

Egg Donation for IVF and Stem Cell Research: Time to Weigh the Risks to Women's Health

By Judy Norsigian

Last year, Barbara Seaman's article, "Is This Any Way to Have a Baby?" in *O (Oprah Magazine)* (February 2004) caused quite a stir among infertility experts as well as women dealing with infertility. It explored women's experiences with fertility drugs and underscored the paucity of long term safety data as well as the serious, occasionally irreversible problems experienced by some women using these drugs. In response, members of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) posted an unusual rebuttal at the ASRM website (www.asrm.org), and the controversies continue.

Because there is now significant debate about embryo stem cell research, and because one type of embryo stem cell research ("somatic cell nuclear transfer" or SCNT) requires women volunteers to undergo egg extraction to produce eggs for research purposes, there is renewed attention to the larger question of risks to women's health from egg extraction procedures. These procedures are the same whether performed for reproductive purposes – as is the case in an infertility clinic where women undergo "in vitro fertilization" (IVF) procedures – or performed for research purposes, as is now being proposed in a number of states pursuing embryo cloning as part of a larger plan to expand stem cell research.

What are the risks of multiple egg extraction? The drug most often used to shut down a woman's ovaries (before stimulating them with other drugs to produce multiple follicles) is Lupron™ (leuprolide acetate), which has caused a range of problems reported to the Food and Drug Administration (FDA), including rash, vasodilation (dilation of blood vessels causing a "hot flash"), paresthesia (sensation of burning), tingling, pruritis (itching), headache and migraine, dizziness, urticaria (hives), alopecia (hair loss), arthralgia (severe joint pain, not inflammatory in character), dyspnea (difficulty breathing), chest pain, nausea, depression, emotional instability, loss of libido (sex drive), amblyopia (dimness of vision), syncope (fainting), asthenia (weakness), asthenia gravis hypophyseogena (severe weakness due to loss of pituitary function), amnesia (disturbance in memory), hypertension (high arterial blood pressure), tachycardia (rapid beating of the heart), muscular pain, bone pain, nausea/vomiting, asthma, abdominal pain, insomnia, swelling of hands, general edema, chronic enlargement of the thyroid, liver function abnormality, vision abnormality, anxiety, myasthenia (muscle weakness), and vertigo. Although approved for several specific uses,¹ Lupron is NOT approved for use in procedures for multiple egg extraction – something not well understood by many women. (It is legal to use a drug for a non-approved use, as long as it is on the market for at least one *approved* use, and Lupron is just one of many drugs used "off-label" in this fashion. But proper studies justifying this use for egg extraction have never been formally submitted to the FDA).

The drugs used to "hyperstimulate" the ovaries also have negative effects, most notably a condition called Ovarian Hyperstimulation Syndrome (OHSS). Serious cases of this syndrome involve the development of many cysts and enlargement of the ovaries, along with massive fluid build-up in the body. As noted in an article about OHSS, "the reported prevalence of the severe form of OHSS is small, ranging from .5 to 5%. Nevertheless, as this

is an iatrogenic complication of a non-vital treatment with a potentially fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility.”² Also, as noted by Dr. Suzanne Parisian, a former Chief Medical Officer at the FDA: “OHSS carries an increased risk of clotting disorders, kidney damage, and ovarian twisting. Ovarian stimulation in general has been associated with serious life threatening pulmonary conditions in FDA trials including thromboembolic events, pulmonary embolism, pulmonary infarction, cerebral vascular accident (stroke) and arterial occlusion with loss of a limb and death.”³

So why is multiple egg extraction the norm in IVF clinics? With such risks involved, why don’t specialists just try to extract the single egg that women normally release each month? If only one egg is “harvested” using so-called “natural” cycling, there is a good possibility that it will not be successfully fertilized, or if fertilized, it may not develop into an embryo that could be successfully implanted into a woman’s uterus, thus requiring repeated surgical procedures to extract more eggs. Extracting multiple eggs obviously increases the likelihood of success with each IVF procedure.

The same reasoning can be applied to the research context, as it would be better to have more eggs with which to conduct research rather than fewer eggs. But given the early stages of embryo stem cell research, with only very hypothetical benefits at hand, it may be far wiser to protect women from the risks of multiple egg extraction solely for SCNT research purposes and to permit only surgical extraction of the usually single egg produced each month. Others argue that whatever the risks are – known and unknown – a woman should have the choice nonetheless to take these risks, especially if she has a strong personal investment in seeing certain therapies developed, even if they are only a distant promise.

