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Egg harvesting for stem cell research: medical risks and ethical problems

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Abstract

Increasingly, researchers are seeking eggs from young women to be used for embryo cloning procedures. The harvesting of multiple eggs often involves the administration of drugs that have not been approved for this purpose. Also these drugs have not been adequately studied for their long-term effects on women despite research providing some evidence of significant harm to women in both the short and long term. Current practices follow a historical pattern of exposing women to risks that ultimately prove unacceptable. In addition, egg harvesting is taking place in a research climate marked by conflicts of interest, the misleading use of language to describe research goals, and a commercial push that may lead to the exploitation of young women. In this article, we outline these matters and explain how they are leading to an international campaign for a moratorium on egg harvesting for cloning purposes.

Keywords: *egg donation, egg harvesting, embryo cloning, health risks, ovarian hyperstimulation syndrome, women's health*

Introduction

Women's health and human rights advocates throughout the world are increasingly concerned that overzealous pursuit of new scientific discoveries may once again be threatening women's health. This time, young women are being asked to donate or sell their ova, not only for use in fertility clinics, but increasingly for non-clinical use in experimental cloning research. The harvesting of multiple eggs often involves the administration of hormonal drugs that have not been approved for this purpose. These drugs also have not been adequately studied for their long-term effects on women despite research providing some evidence of significant harm to women in both the short and long term. The collection of eggs for embryo cloning research is being conducted in the context of an international race for dominance in — and commercialization of — the production of embryonic stem cells and related products that may result in substantial private financial gain while offering no therapeutic benefits that are accessible to the vast majority. While much speculation about its ultimate clinical value and potential benefits is fuelling this embryo cloning research, the risks of egg harvesting, both short and long term, do not receive adequate attention. In this article, we focus on some of the major concerns: a research climate marked by conflicts of interest; the misleading use of language to describe research goals; and a commercial push that may lead to the exploitation of young women. These are leading to the formation of an international coalition of critics who seek to curb a trend to the use of women as sources of raw materials for research, experimentation, and product development related to stem cell research.

Egg harvesting and risks to women

Since the birth of the world's first 'test-tube baby,' Louise Brown, in 1978, egg-harvesting procedures have become increasingly widely used in IVF. This has

led to the assumption by many that egg collection practices have been proven to be safe. Unfortunately this is not the case. In North America, at least, most of these procedures have been conducted in private fertility clinics without independent oversight and, until recently, without systematic voluntary reporting even of serious side effects. The existing research is very limited and often retrospective (Pearson, 2006). Despite a serious absence of long-term independent assessments of the effects of egg harvesting on women's health, this research already reveals a multitude of problems resulting from these procedures. However, in spite of occasional calls for caution, such as an editorial in *Lancet* (9 August 2003) and warnings that exposing healthy women to these risks is 'morally and ethically unacceptable' (Ahuja *et al.*, 2003), little action is being taken to alert potential egg providers to the dangers of egg harvesting.

Short-term effects of ovarian stimulation

The harvesting of multiple eggs is an invasive and uncomfortable two-stage process requiring many clinic visits, multiple injections of hormones, and minor surgery at the least. Both stages, ovarian suppression and what is known as 'ovarian stimulation', require the use of powerful hormones and other drugs to manipulate a woman's body into producing many, often a dozen or more, eggs at a time rather than the normal one or two. The mature eggs are then collected surgically for use in IVF or in research.

The most immediate serious risk from ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). The American Society of Reproductive Medicine (ASRM) acknowledges that mild forms of OHSS occur in 10–20% of cycles (ASRM, 2005) and others have published similar estimates (Hugues, 2002). Symptoms of mild forms of OHSS include nausea, vomiting, diarrhoea, and abdominal distention. These symptoms may persist or worsen over time to include rapid weight gain, accumulation of serous fluid in the spaces between tissues and organs in the pleural and abdominal cavity, respiratory difficulty, and other abnormalities. More severe forms of OHSS requiring hospitalization are 'by no means rare' according to the ASRM (2003). Thromboembolism, renal failure, adult respiratory distress, and haemorrhage from ovarian rupture have all been reported, but the rates of occurrence vary widely. As of June 2005 five women in the UK were known to have died of OHSS (BBC News, 2005).

