Cumulative pregnancy rates after four embryo transfers of either fresh or frozen embryos

D. Lurie, *Ph.D.*; **J. H. Check,** *M.D., Ph.D.*; **A. Nazari,** *M.D.*; **J. K. Choe,** *M.D.*;**G. Lee,** *M.D.*

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey (USA)

Summary

Purpose: To evaluate in the modern era of in vitro fertilization (IVF) cumulative probability of pregnancy for the first four embryo transfers (ET) irrespective of whether the embryos were fresh or frozen.

Methods: Retrospective review over a 2 1/2 year period. Cumulative probability of pregnancy for four consecutive cycles of either fresh or frozen ETs divided into four age groups.

Results: The cumulative clinical and viable pregnancy rates after four ETs were 92% and 88%; 87% and 82%; 83% and 69%; and 68% and 52% for age groups <30, 30-34, 35-39, and 40-44. The cumulative rates decline with age.

Conclusions: Pregnancy rates per transfer for the first four ETs regardless of age are similar even in IVF centers that emphasize frozen ETs.

Key words: Cryopreserved embryos; Cumulative pregnancy rates; Embryo transfer; Life table analysis.

Introduction

Patients who fail their first in vitro fertilization-embryo transfer (IVF-ET) cycle often seek more information from their physicians on which to base their decision whether or not to pursue treatment and if so what treatment to pursue. What are their chances of attaining a pregnancy on a subsequent cycle? The best statistical information to base this decision on would be the cumulative probability of pregnancy following multiple ETs.

Most of the studies on cumulative pregnancy rates have been done using transfers of fresh embryos only [1-14]. Statistics from clinics outside the United States are generally from countries in which there are strict legal limits on the number of embryos [5-7, 9, 11, 15]. These rates are not applicable to the population in the United States. Also, in the years from 1995 through 1997 the National Fertility Association [16] showed a steady increase in pregnancy rates per cycle for both fresh and frozen cycles. None of the published reports on cumulative pregnancy rates reflect these improved rates.

As cryopreservation and thawing techniques have improved, more patients are now having several frozen ETs before undergoing another oocyte retrievel. Thus, a more informative statistic to use in advising the patient is the cumulative pregnancy rate based on consecutive transfers of either fresh or frozen embryos. The objective of this study was to estimate the cumulative probability of pregnancy after four ETs in light of improvements in pregnancy rates and irrespective of the type of embryos used (fresh or cryopreserved/thawed). The rates were stratified by age.

Statement about IRB.
IRB approval was not sought for this retrospective study since it only involved the review of patient charts.

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Materials and Methods

A retrospective review of 742 patients, under 45 years of age, enrolling between January 1, 1997 and June 30, 1999 for their first retrieval cycle at our center was conducted. Patients were stratified into four age groups (<30, 30-34, 35-39, and 40-44). The percent of patients in each age group using the luteal phase leuprolide acetate protocol for their first stimulation cycle was 73.6%, 67.9%, 49.8% and 20.7%, respectively. Patients underwent ovarian stimulation using either a luteal phase leuprolide acetate/gonadotropin protocol or a follicular phase leuprolide acetate/gonadotropin protocol. Generally, the luteal phase protocol was used by younger women with a history of good response to ovarian stimulation [17]. The follicular leuprolide acetate protocol was used by older women (>38 years old) and/or those with a history of poor ovarian response [18]. Fresh embryos were transferred three days after oocyte retrieval. Assisted hatching and intracytoplasmic sperm injection were applied - as needed. For patients who presented with a poor endometrial lining (thickness <8 mm and/or a homogeneous echo pattern) or were at risk for hyperstimulation (estradiol >5000 pg/mL on day of human chorionic gonadotropin), ETs were deferred and all embryos were cryopreserved [19].

All subsequent ET cycles of either fresh or frozen embryos were analyzed until the patients achieved a clinical pregnancy or withdrew from treatment. A total of 1,276 ET cycles were included in the study (714 cycles with oocyte retrieval and fresh ET, and 562 cycles with frozen ETs).

