Editorial Article

A novel method to evaluate pregnancy rates following in vitro fertilization to enable a better understanding of the true efficacy of the procedure

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Summary

Purpose: To propose a new method of evaluating in vitro fertilization (IVF)-embryo transfer (ET) outcome so that statistics are not biased against IVF centers that have strong cryopreservation programs.

Methods: A retrospective review was made of all patients undergoing IVF-ET in a four and a half year time period having at least two embryos transferred. There were no other exclusions. All types of problems and controlled ovarian hyperstimulation protocols were used. Data were analyzed according to four age groups: ≤ 35, 36-39, 40-42, ≥ 43. Pregnancy rates were calculated according to a given oocyte harvest where a pregnancy was counted if the woman conceived on the fresh transfer or any succeeding frozen ET from embryos obtained from oocytes retrieved on that harvest. Also pregnancy rates per transfer and retrieval were evaluated.

Results: For women ≤ 35 to age 39 the new category of clinical pregnancy rate per oocyte harvest was significantly higher than the pregnancy rate per transfer. The pregnancy rate per transfer was significantly higher than the pregnancy rate per retrieval in women up to age 42.

Conclusions: We propose that calculating pregnancy rate per harvest is the best method to evaluate the true efficacy of IVF-ET especially from programs with a strong emphasis on cryopreservation.

Key words: Embryo; Cryopreservation; Oocyte harvest; IVF outcome.

Introduction

The goal of any in vitro fertilization (IVF) center should be to provide the best pregnancy outcome for patients undergoing the procedure. In recent years there has been an emphasis on identifying the best embryos for transfer. There appears to be some benefit (though not absolute) in transferring embryos with the most blastomeres, especially eight cells [1-4]. Similarly, there is some benefit in transferring the embryos with the best morphology as evidenced by the least fragmentation of blastomeres and the most symmetry [5-9]. Proposals for fine tuning some of these embryo selection techniques include using 2 pronuclear morphology [10] or evaluating early cleavage, e.g., the rate of obtaining a 2-cell stage or first cleavage in addition to evaluating the percentage of embryos attaining an 8-cell status by day 3 [11-13].

Another way to select the best embryos, and many believe this to be the most ideal, is to allow the embryo to cleave to blastocyst stage before transfer [14-26]. There are data suggesting that blastocyst culture will decrease the percentage of embryos with aneuploidy [27-29].

However, there are data that still show respectable pregnancy rates despite the fact that there are no 8-cell embryos on day 3 to transfer [4]. Similarly, good pregnancy rates can still be achieved with embryos that have less quality embryos morphologically [9-30].

What is not clear is whether the quest to find the best embryos to transfer on the cycle of retrieval may be at the sacrifice of the overall pregnancy rate per oocyte harvest. An important question to be answered is what percentage of day 3 embryos that fail to progress to blastocyst, in culture could have made live babies had they been implanted on day 3? Another important question is whether less quality embryos are less likely to survive cryopreservation and subsequent thawing but would have resulted in a viable pregnancy had it been transferred fresh? On the other hand, is it possible that some of the best embryos for implantation after fresh transfer might lose viability potential after freeze/thawing? This would be especially valid for centers that are less proficient in the freezing of embryos.

Thus in order to be able to fully compare the impact on the conception outcome of newer technology, evaluating the pregnancy rate per transfer may be misleading. Some IVF centers fail to get any embryos for transfer in up to 40% of the cases of attempted blastocyst transfer [2]. Thus such an IVF center could report an impressive 60% pregnancy rate per transfer but in reality the cycles of controlled ovarian hyperstimulation, followed by oocyte-retrieval, only resulted in a 36% pregnancy rate.

Thus, it would seem that a more reasonable method of reporting data would be the chance that a given oocyte retrieval will result in a pregnancy without requiring another controlled ovarian hyperstimulation, oocyte-retrieval

cycle. This new method of reporting would thus include all transfers fresh or frozen to achieve or not achieve a pregnancy from all the oocytes from a given IVF cycle.

The study reported here provides a comparison of how different the success of the program appears when comparing one of the Society for Assisted Reproductive Technology (SART) criteria, pregnancy rate per retrieval vs pregnancy rate per transfer vs overall pregnancy rate per harvest. This latter statistic would still not be a factor in the full potential pregnancy rate per harvest because it would eliminate estimates of what additional pregnancies could be achieved by the remaining embryos.