Long-term effects of ovarian stimulation

The absence of adequate follow-up means that the long-term risks of ovarian stimulation are poorly understood. As Suzanne Parisian (2005), former Chief Medical Officer of the United States Food and Drug Administration (FDA), explains, 'Pharmaceutical firms have not been required by either the government or physicians to collect safety data for IVF drugs regarding risk of cancer or other serious health conditions despite the drugs having been available in the United States for several decades.' One drug commonly used in the first phase of egg harvesting, Lupron (leuprolide acetate), has not been approved for this purpose, but rather is used 'off label.' Another drug, Antagon, has been approved for such use, but no data are available on its long-term safety. The US FDA currently has on file more than 6000 complaints regarding Lupron, including 25 reported deaths, but none of this has been investigated or analysed sufficiently to provide women contemplating egg donation the information necessary for making an informed choice (Lazar, 1999).

The few studies of long-term effects of ovarian stimulation have reached conflicting conclusions. Nevertheless, many clinical reports associate infertility treatment with ovarian cancer, and two major studies suggest a link between ovarian cancer and ovarian stimulation. Whittemore *et al.* (1992) analysed 12 US case-control studies and found nulligravid (never pregnant) women experienced a sharp increase in risk. Similarly, Rossing *et al.* (1994) estimated that the use of clomiphene, another drug that stimulates the ovaries, was associated with a 2.3-fold increased risk of ovarian tumours in their study of 3837 women evaluated for infertility in the late 1970s and early 1980s. More reassuring conclusions were provided in a meta-analysis by Ness *et al.* (2002), but as Brinton and colleagues (2005) point out, most of the included studies had relatively small numbers of subjects and/or short follow-ups. The latter is a

particularly serious limitation: 'Given that clomiphene was first approved for clinical use in 1967 and gonadotrophins in 1969, the women who first used these drugs during their late 20s and early 30s have only recently reached the age when hormonally related cancers are common.' Extending the length of follow-up to nearly 20 years has yielded evidence of a possible association between clomiphene use and uterine cancer (Althuis *et al.*, 2005). Brinton *et al.* (2005) also note that there has been little attention paid to effects of ovarian stimulation specifically on women who have used other hormones such as oral contraceptives and menopausal hormone therapy. They further caution that more recent assisted reproductive treatments often involve much higher exposures to gonadotrophins than previous procedures, and that 'most IVF protocols include luteal phase support for several weeks with supplemental progestogens. This raises further concern, since these agents have been linked to increases in breast cancer risk' (Brinton *et al.*, 2005). In light of these limits on and concerns with existing data, she and her colleagues conclude that 'it may be some time before epidemiological studies can amass the follow-up times required to fully address long-term effects.'

Risks to offspring

Beyond direct risks to the women undergoing ovarian stimulation, one must also consider possible effects of exposure to the drugs used on the offspring of treated women. Here, too, human data are sorely lacking. However, a recent report that ovarian stimulation treatment in mice results in several significant abnormalities in their offspring does provide reason for concern. These effects include growth retardation, a delay in ossification (bone development) and an eight-fold increase in a significant rib deformity (Steigenga *et al.*, 2006). Questions about the degree to which these findings have implications for the use of ovarian stimulation treatments in women should be answered before thousands of women are exposed to ovarian stimulation purely for research purposes. As the example of the hormone diethylstilbestrol (DES) described below illustrates, risks to offspring from exposure to hormones used in ovarian stimulation would not be the first instance of ill effects of hormones being carried into future generations (CDC, 2006; DES Action, 2006).

Cloning research changes risk–benefit calculus

The risks of egg harvesting, like those of any medical intervention, must always be weighed against potential benefits. A woman who undergoes ovarian stimulation in an attempt to become pregnant or to provide eggs for another woman faces virtually the same risks as one who is exposed solely to obtain her eggs for research. (The amount and manner in which the drugs are administered could change the degree of risk.) But the risk-benefit calculus is very different for each of these women. One has a 10–40% chance of producing a baby either for herself or another women, while the other is but a subject in a research project with still uncertain benefits. Calls for more systematic long-term follow-up are in the interest of women in both categories — as are demands that both categories be informed sufficiently to meet the consent criteria for clinical or research projects (ISSCR, 2006, for example).

