

Outcome of in vitro fertilization-embryo transfer according to age in poor responders with elevated baseline serum follicle stimulation hormone using minimal or no gonadotropin stimulation

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Summary

Purpose: To determine whether decreased ovarian reserve or advancing age are more associated with decreased oocyte quality.

Methods: Women with baseline serum follicle stimulating hormone (FSH) > 12 mIU/ml who demonstrated previous poor response to controlled ovarian hyperstimulation (COH) had oocyte retrieval without gonadotropin stimulation in natural cycles or with minimal stimulation (maximum 75 IU gonadotropins) without agonists or antagonists were evaluated following in vitro fertilization-embryo transfer.

Results: The ongoing/delivered pregnancy rates were 27.3%, 30.8%, 21.7%, and 0.0%, respectively, with a mean of 1.06 embryos per transfer. The implantation rates were 33.3%, 28.6%, 14.7%, and 6.0%. Approximately half of the retrievals resulted in failed fertilization.

Conclusion: Using these minimal or no drug COH regimens in a difficult group of women, age was found to be a more adverse infertility factor than elevated serum FSH.

Key words: Oocyte reserve/quality; Hypergonadotropism; Follicle stimulating hormone; Natural oocyte retrieval.

Introduction

There are data suggesting that patients with elevated baseline serum follicle stimulation hormone (FSH) age \leq 39 have a reasonable chance of conceiving without in vitro fertilization (IVF) with correction of ovulatory dysfunction [1]. However, the outcome was far more bleak for older women age \geq 40. Similar conclusions were reached with patients having IVF-embryo transfer (ET), i.e., that age is a better predictor of pregnancy potential than basal FSH levels [2, 3]. The present study evaluated the outcome according to age in women with elevated baseline serum FSH who needed IVF where no or minimal stimulation with gonadotropins were used.

Materials and Methods

This study evaluated the efficacy of IVF-ET with no or minimal gonadotropins stimulation in women with elevated baseline serum FSH levels requiring IVF-ET for tubal or male factor or unexplained infertility but who had a history of failing to stimulate multiple follicles with previous controlled ovarian hyperstimulation attempts.

The study consisted of women who initiated IVF-ET cycles in other IVF facilities but had the controlled ovarian hyperstimulation stopped because of inadequate response. All women had a serum FSH > 12 mIU/ml. In vitro fertilization embryo transfer

was considered as appropriate therapy because of tubal or male factor or unexplained infertility.

Some women merely observed follicular maturation and then had oocytes retrieved 33-36 hours from the initiation of the luteinizing hormone (LH) surge (urinary LH obtained every 4 hours once a follicle reached 17 mm). If in a completely unstimulated cycle a follicle reached 18 mm with a serum E2 > 200 pg/ml without an LH surge as yet then 10,000 U of human chorionic gonadotropin (hCG) was given and retrieval occurred 34-36 hours later. Sometimes an LH surge occurred without the precise time of initiated rise noted so the best estimated time of retrieval was performed based on the change in LH, change in serum E2, and change in serum P. In circumstances where there was question of a sufficient time interval from LH surge to retrieval, intracytoplasmic sperm injection (ICSI) was performed to determine more precisely oocyte maturity. Germinal vesicle stage or metaphase I oocytes were cultured one more day before ICSI was performed and the embryos were then cryopreserved. The cycle was counted as failure to proceed to transfer if the embryo was cryopreserved and not transferred. Some women added 75 IU of gonadotropins (FSH or hMG) once the serum E2 was \geq 80 pg/ml and/or when a 12 mm follicle was attained.

The clinical, ongoing/delivered PRs and implantation rates were determined according to four different age groups - group 1 (\leq 35), group 2 (36-39), group 3 (40-42), and group 4 (\geq 43).

The policy of natural or minimal stimulation followed by oocyte retrieval under these circumstances was approved by the 12 member panel of the ethics committee for the Cooper Institute for Reproductive Hormonal Disorders. Formal IRB approval was not sought since reporting the results according to FSH and age group is merely anecdotal.

