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Fresh embryo transfer is more effective than frozen for donor oocyte recipients but not for donors

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BACKGROUND: Recipients of donor oocytes need to be synchronized to the donor's cycle if fresh embryos are to be transferred on the cycle of oocyte retrieval. It would be much easier to merely retrieve the oocytes from the donor, fertilize the oocytes with the recipient's male partner's spermatozoa, cryopreserve the embryos, then transfer on an oestrogen/progesterone treatment programme. METHODS: The IVF outcomes of all patients enrolled in a shared oocyte programme from January 1997 to June 1999 were reviewed. Pregnancy and implantation rates were computed and statistically analysed. RESULTS: There was a significantly higher clinical pregnancy rate for recipients who had a fresh embryo transfer compared with recipients whose first embryo transfer consisted of frozen/thawed embryos (63.4 versus 43.6%). CONCLUSIONS: Conception is more likely after fresh than frozen embryo transfer with recipients but is similar to donor conception rates. If a uterine defect, *per se*, even without the use of the controlled ovarian stimulation regimen, could explain the difference between fresh pregnancy and implantation rates in donors versus recipients, then these same differences would have been seen when comparing frozen transfers, but they were, in fact, similar.

Key words: frozen embryo transfer/implantation rates/shared oocyte

Introduction

Oocyte donation has allowed many older couples or younger patients with premature ovarian failure to have successful deliveries (Asch *et al.*, 1987; Leeton and Hartman, 1987; Serhal and Craft, 1987; Correy *et al.*, 1988; Junca *et al.*, 1988; Leeton *et al.*, 1988; Devroey *et al.*, 1989; Formigli *et al.*, 1989; Kennard *et al.*, 1989; Sauer and Paulson, 1989; Sauer *et al.*, 1989, 1990; Angell, 1990; Sauer and Paulson, 1990; Cha *et al.*, 1991; Check *et al.*, 1993a,b, 1994). There are many studies demonstrating higher pregnancy rates in donor oocyte recipients than patients undergoing standard IVF (Rosenwaks,1987; Serhal and Craft, 1987; Ben-Nun *et al.*, 1989; Devroey *et al.*, 1989; Frydman *et al.*, 1990). The higher success rates certainly could be attributed to better quality oocytes from younger paid donors. However, some IVF centres, using a shared oocyte system, where the donor is also a patient who keeps half of the oocytes for herself, have found significantly higher pregnancy and implantation rates in the recipients (Check *et al.*, 1995, 1999). Thus oocyte quality cannot account for improved pregnancy and implantation rates in recipients using shared oocytes. Theoretically, the higher rates could be either attributed to a better uterine environment in recipients or an adverse effect of the ovarian stimulation regimen.

When embryos are cryopreserved, implantation and subsequent pregnancy rates may be adversely affected by freeze/thawing and ice crystal damage to the embryos and by cryopreserved embryos frequently being the result of de-selection, i.e. the best quality embryos are transferred fresh and the poorer quality ones are cryopreserved (Check *et al.*, 2000b). On the other hand, implantation and pregnancy rates can be theoretically helped with frozen embryo transfer if the controlled ovarian stimulation regimen adversely affects implantation (Check *et al.*, 1999, 2000a).

Frequently, because of the risk of ovarian hyperstimulation syndrome, or less frequently because of a substandard endometrium as determined by sonography (Smith *et al.*, 1984; Fleischer *et al.*, 1986; Gonen *et al.*, 1989; Gonen and Casper, 1990; Check *et al.*, 1991, 1993c,d; Sher *et al.*, 1991; Dickey *et al.*, 1992), fresh embryo transfer is cancelled and all embryos are cryopreserved.