Materials and Methods

The study included all patients who initiated a stimulated IVF cycle between 1/1/97 and 5/31/01 as long as they had a fresh or frozen embryo transfer (ET) with at least two embryos transferred on day 3. Excluded from this study were women with either elevated follicle stimulating hormone (FSH) or previous poor response where they were not hyperstimulated and transferred only one embryo. However, women with elevated day 3 FSH or estradiol (E2) levels making two or more embryos were included in these data.

Stimulation protocols included luteal phase leuprolide cycles, short flare cycles, micro flare cycles, and the use of GnRH antagonists (ganireliex and cetrorelix). The study included patients who deferred fresh transfer in favor of frozen ET. In vitro fertilization cycles requiring intracytoplasmic sperm injection (ICSI) were also included.

Patients were stratified into four age groups: ≤ 35, 36-39, 40-42, and ≥ 43. Embryos were cryopreserved using a simplified method using a single-step addition of the cryoprotectant, 1.5M 1,2 propanediol as previously described [31]. Assisted embryo hatching was performed on all fresh and frozen embryos on day 3 prior to transfer [32].

The method of embryo selection for transfer has been described in detail [4] but basically twice as many embryos were allowed to cleave as intended for transfer, and the suitable deselected ones were cryopreserved at the multi-cell stage. The rest of the embryos were cryopreserved at the 2 pronuclar stage.

The main outcome measures were chemical pregnancy rate per ET (beta human chorionic gonadotropin (hCG) level > 100 IU/ml), clinical pregnancy rate per ET (sonographic evidence of a gestational sac in the uterus), and viable pregnancy rates. These were calculated per transfer, per retrieval and per harvest. Patients were included if the fresh ET was deferred because of risk of ovarian hyperstimulation (serum E2 > 5000 pg/ml or 25 or more follicles demonstrated on ultrasound). A fresh transfer was also deferred if the endometrial thickness was < 8 mm on day of hCG injection [32] or if the endometrial echo pattern was homogeneous hyperechogenic [33, 34].

No predictions were made of pregnancy rate based on embryos that remained frozen as long as one fresh or frozen ET occurred. Patients were not included if no pregnancy had been achieved as yet, but frozen embryos from the oocyte retrieval remained.

Pregnancy rates were compared using chi-square analysis. A .05 level of significance was used.

Results

Table 1 provides the pregnancy rates per oocyte harvest. These data thus represent the odds that a woman will conceive according to age from one oocyte retrieval without having to proceed to a second oocyte retrieval.

Table 1. — *Pregnancy rate per oocyte harvest**.

	≤ 35	36-39	40-42	≥ 43
No. =	408	239	135	16
# chemical	329	160	59	6
% chemical	80.6	66.9	43.7	37.5
# clinical	301	143	46	6
% clinical	73.8	59.8	34.1	37.5
# viable/ongoing	265	109	34	4
% viable	65.0	45.6	25.2	25.0

* The rate included subsequent frozen ETs of embryos obtained on that one retrieval if a fresh ET did not occur or fresh ET did not result in pregnancy. Only one pregnancy/patient was allowed even if spontaneous abortion occurred. If a subsequent live pregnancy occurred from the same harvest after a spontaneous abortion it was not counted.

Table 2 provides the pregnancy rate per transfer when a fresh ET occurred. Thus patients deferring a fresh ET because of potential risk of ovarian hyperstimulation syndrome or inadequate endometrial thickness were not included. Also, these data would not include subsequent frozen ETs from that one oocyte harvest if either the fresh ET or even a subsequent frozen ET was not successful.

Table 3 provides another way of recording data according to the SART and that is pregnancy rate per retrieval. In this method if all embryos are cryopreserved, the cycle is counted as a failure to conceive. The data provided in Tables 2 and 3 have been reported to the SART and are listed in their annual report. The data is Table 1 are not included in the SART report.

By evaluating these data in this new manner of pregnancy rate per oocyte harvest the clinical and viable pregnancy rates for ages ≤ 35 were 39.3% and 38.8% higher than the category for clinical and viable pregnancy rate per transfer ($p < .001$), 26.4% and 25.6% higher for ages 36-39 ($p < .001$) and narrowed for the age group 40-42 (5.7% and 12.9% higher) (p = NS).

The pregnancy rate per transfer was significantly higher in clinical and viable pregnancy rates ($p < .05$) in the first three age categories up to age 42 than the pregnancy rate per retrieval.

