Editorial Article

The shared donor oocyte program: the advantages and insights it provides in determining etiologic factors of infertility

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Summary

A shared oocyte program allows a couple to achieve a pregnancy by in vitro fertilization (IVF) when this option may have been precluded because of financial considerations. It also allows recipients to save money since they do not have to pay a donor fee. The shared program offers the availability of a larger pool of oocytes thus reducing waiting times for recipients. The donors are a highly motivated group since they are working for their own infertility problem and are therefore very cooperative. The shared oocyte program is a very valuable research tool because one can evaluate under different circumstances the outcome of the same pool of oocytes being fertilized by different sperm and the subsequent embryos formed being transferred into two different women under different circumstances.

Key words: Oocyte recipients; Donors; Implantation disorders.

History:

Oocyte donation has allowed many older couples or younger patients with premature ovarian failure to have successful deliveries [1-18]. Most centers reported higher pregnancy rates in the recipients than in their normal in vitro fertilization (IVF) program [1-18].

Ethical Issues:

Whereas the use of donated oocytes from fertile siblings seems to be ethically accepted by most countries, there are still several countries not allowing payment to anonymous donors. One way to get around what some consider an ethics question would be the use of an anonymous woman willing to donate some of her oocytes gratis to another woman. However, this is not likely since the extra oocytes could be used for future transfers by cryopreserving the embryos or allow a better chance of attaining the best embryos for day 3 or day 5 (blastocyst) transfer by having a larger pool from which to choose from.

Shared oocyte program:

The first description of the use of a shared oocyte program between anonymous infertile donors and women in need of donated oocytes was reported in 1992 [19]. Studies have found very reasonable pregnancy rates despite using oocytes from infertile women [20]. In fact, we presented data at the 2002 meeting of the American Society for Reproductive Medicine where we found equal pregnancy rates for recipients receiving donated oocytes from anonymous infertile women vs anonymous paid fertile donors.

Advantages of a shared program:

At the Cooper Center for IVF a couple who requires IVF to achieve a pregnancy, but cannot afford it, is allowed to proceed at minimal charge if they are willing to share half of the oocytes collected with a couple requesting donated oocytes for premature ovarian failure, advanced female age, unexplained infertility, or genetic factors.

The shared program not only saves money for the donor, but allows a less expensive charge for the recipient since there is no fee paid to the donor.

Since the donor is working for herself as well as the recipient she is motivated to adhere to all instructions carefully. Furthermore by typically being a little older than paid donors, there is less risk for ovarian hyperstimulation syndrome (OHSS). Actually, it seems more ethical to risk OHSS if the goal is pregnancy than if the goal is predominantly financial award.

Paid donors are not always so easy to find, and many donor oocyte programs using paid donors exclusively have long waiting times. The use of infertile patients sharing oocytes markedly shortens the waiting time for donated oocytes.

Insights into the etiology of infertility provided by analyzing the outcome of a shared oocyte program.

Adverse affect of controlled ovarian hyperstimulation (COH) on the uterine environment:

A preliminary report in 1992 suggested that despite their increased age the recipient pair of donated oocytes had an increased pregnancy rate [19]. This was confirmed by a larger study [21]. Prior to this study, the general belief as to the reason that most IVF centers were finding higher pregnancy rates in their recipient programs using sibling oocytes or paid donors was the higher quality of oocytes from young fertile donors [3, 7, 22-24]. However, since the 1992 study [19] used the same pool of oocytes for donors and recipients, the explanation for decreased pregnancy rates for the donors might be related to an adverse uterine environment either intrinsic or related to the COH regimen.

One way to determine if there may be an intrinsic adverse endometrial environment related to the etiology for infertility of the donors vs adverse affect of COH would be to compare the outcome of fresh vs frozen embryo transfer (ET) in donors vs recipients. A prospective study of 135 matched donor-recipient pairs confirmed the previous preliminary studies [19, 21] that following fresh ET a significantly higher pregnancy rate was found in the older recipients vs the younger donors [25]. Had the subsequent frozen ETs been similar, the data would clearly show that the COH regimen per se is responsible for the adverse uterine environment. However, though the results did not show a significant difference for frozen ETs between donors and recipients, there was a trend still for higher pregnancy rates in the older recipients [25]. Thus these data suggested that possibly both mechanisms were operating, i.e., intrinsic uterine defect and the COH [25].