The study presented herein compared pregnancy rates in a shared oocyte programme of the donor versus their paired recipients in fresh embryo transfers, versus frozen embryo transfers that represented the first transfer (because the fresh transfer was deferred), and versus second frozen embryo transfers. Amongst other things, the study would help to determine how important it is to synchronize donor and recipient cycles to allow fresh transfer versus the easier method of merely cryopreserving the donor oocytes fertilized by the

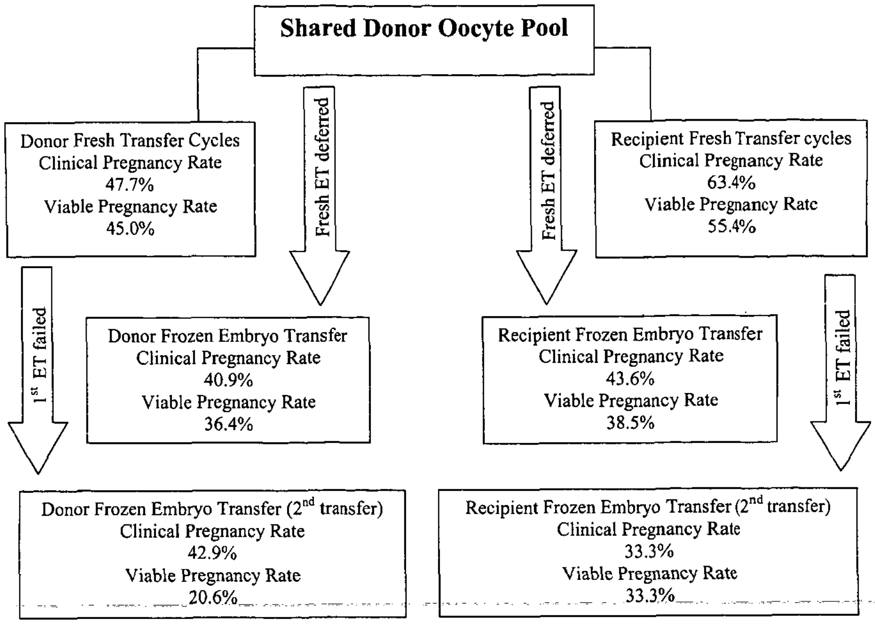

Figure 1. Outcome of embryo transfers (pregnancy rates). ET = embryo transfer.

recipient's male partner's spermatozoa and transferring them back at a more convenient time.

Materials and methods

IVF outcomes of all patients involved in the shared oocyte programme from January 11, 1997 to June 30, 1999 were retrospectively reviewed. Patients were excluded if they were using a gestational carrier. Since in our IVF centre pregnancy and implantation rates are similar for patients having conventional insemination of oocytes and intracytoplasmic sperm injection (ICSI), there were no exclusions if ICSI was performed. Nevertheless, the data was analysed both with all cycles together and separately for the cycles having ICSI, since some studies suggest an effect on embryo quality related to male factor with an influence by ICSI (Oehninger *et al.*, 1996; Terriou *et al.*, 1997; Host *et al.*, 1999).

Frozen embryo transfer cycles were limited to those patients who participated in the shared programme in the designated time period. Thus, patients who cryopreserved their embryos prior to January 11, 1997 were not included even if they had embryos transferred during this time period.

The pregnancy and implantation rates were computed and statistically analysed for: (i) embryo transfer cycles immediately following the retrieval; (ii) frozen embryo transfer cycles for patients who had all embryos cryopreserved and (iii) frozen embryo transfer cycles for patients who had a transfer following retrieval and are now having a second transfer, but with frozen/thawed embryos (Figure 1).

Oocyte donors are infertile women, at most 39 years old, that donate half of the oocytes retrieved in their IVF cycle in exchange for financial assistance for their own medical treatment. Oocyte recipients in the shared oocyte programme receive oocytes from a donor in exchange for financial assistance with the donor's cycle. All oocytes retrieved are divided equally between donor and recipient.