Frozen ETs were performed either in natural cycles or hormone replacement cycles. A graduated dosage of (2, 4, and 6 mg/day for 5 days) oral micromized estradiol (E2) was given without down regulation with leuprolide acetate. The dose of oral E2 was increased if inadequate endometrial thickness or inappropriate echo pattern was found on the last day of 6 mg/day oral E2. Progesterone (P) in the form of vaginal suppositories, 200 mg twice a day and IM 100 mg P in oil was started when adequate sonography endometrial parameters were achieved (minimum 8 mm endometrial thickness and absence of homogenous hyperechogenic pattern) [20, 21].

Table 1. — *Comparison of the ovarian stimulation characteristics by age*

	Group 1 Age <30 years	Group 2 Age 30-34 years	Group 3 Age 35-39 years	Group 4 Age 40-44 years
No. retrievals	106	197	261	159
Average Age	27.8±1.9	32.6±1.5	37.4±1.4	41.9±1.3
No. oocytes retrieved*	20.4±13.0	17.8±12.7	12.7±10.2	7.5±6.0
Fertilization rate	64.0±22.6	61.2±24.5	62.8±26.0	57.7±30.4
No. embryos / patient*	12.3±7.4	10.9±8.6	8.0±6.9	4.7±4.2
No. of embryos transferred				
Transfer 1	3.0±.6	3.1±.8	3.1±1.0	3.5±1.5
Transfer 2	3.6±.9	3.3±1.0	3.6±1.1	3.7±1.4
Transfer 3	3.5±.8	3.6±1.0	3.5±1.2	3.5±1.4
Transfer 4	3.7±1.5	3.7±1.1	3.8±1.1	3.9±1.4

Date presented as mean ±SD.
*p <.05 comparing groups 1 and 2 to groups 3 and 4.

In general, 6-8 zygotes were allowed to develop into multi-cell embryos and the rest of the fertilized oocytes were frozen at the 2 pronuclear stage. The 3-4 best quality embryos (based on the blastomere number, degree of fragmentation and degree of symmetry) were transferred. The remaining multi-cell embryos were cryopreserved. The method for embryo/zygote freezing using a simplified one-step freezing/thaw protocol was previously described by Baker *et al.* [22] and the assisted hatching method was prevoiusly described by Check *et al.* [23].

Frozen embryos available for subsequent transfer on the first frozen ET would be either unselected 2 pronuclear embryos or deselected multi-cellular embryos. If intracytoplasmic sperm injection was used as the method of insemination, the 2 pronuclear embryos might have been formed from fertilization of mature oocytes or ones resulting from in vitro maturation for one day of slightly immature oocytes. Embryos frozen at the 2 pronuclear stage would be chosen before deselected multi-cell embryos except if they resulted from intracytoplasmic sperm injection of in vitro cultured immature oocytes (in which case they were chosen last). Depending on availability, the transfer of embryos could be mixtures of these embryos. Usually, twice as many frozen embryos were thawed as intended to transfer. The remaining embryos that cleaved to the multi-cell stage with adequate morphology would be refrozen since twice-frozen-twice-thawed embryos have been found to result in pregnancies after transfer [24]. Thus, on transfer cycle 3 or 4, additional types of frozen embryos would be available for selection, i.e., embryos that had been first frozen at the 2 pronuclear stage and have then been refrozen at the multi-cell stage. This type of embryo was chosen last. In general, all frozen embryos would be transferred before proceeding to another oocyte retrieval cycle unless there were insufficient numbers remaining for transfer or very poor quality.

The outcome measures studied were clinical pregnancy per embryo transfer (sonographic evidence of a gestational sac in the uterus) and viable pregnancy (viable fetus at the end of the first trimester). An ET was considered to be any transfer of embryos into the uterus either following oocyte retrieval or the thawing of cryopreserved embryos. Cumulative pregnancy rates were computed using a life table analysis [25]. The log-rank test was used to compare the rates by age. A p value of .05 was used.