The above study was conducted between 1991 and 1993 [25]. In 1994 some reports suggested that the presence of a hydrosalpinx could lower implantation rates [26-28]. These data were confirmed by subsequent studies [29-32]. Further proof that the hydrosalpinx could create a toxic uterine environment was provided by the demonstration that either bilateral salpingectomy [33-38] or unilateral salpingectomy [39, 40] markedly improved pregnancy rates.

Thus another series of donor recipient pairs was evaluated after the initiation of the policy to perform salpingectomy for hydrosalpinges. This time with generally higher pregnancy rates following IVF-ET because of technical advances, a significantly higher pregnancy rate was not found in recipients but there was a definite trend; however, the implantation rate was still significantly higher in recipients [41]. This time, however, there was, if anything a trend for lower pregnancy rates following frozen ET in recipients [41]. Thus, we concluded that previously in the original study the difference in pregnancy rates for donors and recipients was partially related to the much more common presence of hydrosalpinges in donors [28]. Nevertheless, with the hydrosalpinx factor removed, it is still quite clear that the COH regimen can adversely impact the uterine environment [41, 42].

Evaluation of uterine senescence:

Previous animal data clearly demonstrated a lower pregnancy rate when oocytes from younger animals were transferred to older recipients vs younger recipients [43-45]. Initially data from oocyte donation pro-

grams in humans reached similar conclusions to the animal studies; women > age 40 have lower pregnancy rates than younger women when receiving donated oocytes from younger donors [46-48].

Initially, we also found lower pregnancy rates in older recipients using shared oocytes [16]. However, it was subsequently found that the senescence factor was mostly related to an increased need of progesterone (P) for luteal phase support [18]. Once the dosage of P was increased for younger and older recipients there were no longer any difference in pregnancy rates between the two groups [18]. The advantage of using a shared oocyte program as opposed to evaluating the effect of age in programs where the donor herself is not trying to conceive, is that by finding comparable pregnancy rates in the donors for younger vs older recipients one is more assured that the similar pregnancy rates were not secondary to fortuitous use of better oocytes in the older group [18].

Evaluation of whether the adverse effect of increased serum P at the time of human chorionic gonadotropin (hCG) injection is related to an adverse effect on the oocyte vs endometrium:

A subtle rise in serum P before receiving an injection of hCG has been associated with a decreased pregnancy rate after IVF-ET both in cycles where no gonadotropin releasing hormone agonists were used to first suppress gonadotropins [49] and even in cycles using leuprolide acetate before human menopausal gonadotropin (hMG) to prevent premature luteinization [50, 51]. The rise in serum P, even without a rise in serum luteinizing hormone (LH), may be secondary to induction of excess LH receptors in granulosa cells by high serum estradiol (E2) and follicle stimulating hormone (FSH) levels, thus making the granulosa cells more sensitive to LH.

There is controversy as to whether this subtle rise has a detrimental effect on the oocyte or the endometrium. Mio *et al.* [49], evaluating clomiphene citrate-hMG cycles, found a decrease in mature (stage 1) follicles with increasing serum P level, whereas Silverberg *et al.* [51] did not find a decrease in mature oocytes with higher sera P levels.

Check *et al.* comparing pregnancy rates between donors and recipients according to whether the serum P was < 1 ng/ml or > 1 ng/ml found a trend for lower pregnancy rates in donors when P was > 1 ng/ml but without any difference in recipients receiving oocytes from donors whose serum P was > 1 ng/ml at the time of hCG injection [52]. Unfortunately, they never performed a larger series to determine if significant differences could be reached because based on these data their policy was to freeze the embryos of the donor if the serum P of the donor was increased. With improving pregnancy rates related to better embryo medias, and the use of 3- and 5-day transfers rather then 2-day transfers, and the use of a variety of different serum P assays from different manufacturers, the threshold of serum P that can distinguish which patients undergoing IVF-ET will have lower pregnancy rates has been raised [53].