The donor undergoes a luteal-phase leuprolide acetate/gonadotrophin ovarian stimulation regimen. Beginning 1 week after ovulation, leuprolide acetate is started at 0.5 mg for 10 days s.c., when serum oestradiol and progesterone concentrations are measured. If the oestradiol concentration is <50 pg/ml and the serum progesterone <2 ng/ml, the leuprolide acetate is reduced further, to 0.25 mg s.c. daily. If the oestradiol and/or progesterone concentrations are not sufficiently suppressed, leuprolide is continued for a few more days and the measurements are repeated. Once the dosage is down to 0.25 mg, 300 IU of gonadotrophins [various combinations of either all FSH, half human menopausal gonadotrophin (HMG) and half FSH, or all HMG] are initiated s.c. and/or i.m. in two divided doses. Human chorionic gonadotrophin (HCG; 10 000 IU) is given i.m. when two lead follicles attain an average diameter of 20 mm and the serum oestradiol is >1000 pg/ml. Rarely, a follicular stimulation protocol was used (Garcia *et al.*, 1990).

Recipients without ovarian function were treated with oral micronized oestradiol, 2 mg ×5 days, 4 mg ×4 days, then 6 mg ×5 days, beginning on the sixth day of the donor's leuprolide acetate treatment. Recipients with ovarian function are suppressed with leuprolide acetate before starting the oestradiol. Recipients are given progesterone vaginal suppositories, 200 mg twice daily, and frequently 50 mg i.m. progesterone beginning the day after the donor takes HCG, and transfer occurs on the fourth day of progesterone supplementation. Donors and standard IVF patients also take supplemental progesterone after transfer.

Supernumerary embryos not used for fresh embryo transfer were cryopreserved and thawed for subsequent transfer in an unstimulated cycle. Also, in cases where the patient was at risk for ovarian hyperstimulation syndrome, or the patients had inadequate endometrial development, all embryos were cryopreserved and thawed at a later time for transfer. In general, patients were considered at risk for ovarian hyperstimulation if the serum oestradiol was >5000 pg/ml on the day of, or the day after, HCG injection or if there were >30 follicles. The endometrium was considered inadequate if the thickness was <8 mm or there was a homogeneous hyperechogenic pattern on the day of HCG injection (Check *et al.*, 1991, 1993c). Frozen embryo transfer could be performed after a deferred fresh embryo transfer cycle or pregnancy failure, but would be deferred for at least one cycle following controlled ovarian stimulation to dilute any persisting negative effects of hyperstimulation on the uterine environment (Figure 1).

The main outcome measures were: clinical pregnancy rate (sonographic evidence of a gestational sac in the uterus); viable pregnancy rate (live fetus at end of the first trimester) and implantation rate

Table I. Outcome of embryo transfers (implantation rates)*

	Donors	Recipients
Fresh implantation rate (%)	26.4 (87/329) [31.2–41.6]	31.8 (114/358) [24.2–40.6][a]
Frozen embryo transfer (deferred transfer) implantation rate (%)	19.9 (29/146) [13.4–26.3]	15.3 (22/142) [9.3–21.2][a]
Frozen embryo transfer (second transfer) implantation rate (%)	31.2 (5/16) [8.5–53.9]	8.6 (3/35) [0.0–17.9]

*Data presented as implantation rates [95% confidence interval].
[a]$P < 0.05$, comparing fresh to frozen within group.

Table II. Oocyte retrieval cycles – patient characteristics

	Oocyte donors (n = 167)	Oocyte recipients (n = 155)
Age (range) [CI]	31 (22–37) [31.4 ± 3.4]	43 (27–55) [42.6 ± 5.8]
Stimulation Protocol	Luteal phase LA – 159 Other – 8	LA/E2 – 82 (52.9%) E2 – 52 (33.5%) None – 20 Other – 1
Mature oocytes available to each (range) [CI]	7 (3–29) [7.9 ± 4.0]	9 (1–23) [9.6 ± 4.5]
Fertilization rates (mature) (%) (range) [CI]	71.4 (0–100) (69.5 ± 24.3]	75 (0–100) [69.1 ± 24.9]
No. of embryo transfers cancelled	58	54
Reason for cancellation		
OHSS	45	
Elevated progesterone	1	1
No fertilization/embryo arrested	3	7
Personal	7	4
Endometrial lining inadequate	2	12
Not synchronized		25
Other		5
No. of embryo transfers (range) [CI]	109	105
No. of embryos transferred	3 (1–5) [3.0 ± 0.9]	3 (1–7) [3.5 ± 0.9]
Positive βHCG (%)	58 (53.2)	67 (66.3)
Chemical	4	3
Ectopic	2	0
Clinical (%)	52 (47.7)	64 (63.4)
1×	26	28
2× (%)	17 (32.7)	21 (32.8)
3× (%)	9 (17.3)	14 (21.9)
4×	1	

CI = confidence interval; LA = leuprolide acetate; E2 = oestradiol.