Results

The percentage of women who had a retrieval but had failed fertilization was 50.5% for group 1, 52.0% for group 2, 47.7% group 3 and 55.9% for group 4 (Table 1). The clinical pregnancy rates per retrieval were 8.3%, 11.4%, 7.6% and 1.8%, respectively ($p = .108$). The corresponding delivery rates per retrieval were 5.1%, 11.4%, 7.6%, and 0.0% ($p = .014$). The first three groups had similar rates and the fourth was lower. Some embryos were cryopreserved for future use. Transfers of fresh embryos occurred in 31.4% (11/35), 27.1% (13/48), 34.3% (23/67) and 22.9% (25/109) (Table 1). The reasons for no transfer included absence of any oocytes retrieved, failure to fertilize, immature or atretic oocytes, and abnormal embryos that did not cleave. The mean serum baseline FSH (mIU/ml) for the four groups was 19.7 ± 7.1 , 20.6 ± 7.5 , 18.8 ± 5.7 and 21.9 ± 8.3 .

The clinical (ultrasound evidence) PRs per transfer according to group was 36.4%, 30.8%, 21.7%, and 8%, respectively (Table 1). The ongoing/delivered PRs per transfer according to group were 27.3%, 30.8%, 21.7%, and 0.0%, respectively (Table 1). When considering the clinical pregnancy rate per transfer there was no significant difference in rates per transfer ($p = 0.18$). There was, however, a significant difference in delivery rates per transfer ($p = .042$). The first three groups were the same and the fourth was lower.

The mean number of embryos transferred was 1.06. The implantation rates according to group were respectively, 33.3%, 28.6%, 14.7%, and 6.1% ($p = .08$) (Table 1). Natural rather than minimal stimulation was used in 62.8% (22/35) group 1 cycles vs 70.8% (34/48) for group 2, vs 61.2% (41/67) for group 3 vs 56.7% (38/67) for group 4.

Table 1. — Outcome following embryo transfer after natural or minimal stimulation protocols.

	Totals	Age ≤ 35	Age 36-39	Age 40-42	Age ≥ 43
# cycles	259	35	48	67	109
# transfers	72	11	13	23	25
# pregnancies	18	4	5	7	2
# clinical pregnancies	15	4	4	5	2
% clinical pregnancies	20.8	36.4	30.8	21.7	8.0
# delivered	12	3	4	5	0
% delivered	16.7	27.3	30.8	21.7	0.0
# embryos transferred	93	12	14	34	33
# implanted	15	4	4	5	2
% implanted	16.1	33.3	28.6	14.7	6.1
# chemical pregnancy	1	0	1	0	0
# ectopic pregnancy	2	0	0	2	0
# spontaneous abortions	3	1	0	0	2
# patients freezing					
all embryos	51	6	10	12	23
# patients no transfer -					
no cryo*	136	18	25	32	61
# no eggs retrieved	50	5	11	12	22
# no fertilization	64	9	11	14	30
# immature or atretic -					
no insemin	14	3	2	4	5
# abnormal embryos -					
no cleavage	8	1	1	2	4

*cryo =

Discussion

The present model clearly demonstrates that the presence of decreased oocyte reserve, as manifested by increased baseline serum FSH levels, is not associated with poor oocyte quality as demonstrated by the ongoing/delivered pregnancy rates per transfer and implantation rates that are comparable to patients with normal baseline FSH levels in most IVF centers at least to age 42. Age, especially ≥ 43 , is associated with poor outcome at least when the serum FSH is increased.

Though some studies with controlled ovarian hyperstimulation (COH) and IVF-ET have reached the same conclusions [2, 3], there are other studies that have reached opposite conclusions [4]. We believe that the model used in this study may provide a more accurate assessment since it eliminates the potential complicating factor of the COH regimen on the uterine environment [5-8]. Theoretically an adverse effect of COH could increase with advancing age.

These data also serve as a reference source for patients who have diminished oocyte reserve and need IVF-ET to achieve pregnancy. They need to weigh the importance of achieving a live pregnancy with their own oocytes with a success rate of $< 10\%$ per retrieval vs approximately 50% seen with most donor oocyte programs.

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