryopreservation and could not be removed at the time of transfer to the stem cell laboratory without thawing. The hESC research assistant was instructed not to read the names on the straws, which was possible even though the print was tiny. The empty straws were returned to the IVF laboratory, and "embryo transfer to hESC research" was documented next to the code in the secure binder. The only information retained in the stem cell laboratory was the code number and quality of the embryos.

DISCUSSION

The observation that only 55% of embryos specifically designated "donation to research" were in fact donated to hESC research adds to previous concerns regarding the inadequate supply of cryopreserved embryos in Canada that are available for this important area of scientific inquiry.¹⁻⁵ The actual percentage of cryopreserved embryos in Canada donated to hESC research may be even lower in the future, as only patients considered "most appropriate" to consider participating in the hESC study were invited to participate in our research on the consent process.

This low rate of embryos designated "donation to research" that were donated to research might have been predicted; Robertson's 1995 hypothesis (that couples may be unwilling to donate their embryos¹¹ even when they are no longer required for reproductive purposes) has recently been confirmed.¹² McMahon et al. observed that women who had completed their families viewed each remaining embryo as a brother or sister of their existing children, making any donation unacceptable.¹³ Other psychological factors may also be relevant in patients' inability to decide to donate their embryos.^{13,14} For example, women who have not become pregnant but who no longer want to continue with any fertility treatment, including receiving their cryopreserved embryos, find it difficult to accept not having a child.¹⁴

Response to re-contact to consider donation of embryos to hESC research



The fact that more than five years had passed since the last embryo transfer may have freed patients from the perception that their physician wanted them to donate their embryos to hESC research.⁴ It has been noted that patients may believe their physician would not offer any option unless it has value, and thus they may feel compelled to choose it to please their physician.^{4,15,16} It is possible that the 40% of couples who did not reply to the invitation to participate found it inconvenient to respond. However, this is unlikely because the participants recruited were patients with a reliable history of communication with the IVF unit to reconfirm or change their “designation to research” status.

Sensitivity to the privacy, anonymity, and confidentiality of patients was identified as important in the interviews conducted for this study. Consequently, the invitation to participate was forwarded in an anonymous package, and an anonymity firewall was created between the clinical team and hESC researchers, preventing the research team from having access to personal information. However, the firewall could have been breached if the hESC research assistant had read the names on the cryopreservation straws. In future hESC studies, strategies to ensure patient anonymity and confidentiality must be included. For example, at the time of embryo cryopreservation, code numbers rather than

patient names could be written on the cryopreservation straws. However, the loss of code records would render the cryopreserved embryos inaccessible to patients for reproductive purposes, and thus, for this strategy to be reasonable, multiple copies of the codes must be securely stored in separate areas.

A preferable strategy would be to thaw the donated embryos in the clinical laboratory just before transfer to the hESC laboratory, although this strategy has two potential drawbacks: first, such late thawing is only possible when the clinical and research laboratories are in close proximity, and second, it could increase the chance of damage to the embryos during transfer. Future strategies must place the preservation of embryos for reproductive purposes, as well as patients’ privacy, anonymity, and confidentiality, ahead of the efficacy of the hESC study.

The AHR Act’s prohibition of creating human embryos for research purposes⁶ has been criticized for limiting hESC research in Canada and restricting Canada’s participation with South Korea, the United States, and the United Kingdom in the World Stem Cell Foundation.¹ However, this prohibition is supported by reports that many of the South Korean women who reportedly volunteered to provide oocytes after IVF treatment for hESC research had in

fact been coerced^{17,18} and by the fact that in the United States economically disadvantaged women, often university students, are the usual paid sources of embryos for hESC research.¹⁹ In addition, the fact that multiple hESC lines have been derived in Australia from cryopreserved embryos²⁰ suggests that cryopreserved embryos can be the sole source of embryos for large-scale hESC research. It must be noted, however, that in Australia, IVF is publicly funded for as many cycles as required for a woman to complete her family,^{21,22} unlike in Canada, where IVF is not part of the publicly funded health care system^{7,8} (except in Ontario for women with bilaterally blocked fallopian tubes). Thus, many more cryopreserved embryos are, and will be, available for hESC research in Australia after no longer being required for the patients' reproductive purposes. Indeed, hESC research in Canada is greatly disadvantaged because IVF remains outside the publicly funded health care system,^{7,8} which is unlike the situation in comparable countries.^{23–25}

The CIHR Pluripotent Stem Cell Guidelines^{9,10} indicate that the process of free and informed choice for donation of embryos to hESC research occurs both "...prior to the collection of gametes..." and "[a]t the time when the embryos are to be used for research...." However, our consultations and the response of the first 40 couples invited to donate cryopreserved embryos to hESC research suggest that a significant time interval, likely several years after the IVF treatment cycle, should pass before "the time when the embryos are to be used for research" and patients are re-contacted for final consent to donate their embryos (unless patients have independently indicated their wish to end embryo storage). This delay would allow patients *time* to be sure that they no longer want their embryos for reproductive purposes, and *distance* to be able to change their decision without the perception that donating their embryos to hESC research will please their physician.⁴ We recommend that processes to ensure free and informed choice for patients to donate embryos to hESC research should be developed by the Society of Obstetricians and Gynaecologists of Canada and the Canadian Fertility and Andrology Society.

CONCLUSIONS

An informed choice process for donating embryos that are no longer required for reproductive purposes to hESC research should begin prior to gamete retrieval. Preliminary intent should be declared at the time of cryopreservation, and final consent should not be considered until a significant time interval has passed since IVF treatment. All steps should be taken to decrease potential harms to patients as a result of re-contact for hESC research. Processes to ensure free and informed choice for patients to donate embryos to

hESC research should be developed by Canadian professional bodies.

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