Low utilization of extra embryos in donor oocyte in vitro fertilization cycles: an ethical dilemma to donor management

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Abstract

Purpose To explore outcomes of donor In Vitro Fertilization (IVF) cycles with regards to cryopreservation and utilization of extra embryos after fresh transfer.

Methods A database search was performed to identify all consecutive fresh donor oocyte cycles from January 1, 2000 to December 31, 2010 at a private fertility laboratory. Parameters analyzed included: number of oocytes retrieved, number of patients choosing embryo cryopreservation, number of patients returning for frozen embryo transfer (FET), and pregnancy outcomes.

Results A total of 1070 fresh oocyte donor cycles were identified. Average number of oocytes retrieved was 16.9 ± 7.9 , and average number of embryos transferred was 2.3 ± 0.96 . Sixty-six percent of patients cryopreserved excess embryos following fresh transfer, and only 40 % of these patients ultimately returned for FET. Patients who conceived in their fresh cycle were much less likely to return for FET than those who did not (25 % v 65 %, $p < 0.001$), however chance of conceiving with FET was no different between these two groups (38 % v 38 %, NS).

Conclusions An unexpectedly low number of patients undergoing a donor oocyte IVF cycle will ultimately return to utilize

extra embryos from their fresh cycle. This is concerning considering the high numbers of oocytes retrieved and the known complications from hyperstimulation, especially in light of the relatively high pregnancy rates associated with donor cycles. This raises concerns not only for donor management, but also raises ethical dilemmas when considering the large numbers of remaining embryos that will never be utilized.

Keywords Embryo donation · Embryo utilization · Cryopreservation · Embryo surplus

Introduction

The advent of in vitro fertilization (IVF) procedures using donor oocytes has allowed fertility options for many women who previously would have not been able to achieve a pregnancy. This includes women with diminished ovarian function due to advanced age or premature ovarian failure, women who have undergone and survived cancer treatment, women with congenital gonadal dysgenesis, and those who have lost ovaries due to surgical procedures or trauma. Additionally, the option of embryo cryopreservation has allowed for additional transfer attempts if the first is unsuccessful, and for the option of sibling children without the expense of an additional fresh oocyte donation cycle. Donor oocyte cycles have now become quite common, and of the 154,412 ART cycles performed in the United States in 2011, donor oocytes were utilized in 15,973 procedures (SART 20011). With the expense and complexity that comes with orchestrating an oocyte donation cycle, it seems desirable for recipient patients to have a surplus of embryos created and stored for “back-up”. Luckily, oocyte donors tend to be young healthy women who have excellent ovarian reserve and oocyte quality. Unfortunately, this also may place donors at higher risk for certain complications associated with IVF, such as ovarian hyperstimulation syndrome (OHSS) and numerous other risk factors [1]. This

Capsule Few patients undergoing donor oocyte IVF ultimately return to utilize their excess embryos causing concern for aggressive donor stimulation considering large numbers of unused embryos.

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brings up several ethical issues related not only to the donor's wellbeing, but also when discussing the fate of a surplus of unused embryos. The aim of the current study is to explore outcomes of donor oocyte IVF cycles with regard to the number of embryos created, cryopreservation of surplus embryos, and overall utilization of extra embryos after fresh transfer.

Materials and methods

A database search was performed to identify all consecutive fresh donor oocyte cycles performed from January 1, 2000 to December 31, 2010 at a private fertility laboratory. The data was examined for fresh cycle outcomes and also for the use of embryos in subsequent frozen embryo cycles. All patient information was stored in a de-identified database.

Patients

Recipient patients ranged in age from 24 to 60 with an average age of 43. The most common reasons for patients choosing to use an egg donor were ovarian failure or insufficiency, and repeated failures of fertility treatments with their own eggs. Endometrial preparation and luteal support were provided based on the preference of the patient's attending physician. Since our laboratory serves many different fertility practice groups, recipient and donor protocols are not standardized.