Results

Our study demonstrated that as age increased, the number of oocytes retrieved decreased from 20.4±13.0 in the youngest age group to 7.5±6.0 in the oldest groups. Thus, the total number of embryos available per patient also decreased from a high of 12.3±7.4 in the youngest group to 4.7±4.2 in the oldest group (Table 1). The average number of embryos transferred did not differ whether it was the first, second, third or fourth transfer within each age group (p=NS, ANOVA) (Table 1).

In the first ET, over 70% of the patients in each group used fresh embryos. However, in subsequent cycles the majority of embryo transfers used were frozen/thawed embryos especially in the three younger groups (Table 2).

The cumulative probability of clinical pregnancy following four ETs was 92% in the youngest age group, 87% for the 30-34 years old, 83% for the 35-39 year olds and 68% for the 40-44 year olds. The rates were similar in the first three age groups, but decreased for the oldest women (p <.05) (Figure 1). Clinical pregnancy rates per ET did not differ by cycle. In the youngest group, the pregnancy rate per transfer was 45%, 49%, 44%, and 50%. In the oldest group the rates were 17%, 27%, 32%, and 23%. A complete summary of the life table analysis is presented in Table 3.

The cumulative probability of viable pregnancy was 88%, 82%, 69%, and 52%, respectively. The viable rates were similar in the younger two groups, and significantly lower (p<.05) in the older two groups (Figure 1).

For the first four transfers the implantation rate per transfer did not differ within age groups (p=NS, ANOVA). The implantation rates were 21.9%, 20.9%, 20.6%, and 13.6% in group 1; 21.3%, 19.8%, 16.0%, and 16.7% in group 2; 21.0%, 15.4%, 13.9%, and 16.1% for group 3; 9.0%, 10.2%, 17.0%, and 5.9% for group 4.

Table 2. — *Percentage of transfer cycles that used frozen embryos*

	Group 1 <30 years old	Group 2 30-34 years	Group 3 35-39 years	Group 4 40-44 years
Transfer				
1	31.0%	30.3%	20.5%	20.4%
2	82.9%	80.2%	78.1%	49.2%
3	88.9%	73.3%	68.6%	72.0%
4	83.3%	88.9%	76.5%	38.4%

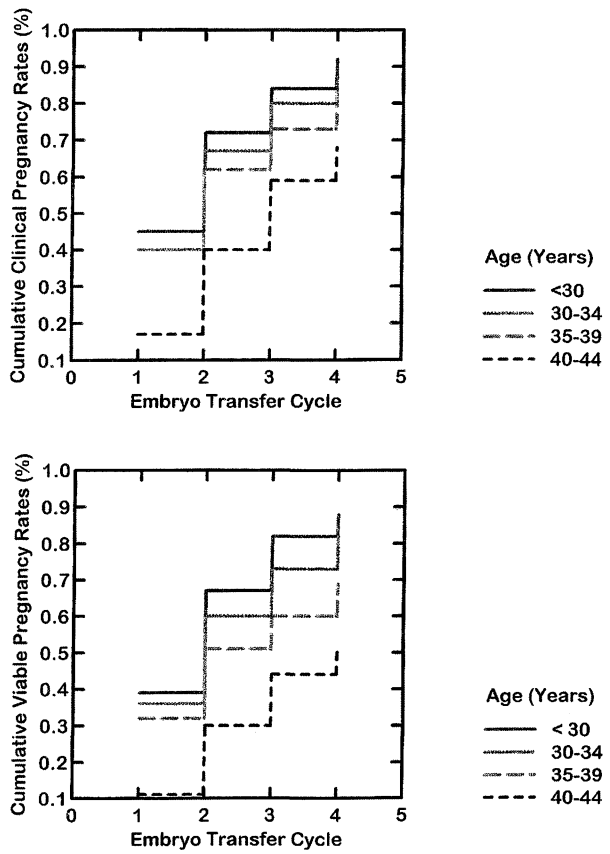

Figure 1. — *Cumulative pregnancy rates for the first four embryo transfer cycles by age. Clinical pregnancy rates were significantly lower for women 40-44 years old. Viable pregnancy rates were significantly lower for women 35 years old and older.*