Historical pattern of hormonal abuse of women

Given the multiple unknowns regarding the long-term consequences of ovarian stimulation, it is appropriate to place today's practices in historical context. The exposure of large numbers of women to heavy doses of exogenous hormones of unknown safety or effectiveness is not new. An early example dates from 1947 regarding widespread prescribing of DES to pregnant women to prevent miscarriage or premature birth. Even though DES was shown not to prevent miscarriage as early as 1953, its use continued for almost 20 years, until a landmark 1971 study documented the alarming occurrence of an often fatal form of vaginal cancer in the young daughters born to women who had been given DES. Five to ten million women worldwide were exposed to DES before its dangers were well understood. The full extent of the damage, which ironically includes infertility in female offspring and problems for many DES sons as well and which may be continuing into a third generation, may never be known (CDC, 2006; DES Action, 2006) although some longitudinal research into those who were exposed *in utero* and their offspring is ongoing.

More recently, hormone replacement therapy (HRT), after being vigorously marketed to menopausal women for decades, often advertised as a way of preventing future disease, was found to increase risks for a variety of serious health problems and to contribute little to preventing others. Two randomized clinical trials, one of oestrogen alone, and one of oestrogen plus progesterone, had to be stopped because of clear evidence of serious adverse effects (Writing Group for Women's Health Initiative, 2002; Women's Health Initiative Steering Committee, 2004). Certainly we must learn from experience with DES and HRT that early reassuring studies often prove wrong in the longer term, and that widespread exposure of healthy women to incompletely-assessed drug interventions can be dangerous. Policy makers have a particular obligation to protect non-patient 'donors' from the possible threat of irreversible harm by insisting that prevention takes precedence over everything else (Ahuja, 1999).

Beyond the embryo: concerns related to egg harvesting for research

Most opposition to embryonic stem cell research to date has been motivated primarily by concern with the moral status of the embryo. This emphasis has obscured a number of other important ethical issues raised by women's health advocates (Norsigian, 2005). Beyond the health concerns already discussed, the most immediate concerns include conflicts of interest pertaining to those promoting egg harvesting, the use of misleading and coercive language in promoting cloning research, and the exploitation of impoverished women both in the West and in less developed countries in the expanding global market for human eggs. Additional concerns about how focusing on embryo stem cells deflects resources from work to eliminate upstream causes of disease, and about the excessive costs (public and private) of these molecular approaches are serious and warrant attention, but are beyond the scope of this paper.

Conflicts of interest

An array of powerful social and economic pressures encourages researchers and research advocates to overlook or play down risks to egg providers (Sexton, 2005). For example, some physicians who harvest eggs are also involved in stem cell research. Seeking consent from women in these circumstances is problematic when clinicians have an interest in obtaining their eggs. This conflict exists whether or not the eggs are being extracted from a woman who is undergoing the procedures for the purpose of IVF, and threatens to violate the requirement in the Declaration of Geneva (1948) of the World Medical Association that physicians give '[T]he health of my patient …. first consideration.' It also contravenes the International Code of Medical Ethics (World Medical Association, 1949) that deems unethical any intervention that 'could weaken physical or mental resistance of a human being' unless used in her interest. When the clinician and researcher are the same person, as is often the case, women are left vulnerable to pressures to provide eggs — especially when payment of any kind is offered.

The recent cloning scandal involving Korean and American researchers illustrates how investigators' needs can distort, if not corrupt, standard ethical principles and underscores our concerns about risks to women from whom eggs are extracted solely for research. In February 2004, Korean scientist, Hwang Woo-suk claimed to have successfully derived stem cells from a human embryo made by inserting the nucleus of a somatic (body) cell from an adult into the enucleated (nucleus removed) egg cell from an unrelated female (Hwang, 2004). Had these reports been true, they would have constituted a major breakthrough in research cloning, also referred to as somatic cell nuclear transfer (SCNT). Initial reports indicated that Hwang's team required 242 human eggs to create one embryo. Then in 2005, he claimed to have generated '11 patient-specific stem-cell lines with a success rate of one line for approximately every 20 oocytes' (Hwang *et al.*, 2005). This seemed to suggest a significant reduction in the number of eggs required to create one clone, and fuelled much media attention to the possible 'cures' of a range of chronic diseases. However, the media reports — and the research — turned out to be far from the truth. Not only were the reported research results fraudulent, but Hwang used well over 2000 eggs without ever creating a viable human clonal embryo. Furthermore, it has been revealed that payment, coercion and lying were used to acquire the

eggs first reported to have been eagerly donated by participating women (Steinbrook, 2006).

