A shared egg donor program: which is the minimum number of oocytes to be allocated?

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Abstract

Purpose To evaluate which is the minimum number of oocytes to be allocated to each recipient in a shared egg donor program.

Methods We analyzed 953 recipients that received at least 4 metaphase II (MII) oocytes in the period 2006–2008. We retrospectively divided the recipients according to the number of MII oocytes actually received.

Results No statistically significant differences were found among the analyzed strata in clinical pregnancy rate (A:43.7%; B:45.6%; C:48.6%; D:45.5%; E:53%, $P=NS$) and miscarriage rate. However, the rate of top quality transferred embryos, and the embryo freezing rate were significantly higher among those recipients that received 7 or more mature eggs.

Conclusions After a large sample was analyzed, no significant differences in fresh embryo transfer outcome were encountered when a different number of oocytes was allocated. A minimum of 4 MII oocytes seems to achieve satisfactory pregnancy rates in our shared egg donor program.

Keywords Oocyte donation · Shared · Reproductive outcomes · Egg donor program · Low costs

Capsule Allocating a minimum of 4 MII oocytes seems to achieve satisfactory pregnancy rates in shared egg donation cycles.

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Introduction

In the early eighties the first experiences with oocyte donation took place in women without ovaries or ovarian function [1–3]. Initially, egg donation was used to treat young women with premature ovarian failure or with surgically inaccessible ovaries. Nowadays, the practice of oocyte donation has become more prevalent as more women delay childbearing, increasing the number of infertile patients with diminished ovarian reserve, multiple IVF failures, and advanced maternal age.

In 2007, the Latin American Registry of Assisted Reproduction reported 4,697 embryo transfers from cycles in which donor eggs were used; moreover, assisted reproductive techniques results from treatments initiated in Europe during 2005 reported 11,475 cases of oocyte donor cycles, and SART reported, in the United States, 9,575 fresh embryo transfers performed with donated oocytes in 2007 [4–6]. The growing demand for this kind of treatment finds a limitation on the number of available donors, leading to long waiting lists among recipients. This relative shortage of oocyte donors impacts on the cost of egg donation which has been progressively increasing during the last decade. In order to decrease costs and waiting time, some oocyte donor programs started sharing the donor oocytes allocating the oocytes from one donor to more than one recipient [7–9].

Historically, shared egg donor programs involved patients undergoing IVF willing to donate some of their oocytes to a recipient in exchange for reduced treatment costs [9, 10]. Most patients undergoing IVF prefer to use all of their harvested oocytes to increase the likelihood of having good quality embryos for transfer and to increase their chances of cryopreserving embryos for future use. This is especially important if we consider that only around

5% of the retrieved oocytes are considered capable of achieving a live birth [11, 12].

There are two different kinds of shared egg donor programs, based on whether a patient shares part of her cohort with a recipient, or whether a volunteer egg donor shares all her oocytes with more than one recipient. The shared oocyte donor program's main goals are decreasing the waiting period and financial costs to recipients in a cost-effective manner. Decreasing waiting period and financial cost have already been demonstrated in previous studies that analyzed these issues, our group have published that sharing the donor oocyte cohort among several recipients offers acceptable results in comparison to exclusive allocation to one recipient, but significantly decreases costs and waiting time [7].

Although there is a significant body of data showing that no significant differences exist between shared and non-shared egg donor programs, little information exists about the best manner to allocate the donated oocytes. This issue was the focus of several publications on egg sharing policies, and none of them showed that receiving more oocytes led to better reproductive outcomes [13, 14]. Most allocation policies vary from a minimum of 4 oocytes to larger number such as 8 or 10 oocytes to each recipient. Obviously, this decision is very important in terms of cost-effectiveness, therefore the objective of our study was to analyze if reproductive outcomes vary according to the number of oocytes allocated in a shared egg donor program.

Materials and methods

Patients

In 2006–2008, 953 women received oocytes in our shared egg donor program (range 31–49 years old). Our oocyte-donation program is based on sharing fresh donor oocytes from one volunteer donor among several recipients, on the basis of the number of metaphase II (MII) oocytes retrieved at aspiration. Therefore, mature oocytes from one donor were always shared by 2 or more recipients. We allocate a minimum of 4 metaphase II (MII) oocytes to each recipient, unless by chance, fewer than expected matching recipients are available at that time, in which case each of the recipients gets a higher number of MII oocytes. The final number is determined by the number of MII oocytes retrieved from the donor and the number of available matched recipients with their endometrium already prepared and ready for transfer.

All of our voluntary oocyte donors are between 21 and 34 years old, are normal ovulators, and are screened according to the American Society for Reproductive Medicine guidelines [15].