Discussion

The complexity and excessive costs of assisted reproductive technologies demand that infertile couples have as much information as possible on the success rates of standard IVF-ET and other available treatment options. This information is available in reports on cumulative pregnancy rates following multiple cycles of IVF-ET. The studies published to date [1-14] have focused on success rates following successive cycles of oocyte retrieval and transfer of fresh embryos.

As cryopreservation techniques have improved, many centers can offer their patients the option of undergoing one or more frozen ETs prior to undergoing another oocyte retrieval. Frozen ETs are less costly and less invasive to the couple. This study evaluated the cumulative pregnancy rate for patients who availed themselves of this option and calculated the cumulative pregnancy rate based on the first four ET cycles a patient underwent, irrespective of the type of embryo transferred.

These data demonstrate that within age groups, the pregnancy rate per cycle remains constant for the first four ETs irrespective of the type of embryos transferred (fresh or frozen). It is important to note that for these cycles, the number of embryos transferred per cycle did not differ statistically on repeat cycles. Though there was a trend toward more embryos transferred in cycle 4, it was possibly related to the availability of less quality frozen-thawed embryos or patient frustration from failure to conceive after three transfers. At out center, patients are encouraged to use their frozen embryos before undergoing another oocyte retrieval if they have at least three embryos left in storage. With our survival rates following thaw at over 90% for embryos frozen at the 2 pronuclear stage and over

Table 3. — *Life Table Analysis*

	No. patients	No. pregnancies clinical/viable	Probability of pregnancy/ transfer clinical/viable	Cumulative prbalibility rate clinical[a]/viable[b]	95% confidence intervals for cumulative pregnancy rates clinical/viable
Group 1					
1	104	47/41	.45/.39	.45/.39	(.36-.55)/(.30-.49)
2	41*	20/19	.49/.46	.72/.67	(.62-.82)/(.57-.78)
3	18*	8/8	.44/.44	.84/.82	(.76-.93)/(.72-.91)
4	6*	3/2	.50/.33	.92/.88	(.85-1.0)/(.78-.97)
Group 2					
1	205	83/74	.40/.36	.40/.36	(.34-.47)/(.30-.43)
2	106*	48/39	.45/.37	.67/.60	(.61-.74)/(.52-.67)
3	45*	18/15	.40/.33	.80/.73	(.74-.87)/(.66-.80)
4	18*	6/6	.33/.33	.87/.82	(.81-.93)/(.74-.90)
Group 3					
1	265	107/86	.40/.32	.40/.32	(.34-.46)/(.27-.38)
2	114*	41/32	.36/.28	.62/.51	(.55-.68)/(.45-.58)
3	51*	15/9	.29/.18	.73/.60	(.66-.80)/(.52-.68)
4	34*	13/8	.38/.24	.83/.69	(.77-.89)/(.61-.78)
Group 4					
1	168	29/19	.17/.11	.17/.11	(.12-.23)/(.06-.17)
2	63*	17/13	.27/.21	.40/.30	(.30-.49)/(.20-.39)
3	25*	8/5	.32/.20	.59/.44	(.46-.72)/(.31-.57)
4	13*	3/2	.23/.15	.68/.52	(.55-.82)/(.39-.66)

* Number of patients = number of patients in previous cycle-number of pregnant patients-number of dropouts.
[a] The cumulative clinical pregnancy rates are similar for groups 1 and 2 and 3, but lower for group 4 (log-rank test, $p<.05$).
[b] The cumulative pregnancy rates are similar for groups 1 and 2, but lower for groups 3 and 4 (log-rank test, $p<.05$).

80% for embryos cryopreserved at the multi-cell stage, the patients will usually have at least two embryos for transfer.