(number of gestational sacs per embryo transferred). Chi-square analysis was used to compare the rates obtained using fresh or frozen embryos within each patient group. The rates between the two patient groups for each type of embryo transfer were also compared using χ^2 analysis. A P value of 0.05 was used to determine significance, 95% confidence intervals for the rates were also computed.

The ICSI technique was performed as previously described (Palermo *et al.*, 1993; Van Steirteghem *et al.*, 1993, 1994). The technique for assisted embryo hatching using acidic Tyrode's solution was based on the one described originally by Cohen *et al.* (Cohen *et al.*, 1992) and has been previously described for frozen embryos (Hoover *et al.*, 1995; Check *et al.*, 1996).

Results

The clinical and viable pregnancy rates are seen in Figure 1. The clinical pregnancy rate was significantly higher in recipients than their respective donors (63.4 versus 47.7%) despite equal distribution of oocytes.

There was a significantly higher clinical pregnancy rate for recipients who had a fresh embryo transfer compared with recipients whose first embryo transfer consisted of frozen/thawed embryos (63.4 versus 43.6%) because of cancellation of fresh transfer (usually because of failure to synchronize cycles) (Figure 1). However, no differences were found when comparing first embryo transfers in donors (fresh versus frozen) (47.7 versus 40.9%) (Figure 1).

The implantation rates, as seen in Table I also showed a significant difference in fresh versus frozen/thawed (but first transfer) in recipients (31.8 versus 15.3%) but once again did not reach a significant difference (26.4 versus 19.9%) when comparing first transfer fresh versus frozen in donors. Actually if all frozen embryo transfer cycles are combined, the difference of fresh versus frozen embryo transfer implantation rates increased more (32.4 versus 14.0%) in recipients but became narrower in donors (26.4 versus 20.9%). No differences were seen between recipients and donors in implantation rates after fresh embryo transfers though there was a trend toward a higher rate in recipients (31.8 versus 26.4%).

The large majority of patients received the luteal phase leuprolide acetate-gonadotrophin regimen. Only 5.6% used leuprolide in the follicular phase because of time constraints (Table II). The median age of the donor was 31 versus 43

Table III. Oocyte retrieval cycles according to whether ICSI was performed or not

	ICSI Donor (n = 60)	Non ICSI Donor (n = 107)		ICSI Recipients (n = 61)	Non ICSI Recipients (n = 94)
Age range (years)	22–37	22–37		31–55	27–55
Average age (years)	31.2	31.6		43	42.3
Stimulation protocol					
Long Lupron	59	100	Estrace	22	30
Other	1	7	Lupron/Estrace	30	52
			None	9	11
			other		1
Mature oocyte range	3–20 (8.7)	3–29 (9.7)		1–18 (8.6)	1–23 (10)
Fertilization range	0–100	0–100		0–100	0–100
Average % fertile	71.2	66.6		71.0	68.0
Embryo transfers cancelled (n)	19	39		22	32
Reason					
OHSS	16	29		0	0
Elevated progesterone	0	1		0	1
No fert/embryo arrested	1	2		2	5
Personal	1	6		3	1
Lining	1	1		5	7
Not synchronized				11	14
Other				1	4
No embryo transferred	41	68		39	62
Embryos transferred (n)	1–5 (3)	1–5 (3)		1–5 (3)	1–7 (3.5)
With positive beta (n)	21	37		24	43
Chemical (n)	3	1		1	2
Ectopic (n)	0	2		0	0
Clinical (n)	18	34		23	41
1X	11	15		11	17
2X	5	12		6	15
3X	2	7		6	8
4X	0	0		0	1

Table IV. Outcome of embryo transfers according to whether ICSI was performed or not