Donors were stimulated with a luteal-phase GnRH-agonists and after ovarian suppression was accomplished, daily recombinant gonadotropins (recombinant FSH, Puregon, Schering Plough, Buenos Aires Argentina) was started with doses between 150 IU/day and 300 IU/day based on their antral follicle count. Once the leading follicles reached 18–20 mm in diameter, urinary hCG (Pregnyl, 10,000 IU SC; Schering Plough, Buenos Aires, Argentina) was administered 35–36 h before oocyte retrieval was performed. All MII oocytes obtained from the donor are fertilized by ICSI by using the recipient's partner sperm or donor sperm if indicated. All ovulating recipients received a single intramuscular injection of depot tryptorelin (Gonapeptyl depot; Ferring, Buenos Aires, Argentina), and after ovarian suppression was demonstrated, estradiol valerate 4–6 mg/d orally (Ronfase; Pfizer, Buenos Aires, Argentina) was administered during at least 8 days and for no more than 45 days. Recipients were eligible for embryo transfer only when the endometrial thickness was above 7 mm. After the oocyte allocation is performed, the oral estrogen was continued, together with a vaginal progesterone regimen, in which 600 mg/d of micronized progesterone (Utrogestan; Pfizer, Buenos Aires, Argentina) was administered, starting the day after the oocyte retrieval from the donor.

All the embryo transfers were performed in cleavage stage (either days 2 or 3 post aspiration, based on whether the embryos to be transferred were already identified on day two, or whether there was a need for another 24 hs in culture). Two embryos were transferred if available in all cases regardless of embryo morphology. The rest of the embryos were frozen on day 3 (only good quality embryos on day 3 are frozen in our program) or at blastocyst stage or discarded when they showed arrest or major fragmentation during extended culture.

Outcomes

A beta hCG level in blood was measured 14 days after the egg retrieval. If positive, estradiol and progesterone were continued until week 12th of pregnancy (or until a miscarriage was diagnosed). A transvaginal ultrasound was performed four weeks after the oocyte retrieval, and clinical pregnancy was diagnosed when at least one gestational sac was seen in the uterine cavity. When miscarriage occurred before seeing a gestational sac, it was named a biochemical miscarriage. When it occurred after seeing a gestational sac, it was named a clinical miscarriage.

Statistical analysis

For this analysis, we retrospectively divided the recipients cohort according to the number of MII oocytes received (Groups A:4; B:5; C:6; D:7; E: 8 or more MII oocytes).

Our hypothesis was that the greater the number of MII oocytes received, the higher the pregnancy rate achieved. We used chi square test to analyze the data. The sample size was calculated to have alpha and beta errors at 5% and 20% respectively, to find a duplication of the pregnancy rate between the higher and the lower strata (60% and 30% respectively).

We used chi square test to evaluate if there was any difference among the previously mentioned strata, with 95% confidence intervals. Stata 8.0 software was used for the analysis.

Results

A total of 339 oocyte donors' cycles were included in the study. During that time, 953 women received at least 4 MII oocytes coming from those donors. A mean of 5.4 MII oocytes (range 4–11) were allocated to each recipient, with a ratio recipient/donor of 2.6 (Table 1). Severe male factor incidence was similar in all the strata, with 12% of patients had a Kruger index of 4% or less. A total of 6.8% of the recipients used donor sperm, with no differences among the strata. The normal fertilization rate was 77.3%, with a mean of 4.2 normally fertilized oocytes for each recipient. Seventy one recipients did not have embryo transfers due to lack of fertilization, lack of normal fertilization or embryo(s) with poor morphology on day 3 and that left in extended culture did not reach blastocyst and were discarded.

A total of 882 embryo transfers were finally performed. From those recipients that received at least 7 MII oocytes, 85% had two top quality embryos to be transferred, in comparison to 70% among those recipients that received 6 MII oocytes or less ($p<0.05$). No significant differences were found in number of cases with at least one top quality embryo transferred. No statistically significant differences were found in implantation rate, clinical pregnancy rate and miscarriage rate among the various groups (Table 2). We found a significantly higher embryo freezing rate when recipients received more than 6 MII oocytes ($p<0.05$).

Table 1 General characteristics in our shared egg donor program

Donor egg retrievals (n)	339
Retrieved oocytes (per donor)	19.6
Retrieved MII oocytes (per donor)	15.1
Number of MII allocated oocytes (per recipient)	5.4±1.5
Fertilization rate (%)	77.3±18.2
Embryo transfers (n)	882