The full extent of the damage to the health of the Korean women who provided the eggs used by Hwang remains unknown. Nonetheless, a coalition of 35 women's groups reportedly is suing the South Korean government on behalf of women who appear to have been harmed in the process of egg harvesting, and there are reports that about 20% of the donors have experienced side effects (Hwa-young, 2006).

Concerns about conflicts of interest are also raised by the fact that achievements — or supposed achievements — in embryonic stem cell research often bestow a kind of international stardom on those reporting them. This was evident in the international news coverage once given to Hwang Woo-suk. But they also arise from the fact that current patenting laws, particularly in the US, have made embryo stem cell research a virtual biotech gold rush.

Cloning technology is a particularly fertile field for the development of commercial patents — and grounds for patenting disputes such as that reported between Hwang and his US collaborator, Gerald Schatten, who have both filed applications based on the Korean effort (Bails, 2006; Hwa-young, 2006; Kim, 2006). But this is not an isolated case. To lure voters to approve California's 'Proposition 71,' an initiative to fund and make SCNT a right under the state constitution, proponents promised citizens a share of patent royalties. However, debate broke out soon after its passage over what share of the proceeds from patents, if any, to give the state (Reynolds and Darnovsky, 2006) and these debates continue today. The potential for financial profit from patents clouds not only the ability of clinician/researchers to get consent from women to extract eggs, but may also colour the decisions of institutional review boards reviewing protocols: members of these committees may indirectly profit when patents are shared with the universities at which they work.

Misleading language

Critiques of egg-harvesting procedures by women's health advocates and feminists have raised further concerns about how the apparently purposeful use of misleading language to describe this research has the potential to be coercive. Engaging with embryo stem cell research requires that laypersons understand complex scientific issues, but this task has been made unnecessarily difficult by the language often used by scientists trying to garner public support for cloning research and, in the US, votes for funding or for egg 'donation'.

Too often, for example, the focus is put on promises of imminent 'cures' for diseases, and help for one or more of the conditions many of our family members may already have and which most of us will one day develop, a stance that even a vocal advocate of stem cell research has characterized as bordering on 'over-promising at best and delusional fantasising at worst' (Tilghman, 2004).

Moreover, kept from the public discourse is the scientifically accurate term for the outcome or end result: a 'clone' or 'clonal embryo'. Instead, in promoting their research agendas, proponents of cloning research talk of somatic cell nuclear transfer (SCNT), a process. This practice tends to obscure the purpose of the process, which is to create a human embryo comprising cells that are genetically identical to those of an existing human being. Also left out of the discourse is the fact that embryo cloning is the 'gateway' technology to other non-therapeutic goals (Newman, 2003) fervently espoused by certain prominent individuals such as former Nobel laureate James Watson (Bhattacharya, 2003). These goals include the genetic modification of offspring to influence such traits as intelligence, height, and other characteriztics, and in ways that would inevitably affect future generations, for better or worse.

Although most who support research cloning condemn reproductive cloning — and thus endorse proposals to ban any implantation of a clonal embryo into a woman — many countries such as the United States do not yet have a universal ban on human reproductive cloning. This fact makes it possible for any

advances in this research to be applied to human reproductive cloning regardless of the intent of researchers.

Many discussions of this topic also tend to use the inaccurate term 'therapeutic' cloning — rather than 'research' cloning— and thus further cloud the reality of what is now possible. Many potential research participants, as well as the broader public, now wrongly believe that therapies are likely to result in the near future and thus see providing eggs as a way to help others.