	ICSI Donor	Non ICSI Donor	ICSI Recipients	Non ICSI Recipients
Fresh				
Embryo transfer (n)	41	68	39	62
Clinical (n)	18	34	23	41
Clinical (%)	43.9	50.0	59.0	66.1
Viable (n)	18	31	20	36
Viable (%)				
Frozen embryo transfer – deferred transfer				
Embryo transfer (n)	16	28	13	26
Clinical (n)	7	11	5	12
Clinical (%)	43.8	39.3	38.5	46.2
Viable (n)	7	9	5	10
Viable (%)				
Frozen embryo transfer – second transfer				
Embryo transfer (n)	3	4	5	4
Clinical (n)	1	2	2	1
Clinical (%)	33.3	50.0	40.0	25.0
Viable (n)	0	2	2	1
Viable (%)				

years in the recipient (Table II). The median fertilization rates were similar in recipients (75%) versus donors (71.4%).

The median numbers of embryos transferred were similar in donors and recipients. The number chosen to transfer was decided by the couple after counselling. The percentage of twins was 38.8% in recipients versus 29.3% in donors and the respective triplet rate was 25.9% versus 15.5% (Table II). Though the median number of embryos transferred was the same, the recipients had a higher mean number transferred (3.5 versus 3) and this could at least partially explain the tendency toward higher multiple birth rates. The only quadruplet pregnancy was in the recipient group.

When the data was evaluated the results were similar whether ICSI was performed or not (Table III). Thus, although embryo quality may depend on paternal factors (Oehninger *et al.*, 1996; Terriou *et al.*, 1997; Host *et al.*, 1999) in this study it did not seem to matter.

Table IV demonstrates that conclusions reached about frozen embryo transfer for the entire group were not influenced by whether ICSI was performed or not.

Discussion

There was no significant difference between clinical pregnancy rates or implantation rates in donors following fresh or frozen embryo transfer. If similar results were found with donor oocyte recipients, then it would make sense to merely cryopreserve all fertilized donor oocytes rather than to make the effort to synchronize the recipient's cycle with the donor's in preparation for fresh embryo transfer. The present data clearly show it does make sense to synchronize cycles for fresh embryo transfer in recipients.

On the other hand, since the pregnancy rates and implantation rates with fresh versus frozen embryo transfer were at least comparable in donors, these data reconfirm our policy of freezing all embryos in patients having IVF–embryo transfer if there is a risk, in our judgement, of severe ovarian hyperstimulation syndrome if complicated by a pregnancy and continued HCG secretion, or an endometrium that does not seem to be ideal for implantation based on ultrasound criteria. Since one of the drawbacks of being a shared-oocyte donor is that they are not allowed to be on protocols aimed at stimulating only a few follicles, it is heartening to know that they can be advised that if their fresh cycle is deferred for subsequent frozen embryo transfer, because of the risk of ovarian hyperstimulation syndrome, that it does not seem detrimental for their chances of conception.

The higher clinical pregnancy and implantation rates in recipients versus donors, despite equal sharing of oocytes, but similar pregnancy and implantation rates in recipients versus donors following the first frozen embryo transfer with fresh transfer deferred, corroborate previous data. It has been shown (but with a much larger series) that the medication used for controlled ovarian stimulation may create a hostile uterine environment that is not conducive for successful implantation (Check *et al.*, 1995, 1999, 2000a). The higher pregnancy and implantation rates in recipients receiving fresh embryos versus frozen/thawed ones clearly shows that the frozen/thawed embryo, even when given the opportunity for selection of the morphologically 'best' embryo (higher blastomere number and less fragmentation) is not as good as the fresh one. Thus, similar pregnancy and implantation rates with fresh and frozen transfer in our centre in our general IVF population has to be related, to a significant degree, to an adverse effect of the controlled ovarian stimulation regimen for implantation. If a uterine defect, *per se*, even without the use of the controlled ovarian stimulation regimen, could explain the difference between fresh pregnancy and implantation rates in donors versus recipients, then these same differences would have been seen when comparing frozen transfers, but they were, in fact, similar.

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