Oocyte donors ranged in age from 18 to 44 with a mean age of 28.5. The high upper age limit in this group represents donors known to the recipient who are clearly not the typical or ideal oocyte donor. All donors were screened per the specific donor agency representing them, as well as by the

fertility physician providing treatment. Some donors donated more than once, and the maximum number of donation cycles by any one donor was 4. Again, donor stimulations were at the discretion of the treating fertility clinic and were not standardized. Following oocyte aspiration, donor oocytes were inseminated with donor sperm or the recipient's partner's sperm approximately 39 h post-HCG. Natural insemination or intracytoplasmic sperm injection was performed based on sperm parameters and at the discretion of the treating physician. Embryos were examined the next day to assess for fertilization, and were transferred to the recipient on day 3 (39 %) or at the blastocyst stage (61 %) depending on morphologic characteristics. No oocyte cycles were split between recipients, and any surplus embryos or oocytes were designated to the original recipient.

Embryo cryopreservation and thawing

Viable blastocysts in excess of those transferred to the intended parent were cryopreserved. From January 1st 2000 until February 28th 2010, the "slow freezing" method was used as previously described in Gardner et al. [2]. The freezing solutions were 5 % glycerol and 0.1 M sucrose incubated for 10 min at room temperature, followed by 10 % glycerol and 0.2 M sucrose incubated at room temperature for 7 min. Both solutions were prepared in a base medium of HEPES buffered HTF (Irvine Scientific) and supplemented with 2.5 mg/ml recombinant human albumin. All blastocysts were then loaded into Nunc Cryovials (Nunc). In group I, blastocysts were placed into a Planer KRYO 10.1 programmable freezer, cooled from 20 °C at 2 °C/min to −6 °C, seeded and held for 10 min, followed by cooling at 0.3 °C/min to −35 °C and being plunged into liquid nitrogen [2].

Fig. 1 Outcomes of fresh donor IVF cycles with regards to cryopreservation and subsequent FET

Table 1 Utilization of surplus embryos: a comparison between women who conceived with their fresh cycle and those who did not

	Conceived in fresh cycle	Did not conceive in fresh cycle	P Value
Patients with cryopreserved embryos	73 % (445/609) cycles	56 % (239/426) cycles	<0.001
Patients who returned for FET	25 % (99/403) women	65 % (140/215) women	<0.001
Patients who conceived with FET	38.7 % (65/168)	38.7 % (92/238)	> 0.99

From March 1st 2010 onwards, vitrification was used to cryopreserve excess blastocysts. The Cryotop® method for vitrification was used as described elsewhere by Kuwayama et al. Embryos were equilibrated in equilibration solution (7.5 % ethylene glycol [EG]+7.5 % dimethylsulfoxide [DMSO] in TCM199 medium + 20 % synthetic serum substitute [SSS]) for 5 min at room temperature. They were then placed into vitrification solution (VS; 15 % EG+15 % DMSO+0.5 M sucrose). After less than 1 min in VS, the embryos were placed on the Cryotop® strip and plunged into liquid nitrogen immediately. Tools and solutions required for vitrification were obtained from Kitazato (Kitazato BioPharma Co.) [3].

Statistical methods

Pregnancy was defined as a documented clinical pregnancy determined and reported by each patient's primary fertility office. The p values for comparing mean age were computed using t tests. P values for comparing independent proportions on the level of patients were computed using Fisher's exact test. P values for comparing proportions/rates on the level of patient-cycles were computed using methods for incidence or prevalence rates based on the marginal Poisson or beta-binomial distributions. Computations were carried out using SAS 9.3 (SAS Inc, Cary NC) and StatXact 8 (Cytel Inc, Cambridge MA).

Results

We identified a total of 1070 fresh oocyte donor cycles between January 1, 2000 and December 31, 2010. The average number of oocytes retrieved per donor cycle was 16.9 (SD 7.9) and the average number of embryos transferred per fresh cycle was 2.3 (SD 0.96). Six hundred and nine patients (56.9 %) conceived with their fresh cycle, 426 patients (39.8 %) did not conceive, and 35 patients (3.3 %) had no pregnancy data available (Fig. 1). Of the original fresh cycles, 708 (66.2 %) resulted in cryopreservation of surplus embryos following the fresh transfer. This included 638 total women, as some women underwent multiple fresh donor cycles. Of these 638 women, 60 % (382) never returned to utilize their cryopreserved embryos for a subsequent frozen embryo transfer (FET). Forty percent of

women (256) returned for a subsequent FET in a total of 475-cycles, 19 % returning more than once.