The combination of ambiguous language, financial pressures to push the research, and promises of imminent 'cures' clearly shape the decision-making context of potential providers of eggs for research. However, it was not until after the Hwang debacle that mainstream bioethicists publicly acknowledged the coercive effects of misleading language on potential egg providers who are family members or friends of patients who hope eventually to benefit from stem cell research and who are thus more vulnerable than altruistic donors. As Magnus and Cho (2005) recently noted:

'[I]t is important not to use the term "therapy" when what is meant is "research" and not to refer to hESC [human embryo stem cell] research as "therapeutic cloning." There is currently no such thing as "therapeutic cloning" and this is not "therapeutic cloning research," nor can we say with any certainty that "cell therapy" is in the near future.'

They further state that use of such terminology 'increases the likelihood that there are individuals who have been or will be misled into exposing themselves to risk.' Certainly young women concerned about the serious health problems of loved ones are more likely to 'volunteer' to risk their own health by donating eggs to science in a social context that exaggerates the potential benefits of research cloning.

Exploitation of young women

The potential for exploitation of young women can be expected to rise with an increasing demand for human eggs created by embryonic stem cell (or cloning) research, thus complicating an already problematic situation. An international market for human eggs emerged in the early 1990s in response to the growth of the IVF industry, and this market has become the most competitive link in the supply chain of what Debora Spar (2006) refers to as 'the baby business'. The magnitude of the impact that research cloning will have on the demand for eggs is yet to be determined, but it is difficult to imagine it will be minor. Human embryo cloning has been described as 'a wildly inefficient process, often requiring hundreds of eggs to [merely attempt to] produce a single viable clone' (Dennis, 2006). Strictly for research alone, then, eggs will need to be harvested from many thousands of women. And, if embryonic stem cells were to prove useful in medical treatments, something not yet accomplished even with proof-of-principle laboratory research, countless more eggs would be needed for the many millions of people with conditions that the treatments will supposedly cure. As one leading pioneer in SCNT, Robert Lanza, of Advanced Cell Technology, recently told a *Nature* reporter, 'I can't conceive there will be enough eggs to use on a wide scale' (Dennis, 2006).

While some other jurisdictions reject all payment for eggs (e.g. Canada) it is not the case in the US where the fees that women are paid for eggs for IVF has been rising. This can be seen in the proliferation of advertisements in college newspapers recruiting egg 'donors.' Depending on the location and on features of the potential 'donor,' compensation may range from a low of US$3000 in some parts of the US to many times that. Advertisements employ the euphemism of 'donation', provide altruistic rationales, and usually define payment as reimbursement for time and expenses to make the exchange more palatable to all parties. As a result, young women who face large education-related debts can, and often do, undergo repeated rounds of ovarian stimulation to finance their schooling or other needs without giving adequate consideration to the potential long-term health consequences for themselves (Derek, 2004, Hempel, 2006). Female students attempting to cope with rising tuition costs by selling their eggs are not making autonomous choices (Papadimos and Papadimos, 2004). While there are strong pressures in the US and UK to

prohibit the selling of eggs for research purposes, including a ban on any reimbursement other than for out-of-pocket expenses (National Academy of Sciences, 2005, Jensen, 2006) it is not yet clear what strategies and loopholes will be found to circumvent these recommendations. One major possibility is that eggs will be purchased from countries where ethical standards are more lax. Heng (2005) reports that in many countries where the sale and purchase of human eggs is prohibited, medical professionals use free air tickets and hotel stays in lieu of monetary compensation to entice prospective egg providers.

The trade in human eggs already crosses national borders, and numerous examples demonstrate that this growing international trade is exploiting young women living in Eastern Europe and other countries. For example, impoverished, semi-literate young Romanian factory workers are reported to repeatedly sell their eggs for US $250 to make up for the absence of employment opportunities that provide a living wage. Finding themselves suffering from new and mysterious health problems, some of them have taken legal action complaining of inadequate informed consent, poor medical follow-up, and other violations of established medical standards (Magureanu, 2005, Sexton, 2005).