Those who oversee the ethical conduct of research, especially members of Institutional Review Boards (IRBs), are supposed to think carefully about the matter of “risk/benefit” ratio when making decisions about whether to approve a research protocol. Embryo cloning research (SCNT) poses significant challenges in this regard. One IRB for Advanced Cell Technology in Massachusetts did approve a protocol for somatic cell nuclear transfer several years ago and included in the informed consent document the following language: “Severe lung and blood clot events have resulted in death.”⁴ They clearly decided that it was ethical to ask women to take such a risk, though others might argue just the opposite.

Reading the stories of young women who agreed to be multiple egg donors for IVF clinics and ended up with tragic consequences should give us all reason to think carefully about whether these risks are justifiable in the research context. Many advocates believe that such risk-taking would not be ethical, partly because true informed consent is not possible in the absence of better data regarding Lupron in particular.⁵

One of the more serious issues needing far greater attention is the absence of any good quality long term safety data on the infertility drugs commonly used. There are hundreds if not thousands of anecdotal reports, where complications were NOT short-lived. As noted in a three-part series in the Boston Herald:

“Seven of the women interviewed for this story say they suffered memory loss and bone aches while on Lupron, and that the problems continue years after stopping the

drug. Some say seizures and serious vision problems that started while on Lupron also haven't gone away.

One woman, Linda Abend in southern New Jersey, started a National Lupron Victims Network after her 34-year-old sister was hospitalized with seizures while taking Lupron in 1991 for a benign fibroid. Abend says her sister continues to suffer daily seizures, plus debilitating bone and muscle pain eight years later. And Abend said she has heard from more than 1,000 people nationwide - mostly women - who also report serious side effects that continue after stopping Lupron.

The FDA says it has not tracked claims of such long-term effects....”⁶

In a report submitted by TAP Pharmaceuticals to the FDA in April 1998, researchers wrote that they were “concerned” because more than one-third of the women they studied who took Lupron did not “demonstrate either partial reversibility” or “a trend toward return” of bone mass in the six months after they stopped taking the drug. Further, the researchers noted some women lost as much as 7.3 percent of their bone density during treatment - more than twice the amount the drug's packaging lists in its warnings. The researchers concluded, “A more complete assessment of the effects of Lupron on (bone density) can only be made with longer term follow-up of these patients.”⁷

Some women's health advocates argue that it is premature to conduct SCNT, especially when it involves multiple egg extraction, because the substantial risks involved are not offset by any clear benefit. In the case of IVF, the best infertility clinics can now offer 30-40% success rates, so that women undergoing multiple egg extraction – whether to achieve a pregnancy themselves, or to be an egg donor for another woman – do know that there is a clear potential benefit, and one that is of inestimable value: a baby.

The risk/benefit ratio is vastly different in the case of SCNT, where the possible benefits of such research are quite hypothetical at this stage. It is far from clear that SCNT will lead to any viable therapies, and much of what we need to learn in this realm of research can result from studying embryo stem cells derived from “conventional” embryos that would otherwise be discarded by couples who are no longer pursuing IVF at an infertility clinic. (Thousands of such embryos are now available for embryo stem cell research being conducted around the country.) It is conceivable that, over time, when embryo stem cell research has demonstrated that viable therapies are possible, a stronger case can be made for pursuing SCNT. (SCNT theoretically will make it possible to develop therapies that will be immuno-compatible, thus avoiding the problem of tissue rejection, which is more likely to occur with stem cell therapies that have a different genetic make-up.)

Although SCNT does provide an opportunity to study the progression of certain rarer diseases, some of this research can be done with embryos that were rejected during the process of preimplantation genetic diagnosis (PGD). Again, these are embryos that will not be used for reproduction purposes, because problems were detected, and thus would likely be discarded if not used for research.

Some women's health advocates urge that multiple egg extraction for research cloning purposes not be pursued at this time, and that any eggs for such research be obtained only via "natural cycling" – where a woman would not use fertility drugs but simply have the (typically) one follicle per month that she releases surgically collected. Given that South Korean researchers had to extract 242 eggs from 16 women to create one clonal embryo from which they developed a line of embryo stem cells to study further, there will certainly be pressures to accelerate the collection of eggs through more widespread use of multiple egg extraction procedures. Ads for egg donors are already commonplace on many college campuses, where young women are motivated to undergo egg extraction for much-needed income (\$4-7,000 in most cases) as well as for altruistic reasons. Both of these motivations could influence thousands more young women and economically disadvantaged women to undergo risky egg extraction procedures solely for research, and under circumstances where the benefits are far less clear and mostly still hypothetical. This will be another arena where we will see the mantra of "reproductive choice" once again co-opted and falsely applied.