Discussion

This study demonstrates that after a large sample was analyzed there was no difference in pregnancy outcome among the various groups, suggesting that if a small difference exists in reproductive outcomes among strata, it may only be manifested after transferring the frozen embryos among those patients receiving a high number of MII oocytes, since the embryo freezing rate was greater in the group of recipients that received 7 or more MII oocytes. Cumulative pregnancy rate, including the frozen embryo transfers, was not evaluated in this study and it could show a difference between the evaluated groups. On the other hand, we should mention that clinically not statistically significant differences were found among the strata, which may be due to an underpowered sample. Although costs were not evaluated in this study, when splitting the oocyte cohort among several recipients, costs are shared (medication, donor reimbursement etc.) making it a cost-effective alternative. Theoretically there is a potential clinical difference with a higher cumulative pregnancy rate, therefore a cost-effective analysis will need to be performed in order to understand if this difference changes the cost-effectiveness profile. One aspect that could be seen as an adverse effect of sharing a minimum of 4 donated oocytes per recipient, is the fact that 7.4% did not have embryo transfers due to lack of fertilization, abnormal fertilization or poor embryo cleavage. The number of cancelled embryo transfers was higher than in our standard IVF in normo-responders using their own oocytes, and it may have been due to the high incidence of severe male factor (cases with azoospermia (requiring sperm retrieval procedures) or Kruger index of 4% or less, in this population); one can speculate that if a higher number of mature oocytes were allocated per recipient the number of cancelled embryo transfers would have been lower. Yet analyzing the entire study population, one can conclude that reproductive outcomes were satisfactory when allocating at least 4 MII oocytes.

One of the strengths of this study is the large number of recipients evaluated during a prolonged period of time without changes in the egg donor program policies. As all metaphase II oocytes from every donor are randomly divided into the matched recipients, chances of selection bias are really low. When sharing donor screening costs, donor stimulation costs and donor reimbursement cost among several recipients, each patient pays a smaller portion of the total cost, making the treatment more affordable. The lack of differences encountered in most relevant clinical outcomes, seems to suggest that this kind of program has a good cost-effectiveness profile. We recognize however, that this conclusion should only apply to the fresh embryo transfers since the frozen-thawed embryo transfers (past and future) are not included in the analysis.

Table 2 Reproductive outcomes according to the number of allocated MII oocytes, in a shared egg donor program

	Group A (4MII) <i>n</i> =240	Group B (5MII) <i>n</i> =329	Group C (6MII) <i>n</i> =173	Group D (7MII) <i>n</i> =55	Group E (8MII) <i>n</i> =85
Recipient age ^a	41.6±6	41.1±4	40.5±5	41.5±5	41.4±5
Duration of endometrial preparation (days) ^a	25.4	25.8	24.6	24.8	25.2
Implantation Rate ^a	26.3%	27.8%	30.5%	29.4%	32.2%
Transferred embryos (n)	2.0	2.0	2.0	2.0	2.0
Transfer cancellation rate	7.4%	7.4%	6.2%	8.6%	6.9%
Clinical Pregnancy Rate per transfer ^{ab}	43.7%	45.6%	48.6%	45.5%	53.0%
Miscarriage Rate ^a	8.9%	4.1%	8.0%	16.1%	10.5%
Live Birth Rate ^a	39.8%	43.7%	44.7%	38.1%	47.4%
Multiple pregnancy rate (all twins) ^a	20.3%	21.9%	25.5%	29.2%	21.5%
Embryo Freezing Rate	8.5%	18.1%	19.2%	41%*	48.8%*

^a *P* = NS^b Patients that had to cancel their embryo transfer were matched with another donor, with no extra charge.**P*<0.001 (chi square test)

We found few studies regarding the ideal number of oocytes to be allocated to each recipient. Most of them showed good outcomes when sharing the donor oocyte cohort, with no clinical differences versus those cycles that allocate all oocytes to only one recipient. In agreement with our findings, most studies found that recipients who received higher number of oocytes have higher chances of freezing embryos [14]. Recently, Mullin et al. compared exclusive and shared donor oocyte cycles and found no significant differences in clinical pregnancy rate among both types of donations; [13] however, and in agreement with our findings the group that received all the oocytes retrieved had a significantly greater number of cryopreserved embryos.

A possible explanation about the lack of significant differences among all the strata evaluated is that young healthy donors have a high rate of good quality eggs, and the chances for each recipient of receiving at least one or two good oocytes is also high when receiving at least 4 MII oocytes. One of the most important issues in an egg donor program is to have a good screening protocol, where only potentially successful donors are accepted into the program. Unfortunately, this is not an easy task and studies showed that selecting only young donors, [16, 17] failed to show any variables that would make a difference in future outcome [18–20]. In our program, we include donors younger than 35 years old with regular menses, with normal basal FSH/estradiol levels and basal antral follicle count, without androgenic characteristics, and without history of repeated spontaneous miscarriages. In screening tests for ovarian reserve in oocyte donors, most scientific

guidelines have not suggested any clear cut-off points [21, 22] pointing toward the lack of specific characteristics among the oocyte donors that are relevant in the success rates, when they are young.

Conclusion

To our knowledge, this is the first study that analyzes different cut-off points for the number of allocated oocytes to multiple recipients, adding a significant body of evidence to support the sustainment and development of shared oocytes donor programs. More studies are needed evaluating and comparing cost-effectiveness of shared and non-shared egg donor programs, but in our opinion shared egg donor programs seem to be a good option in order to reduce the total costs and shorten the waiting time to treatment for recipients. In conclusion, allocating at least 4 MII oocytes to each recipient seem to be a rational and good enough cut-off point, generating a satisfactory pregnancy rate after fresh embryo transfers.

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