These results are consistent with most of the reports on cumulative pregnancy rates following multiple IVF-ET cycles [1-14], with the exception of Hershlag *et al.* [3] who found a decreasing rate after the third cycle. However, Herslag's *et al.* study was based only on transfers of fresh embryos following oocyte retrieval. Thus, from the studies cited above it is not clear how many additional frozen ETs were performed before the fourth oocyte retrieval-fresh ET cycle. Only 7.5% of the patients in our study had more than two oocyte retrievals.

The results of several large multi-center studies [4, 6, 11, 12] are similar to ours. Large multi-center studies reflect a wider range of patients [12]; however, since participation in the study is elective, there is the possibility that only the centers with the better pregnancy rates participated. Pregnancy rates have more than doubled in our IVF center since we published our first study of cumulative probability of pregnancy in 1994 [8]. These improved pregnancy rates have been realized in most IVF centers in recent times so that previous conclusions that pregnancy rates do not decrease for the first four IVF-ET cycles would not necessarily apply to the modern IVF era. The study presented herein corroborates conclusions from the other three studies of the modern era that pregnancy rates still do not decrease for the first four transfers [12-14]. However, the present study is the first to evaluate cumulative probability for the first four transfers irrespective of whether it was a fresh or frozen ET. Thus, these data would be most important for those centers that emphasize a cryopreservation program.

Studies have shown that controlled ovarian hyperstimulation (COH) can adversely affect the implantantion of embryos [26-29]. The majority of the embryo transfers were frozen/thawed for transfers 2-4 in the three younger groups so this study would eliminate this effect of COH on embryo implantation. Theoretically, studies involving only transfers following oocyte retrieval might be influenced by this factor. Nevertheless, it should be reiterated that three studies of fresh embryo transfers during the modern IVF era of improved pregnancy rates also showed similar pregnancy rates for the first four transfers [12-14].

Another theoretical possibility is that for some patients embryo freezing in some way decreases an embryo's viability even if it does appear to be adequate from a morphologic standpoint. Thus, this study, with the majority of transfers being frozen, showed that this viability factor of the frozen embryo does not seem to be a significant factor either. Perhaps if there is some viability lost in an embryo that survives freeze-thawing, pregnancy rates remain comparable to fresh ET because of the elimination of the adverse effect of COH on the uterine environment.

The cumulative pregnancy rate declined with age. This is consistent with previous reports [5, 10, 14]. Women 40-44 years old, however, had a 52% viable pregnancy rate after four ETs and therefore this age group should not be discouraged from continuing treatment.

Patient selection has been considered as a possible factor in the estimation of cumulative pregnancy rates. Rates might be inflated if only the best patients continued treatment, while those with a poor medical prognosis discontinued treatment. However, studies [4, 13, 30, 31] have shown that patients who dropped out for the most part did not differ from patients who continued treatment. In the United States, the drop out rate may be affected by financial constraints more so than medical concerns. Patient selection criteria for treatment at a center may also affect the results. In this center, patients were not excluded on the bases of serum follicle stimulating hormone levels in the early follicular phase or previous IVF failures.

Statistical methodology used in all the cited studies have differed in terms of study design, outcome measures reported, and type of life table analysis used. Cumulative pregnancy rates differ depending on what method is used to calculate the number of patients at risk for pregnancy in a particular cycle. A traditional actuarial method assumes that half the patients who withdrew would be at risk for pregnancy. Slowjik *et al.* compared the different methods and found that the most realistic method assumed that only patients who discontinue treatment for medical reasons had no chance of pregnancy [32]. In our paper, we assumed that patients who withdrew from treatment were not at risk of pregnancy and were excluded from the calculation of pregnancy rates in the next transfer cycle [32]. These estimates are consistent with the estimates of cumulative pregnancy rates obtained from the Kaplan-Meier product limit method in which no assumptions are made on the risk of patients who withdraw from treatment. Irrespective of the methods used, the consensus is that the pregnancy rates for the first four ET cycles did not differ.

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Address reprint requests to:
JEROME H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027