Given that there may be new techniques developed soon that would obviate the need for multiple egg extraction, there is even more justification for a cautious approach. As noted in the *New York Times*, a technique called "in vitro maturation," or I.V.M., may make it possible to obtain multiple eggs without using hormone injections. "Doctors have found that a few days before ovulation, as many as 30 to 50 egg follicles have begun to mature. Normally, only one will fully ripen for ovulation, and the rest are lost. But if the eggs are removed before ovulation, many of them can be matured in the laboratory."⁸

The push for SCNT (also called research cloning or "therapeutic" cloning) will be strong in the coming years. Because the most vocal critics of this research are from the anti-abortion community, many pro-choice advocates are reluctant to get involved with this debate for fear of lending support to a larger anti-choice agenda. Although there are those who have deliberately confused this issue, sometimes conflating embryo cloning research with ALL embryo stem cell research, it is important to keep the two separate and to insist that health concerns for women don't take a back seat.

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¹ For example, the treatment of endometriosis and fibroid-associated anemia.

² Delvigne, Annick and Rozenberg, Serge. "Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review" *Human Reproduction Update*, vol. 8, no. 6, 2002, pp 559-577.

³ From Dr. Parisian's February 2005 memo now posted at www.ourbodiesourselves.org

⁴ Other language from this document, titled “Consent to Participate in a Study Involving Egg Donation for Stem Cell Research”: Complications associated with being an egg donor include unpredictable response to the hormones provided to you, surgical complications during the egg collection, and unknown long-term side effects from the hormones. If any of these complications arise the reproductive biologists involved in this research may choose, at their discretion, to terminate your continued participation in this research.

1. Risks and side effects associated with hormones (gonadotropins, hCG and GnRH agonists).

The gonadotropins will be used in order to stimulate your ovaries. Adverse reactions reported in women treated with gonadotropins include ovarian hyperstimulation. This is a condition in which the ovaries continue to enlarge even after the eggs have been collected. In addition to enlarged ovaries, fluid begins to be retained in the abdomen and becomes very difficult to control, resulting in fluid imbalance. Rare, but serious, consequences of this imbalance include lung and circulation problems such as collapse of a lung, acute respiratory distress syndrome, blood clot which may lead to inflammation of the veins, obstruction of blood vessels in the lungs, damage to the lung tissues, stroke, obstruction of an artery resulting in the loss of limb(s); blood in the abdominal cavity; kidney damage; large ovaries; increased heart rate; shortness of breath; rapid breathing; flu-like symptoms of fever, chills, musculoskeletal aches, joint pain, nausea, headache and tiredness; breast tenderness; and skin reactions such as dry skin, blood rash, hair loss and hives. Severe lung and blood clot events have resulted in death.

The following adverse reactions have been reported in patients receiving human chorionic gonadotropin therapy: headache, irritability, restlessness, depression, fatigue, edema, and pain at the injection site.

Adverse reactions regarding GnRH agonists include anemia; changes in various heart problems; high blood pressure; fluid accumulation in the limbs; formation of blood clots which potentially could be dislodged from the involved vein or artery causing damage to vital organs such as lungs, heart or brain; intestinal problems such as decreased appetite, constipation; nausea and vomiting, diarrhea, difficulty in swallowing; intestinal bleeding, intestinal ulcers and polyps; thyroid enlargement; breast tenderness; hot flashes; bone, muscle and joint pain; anxiety; depression; blurred vision; mood swings; nervousness; numbness; taste changes; memory problems; lightheadedness; blackouts; and headaches.

⁵ See “Risks to women in embryo cloning,” op ed by Judy Norsigian, February 25, 2005, *Boston Globe*.

⁶ Lazar, Kay “Wonder drug for men alleged to cause harm in women” *Boston Herald*, August 22, 23, 24, 1999.

⁷ Ibid.

⁸ Duenwald, Mary “After 25 Years, New Ideas in the Prenatal Test Tube,” *New York Times*, July 15, 2003.