Table 2. — *Pregnancy rate per transfer in cycles where fresh ET was performed*.*

	≤ 35	36-39	40-42	≥ 43
No. =	309	201	99	15
# chemical	179	106	42	3
% chemical	57.9	52.7	42.4	20.0
# clinical	163	95	31	3
% clinical	52.8	47.3	31.3	20.0
# viable/ongoing	145	73	23	3
% viable	46.9	36.3	23.2	20.0

*If fresh transfer was deferred to frozen ET that patient was not included.

Table 3. — *Pregnancy rate per retrieval*.*

	≤ 35	36-39	40-42	≥ 43
# retrievals	522	339	223	21
# pregnancies	201	125	52	3
% pregnancy/retrieval	38.5	36.9	23.3	14.3
# chemical	12	7	10	0
# clinical	181	114	39	3
% clinical/retrieval	34.7	33.6	17.5	14.3
# delivered or ongoing	162	89	25	3
% delivered or ongoing	31.0	26.3	11.2	14.3

*If fresh transfer was deferred for cryopreservation of all embryos, the patient was counted as a failure.

Discussion

The simplified freezing/one-step removal of cryoprotectant method used provides a better embryo survival when freezing occurs at the 2 pronuclear stage [31]. Thus, an IVF center emphasizing freezing at the 2 pronuclear stage and thus limiting the number of embryos allowed to cleave, would not have as many potential embryos to reach an 8-cell stage by day 3 or blastocyst by day 5. We only allow twice as many embryos intended for transfer to undergo cleavage.

Reporting to various registries including the SART for IVF-ET centers is somewhat unique in the medical field. One of its purposes is to allow a couple to make their best cost-effective choice. However, evaluating pregnancy rates following ET of fresh embryos for an IVF center performing limited deselection as described above compared to one allowing all embryos to cleave is not fair and the patient would be unaware of this difference in embryo selection the way things are presently recorded. However, evaluating the pregnancy rates per harvest would allow more appropriate comparisons between these two centers.

Typically, the younger the patient, the more oocytes retrieved, and the more embryos made. Thus, it is not surprising that the difference in clinical and viable pregnancy rates per oocyte harvest vs per embryo transfer narrows with advancing age because there would be less frozen embryos available for subsequent ET.

A younger woman is more apt to freeze all oocytes because of a greater risk of ovarian hyperstimulation syndrome, so it is not surprising that in the category of pregnancy rate per retrieval the younger group, who had the best pregnancy rate per oocyte harvest, did not show any differences compared to the group aged 36-39.

The new proposed method of pregnancy rate per oocyte harvest would not only help to better compare the success of different IVF centers, but would allow one center comparing two different techniques a better way to assess the outcome. For example Plachot *et al.* compared day 2 to day 5 transfers [23]. The pregnancy rates were similar (41.7% for day 2 vs 38% for day 5) but there were significantly more cycles with cryopreservation (63.3%) on day 2 than day 5 (46.7%). The reader is left to speculate that the pregnancy rate per harvest might be higher with day 2 transfer because of more frozen embryos available. However, there have been some recent studies suggesting higher pregnancy rates after transferring thawed blastocysts than cleavage stage embryos [35]. The reader would not have to speculate as to which technique is overall more efficacious in achieving the ultimate goal, i.e., a live pregnancy, if the data had been analyzed according to the newly proposed method of pregnancy rate per harvest or chance that a successful pregnancy would be achieved from one oocyte retrieval without having to proceed to a second retrieval.

Unfortunately, some of the goals of achieving the highest pregnancy rate per transfer without caring about the pregnancy rate per harvest may be financially motivated. Competition among IVF centers may cause some to do whatever they can to have the highest pregnancy rate per transfer to attract clients even at the potential sacrifice of the overall pregnancy rate per harvest since the patient focuses on pregnancy rate per transfer. Some centers have almost abandoned their cryopreservation program to search for the "best embryos" to transfer. Some centers have wrongly used the SART statistic of pregnancy rate per retrieval by sending copies of recent comparative statistics among IVF centers to potential referring physicians, but only including the category pregnancy rate per retrieval, probably to make competing IVF centers that frequently defer fresh transfer in favor of frozen ET to look inferior. We propose that emphasis on using this new method of pregnancy rate per oocyte harvest will take a giant step to allow much better interpretation of statistics and inter-IVF center comparisons.

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