Demonstration that certain sperm abnormalities can cause embryo implantation defects:

A previous study found that males whose semen evaluations showed hypoosmotic swelling test (HOST) scores < 50% did not achieve pregnancies even if all other semen parameters were normal [54]. However, the importance of this test came into question with the finding that when evaluating fertilization rates with IVF, this test was the least valuable in predicting failed or poor fertilization [55-59]. Interestingly, all of the above studies failed to include pregnancy rates [55-59].

Since the in vivo study so vividly demonstrated failure to conceive with low HOST scores [54], yet IVF showed normal oocyte fertilization rates even with low HOST scores [55-59], possibly this test might detect a sperm defect that allows normal fertilization but inhibits implantation. Possibly the studies finding normal fertilization with low HOST scores following IVF left out pregnancy rates because they were embarrassingly low [55-59].

The shared oocyte program was used to test the hypothesis that low HOST scores could cause implantation disorders without adversely affecting fertilization rates. Twenty-two pairs of donor-recipients were chosen where both male partners had normal semen parameters but where one male partner had a HOST score < 50% and the other ≥ 50% [60]. Fertilization rates, number of embryos transferred, and embryo morphology was similar between the groups with normal vs subnormal HOST scores [60]. However, whereas the clinical pregnancy rate per transfer was 50% for the group with HOST scores ≥ 50%, there were no clinical pregnancies for those with HOST scores < 50% [60].

Subsequently, further studies showed the same clinical pregnancy rate (49%) and a viable/ongoing pregnancy rate of 45% if the oocytes were fertilized by intracytoplasmic sperm injection (ICSI) [61]. Thus these data strongly suggest that some toxic substance(s) associated with the sperm cause(s) a functional impairment of the sperm membrane, and this toxic factor can be transferred to the zona pellucida of the oocyte with the attachment of the supernumerary sperm [62]. The hypothesis continues that the toxic factor gets internalized and becomes associated with the subsequent embryo; possibly by adversely affecting the function of the embryo membrane, embryo implantation is inhibited [62]. This factor would be eliminated by the process of ICSI [61]. There are some data suggesting that this factor is proteinaceous by nature [63].

Endometriosis and infertility:

There are many theories as to how endometriosis may be associated with infertility as summarized by Damewood [64]. Included in these theories are adverse effects of endometriosis on the oocyte [65, 66] or adverse affects on implantation either through activation of cellular immune mechanisms [67, 68] or by decreasing the endometrial levels of integrins, e.g., alpha 5-beta 3 integrin [69].

In vitro fertilization would overcome some of the theorized and disputed ways that endometriosis can cause infertility, e.g., tube-ovum pickup [64], luteal phase defects [70-72], or luteinized unruptured follicle syndrome [73, 74], or increased sperm phagocytosis from peritoneal factors [64].

A study using outcome of embryo transfer from donor oocytes according to whether the recipient had endometriosis or not found no difference in pregnancy rates or implantation rates between the two groups [75]. They thus concluded "that the adverse effect of endometriosis on reproductive outcome is not related to implantation but, in fact, is most likely an effect on oocyte or embryo quality" [75].

However, using a shared donated oocyte program we reached opposite conclusions. The data clearly showed no adverse affect of endometriosis on oocyte or embryo quality since the clinical and viable pregnancy rates and implantation rates were from 73.1%, 61.5% and 37.8% for recipients receiving oocytes from donors with endometriosis vs 54.9%, 47.2%, and 29.5%, for recipients receiving oocytes from donors without endometriosis (p=NS). These data have been presented at the 2002 American Society for Reproductive Medicine meeting in Seattle, Washington.

In that same study, the donors with endometriosis had a clinical and viable pregnancy rate and implantation rate of 41.2%, 35.3%, and 20.4% vs 50.4%, 48.0%, and 28.4% for donors without endometriosis (p=NS).

Thus, by evaluating outcome of the shared donor oocyte program, the data are clear that endometriosis does not have any adverse effect on the oocyte or on the embryos that are subsequently formed. The data could suggest a possible trend for women with endometriosis to have a lower chance for embryos to implant. However, even if a larger series would show significant differences, one could still conclude that in the majority of women with endometriosis, there is usually no problem with embryo implantation.

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