Of patients who conceived with their fresh cycle, significantly more patients had embryos to cryopreserve than those who did not conceive with their fresh cycle (73 % v 56 %). Of patients who conceived in their fresh cycle, only 25 % returned to utilize their surplus frozen embryos. This was significantly different than patients who did not conceive with their fresh cycle, in which 65 % returned for a subsequent FET. Interestingly, patients who conceived in their fresh cycle and underwent an FET, were no more likely to conceive with their FET than those patients who did not conceive in their fresh cycle and underwent FET (Table 1).

When comparing characteristics of patients who chose to return for an FET with those who did not, patients who returned to utilize their surplus embryos were significantly less likely to have conceived with a fresh transfer than those who did not return, however age between these two groups was similar (Table 2).

Discussion

Because IVF procedures are not without risk, oocyte donation becomes a relatively complex ethical area in the ART arena. Young women are being put at risk for complications such as bleeding, infection, ovarian torsion, and OHSS for procedures that give them no benefit to their own health. The American Society for Reproductive Medicine has published practice guidelines that describe possible risks to oocyte donors, quoting a 1 % rate of OHSS [4]. Other studies have examined both serious and minor complications experienced by oocyte donors and have found a slightly lower rate of

Table 2 In patients with cryopreserved embryos, a comparison between patients who returned for FET and those who did not

	Returned for FET (n=256)	Did not return for FET (n=382)	p value
Mean Age (SD)	42.9 (5.1)	43.1 (4.7)	0.5384
Conceived with fresh cycle	41 % (99/239*) women	80 % (304/379*) women	<0.001

* 17 of 256 returned and 3 of 382 not returned had unknown conception status

serious complications of 0.7 %. However, 8.5 % of women in this study experienced minor complications that although not classified as severe, were severe enough to prompt them to seek medical attention [1].

Other than the risks to donors, oocyte donation cycles raise ethical concerns regarding disposition of the numerous surplus embryos created from these cycles. Many studies have explored the ethical issues behind the disposition of embryos in general, and options usually include: donation to research, donation to a known or unknown couple, or destruction of embryos [5–7]. This can be specifically pertinent to donor cycles since oocyte donors tend to be fertile women who make relatively large numbers of oocytes resulting in large numbers of surplus embryos. Lazendorf et al. [8] reviewed 149 patients' decisions regarding disposition of their embryos and found that 59 % donated to research, 38 % were discarded and 3 % were donated to a known or anonymous couple for fertility treatment.

In the current study, the average number of oocytes retrieved per cycle was almost 17, with only 2 embryos transferred on average. Remaining viable embryos were cryopreserved in 66 % of cycles. Overall, only 60 % of these patients ever returned to use their frozen embryos in a frozen cycle. More patients that conceived in their fresh cycle had embryos cryopreserved than those that didn't conceive, however only 25 % of these patients ever returned to use their frozen embryos. Surprisingly, of the patients that didn't conceive with their fresh cycle and had frozen embryos, only 65 % of this group returned for an FET. Unfortunately, we were unable to evaluate return rates based on delivery of multiple versus singleton pregnancies since this data was not available for the majority of our patients. Although this is a limitation of the study, we do not feel that it takes away from the overall message of low embryo utilization. Based on this information, it seems that oocyte donors may be undertaking risks associated with hyperstimulation in order to acquire oocytes that may never

be utilized. Consideration should be given to lowering the amount of gonadotropins used for stimulation in order to decrease risks to donors. Additionally, with so many unused embryos, patients are forced to make difficult decisions regarding embryo disposition and many embryos are ultimately wasted. Such ethical dilemmas may give support to alternative methods of obtaining donor oocytes such as oocyte banks. For now, it is prudent for physicians to recognize not only the risks for oocyte donors, but also the ultimate utilization of embryos that results from such cycles.

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