Eggs must be harvested by doctors, but egg collection for research purposes marks a transformation in the doctor–patient relationship, which has historically been based on the assumption that the doctor's primary goal and responsibility is to protect or restore the patient's health. When the doctor becomes the agent of a third party, in this case a researcher, and relates to the patient with the researcher's interests in mind, the doctor is violating the basic assumptions of the doctor–patient relationship. Abandonment of these traditional assumptions leaves the patient in a particularly vulnerable position. Physicians also deserve to be spared the distortions this creates in their relationship with their patients. It is the appropriate role of policy makers and physicians to see that patients, who often feel a need to please their health providers by being 'good patients' to get the best possible care, are not called upon to make decisions that are based on an oversimplified understanding of information on which even experts are not in full agreement. Such situations would be in violation of the traditional understandings of the role of medical expertise in the doctor–patient relationship.

When traditional assumptions about the physician–patient relationships are violated, as they can be when eggs are being taken to serve the interests of the physician or another third party, not a loved one, it is not surprising that some women will find the experience emotionally damaging. Yet, there has been very little exploration of the emotional impact of selling one's eggs. A small qualitative US study of 33 paid US 'donors' reported that at least seven 'felt that promises clinic staff made when they were trying to recruit the women were not kept once the women were engaged in the process'. These ranged from requests for a specific kind of anaesthesia or for a female physician to the promise of follow-up care. The authors report that many of the women described their care as cold and impersonal: They used metaphors such as 'farm animals', 'produce', 'meat', and 'prostitution' to describe how the experience made them feel (Kalfoglou and Gittelsohn, 2000). This suggests we need to examine the impact of egg harvesting on the emotional well being of egg providers and also the social fabric before expanding these practices.

Conclusion

Clearly there is cause to be concerned about the negative short and long-term effects of the expanding demand for human eggs on young women's health, and possibly for their offspring as well. Risks that may be justifiable for women seeking to become pregnant are not justifiable for the purposes of research. Encouraging young healthy women to risk damage to their own health by providing eggs for hypothetical treatments for others is not ethically or socially justifiable. Furthermore, it will inevitably be exploitative to take and use biological material from donors to generate products or processes for commercial use. This exploitation becomes even more extreme when these materials are patented, and the patents become barriers to treatments, possibly even to treatments needed by the original donors (Andrews, 2002).

Increasingly, questions about the push for women to provide more eggs for research are being asked. Recently, two prominent stem cell scientists and advocates for embryonic stem cell research admitted:

'SCNT ... plays only a minor role in the wider discipline of stem-cell biology — a branch of developmental biology that has no lack of other challenges to occupy its practitioners' time. The focus of most investigators will continue to be developing an understanding of important core issues concerning the molecular basis of stem-cell growth and differentiation, how a cell acquires its mature identity, and the therapeutic needs of potential target diseases' (Snyder and Loring, 2006).

Surely this gives us time to consider more seriously the welfare of the egg provider, to do the kind of serious research on long-term consequences of egg harvesting that is needed, and to establish appropriate enforceable international oversight and regulation before encouraging more young women to put themselves at risk.

Biotechnology may have great potential for advancing healing, but in the context of inadequate regulation and extreme social inequality, it threatens to convert the bodies of women into instruments for use by the more privileged. While supporters of egg harvesting for research have sometimes wrapped themselves in the mantle of women's autonomy, or right to choose how to employ their own bodies, such appeals seem disingenuous when considered in the context of uncertainties (to the women and experts alike) about health effects of the procedures and the speculative nature of any beneficial outcomes. Scepticism is appropriate after a quarter century of experience with other vaunted biotechnologies such as DES, HRT and gene therapy that have failed to fulfil their promises.

In light of the existing problems with egg harvesting and the intensification of these problems resulting from increased investments in cloning research, an international coalition of pro-choice and pro-life women's health and human rights advocates has united under the banner of 'Hands Off Our Ovaries' (2006). Maintaining a focus on women's health and social justice issues, and refusing the simplistic reduction of concerns in this area to debates over the moral status of the fetus, this coalition is calling for an international moratorium on egg harvesting for cloning research purposes, at least until we understand its human costs more fully. This moratorium is consistent with the United Nations Declaration on Human Cloning, which calls for prohibition of all forms of human cloning and especially calls upon member states to take measures to prevent the exploitation of women in the application of the life sciences.

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