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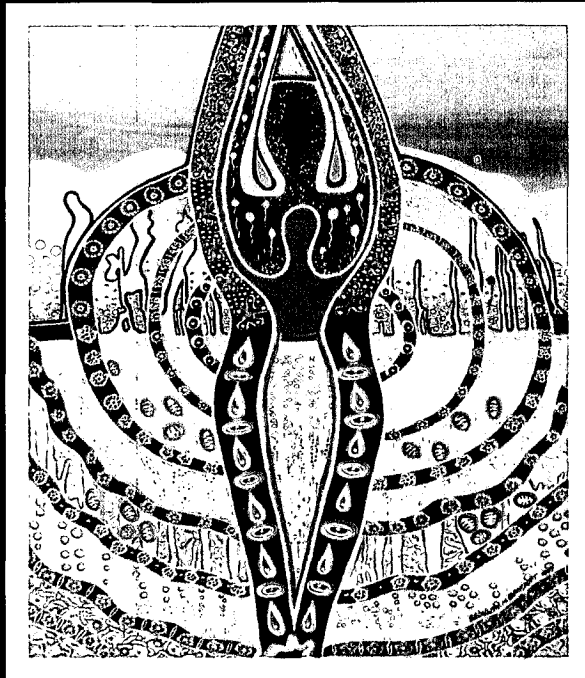
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In Vitro Fertilization-Embryo Transfer (Ivf-Et) Can Be Successful in Women Over Age 40

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Summary

This study reported the clinical outcomes of series of IVF-ET cycles in women aged ≥ 40 years old following the introduction of the use of ultrasound guided ET in conjunction with variations of the follicular phase leuprolide-acetate (LA)/gonadotropin stimulation protocol. Seventy-four women underwent stimulation with a reduced dosage of LA in the follicular phase (group 1), 61 used the standard dosage of LA (group 2). Oocyte retrieval was performed if at least 1 follicle matured. Choice of protocol was based on baseline FSH levels and prior history of ovarian response. The gonadotropins used were the same in both groups. The viable pregnancy rates per transfer were 35.5% in group 1, and 29.2% in group 2. The respective implantation rates were 14.4% and 11.6%. Older women should be given an opportunity to undergo IVF and should not be excluded on the basis of age.

Introduction

One of the largest studies on in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) in women age ≥ 40 found a significantly reduced pregnancy rate (PR) following fresh embryo transfer (ET) compared to those ≤ 39 (1). Many IVF centers demonstrate much lower PRs and implantation rates following frozen/thawed ET versus fresh ET irrespective of

age. It thus stands to reason that PRs following frozen/thawed ET in women age ≥ 40 might be quite low. In fact, Karlstrom et al reported a delivery rate per transfer of frozen/thawed embryos of 19% for women < 40 versus only 5% for those ≥ 40 (2).

There have been many improvements in the IVF procedure since the cases reported in the two aforementioned studies so that most centers have reported significant improvements in their overall PRs following IVF. The study presented here evaluated PRs in women age ≥ 40 (since changes in various techniques in our IVF program has resulted in marked improvement in PRs and implantation rates) to see if this older group has also benefitted from new technology.

Materials and Methods

A retrospective review of all IVF stimulation cycles between 1/1/97 and 8/31/98 at the Cooper Center for IVF was conducted. All patients who were ≥ 40 years old at the time of ovarian stimulation were included in the study. All patients were informed that because of their age, the possibility existed that they would produce fewer oocytes than younger women would and they were prepared to undergo oocyte retrieval even if only 1 mature follicle was present.

The baseline follicle stimulating hormone (FSH) levels and prior history of response to ovarian stimulation determined the ovarian stimulation protocol for women 40 years old and over. In the standard protocol (short flare), leuprolide (.75mg = 0.15 cc/day) was administered beginning on day 2 of the cycle and was continued until the day of human chorionic gonadotropin (hCG). Gonadotropin therapy began on day 5 and continued until 1 or more follicles reached a mean diameter greater than 20mm; then 10,000U of hCG was administered. In the reduced protocol, the leuprolide dosage was reduced by diluting it 1:20 with normal saline. Gonadotropin stimulation was as indicated above.

All embryos were transferred 3 days after oocyte retrieval. Assisted hatching was performed prior to transfer even on frozen/thawed embryos (3). Embryo freezing was performed as previously described (4).

The outcome measures evaluated were number of oocytes retrieved, fertilization rate, viable PRs (viable past first trimester), and implantation rates (number of gestational sac/embryo transferred). Data were presented as median (minimum-maximum) or percentages as appropriate.

Results

The median age was 42 (range 40-49) in the reduced LA group and 41 (range 40-48) in the standard LA group. Median baseline serum FSH levels were 7 mIU/mL (range 1-37) in the reduced group and 7 mIU/mL (range 2-18) in the standard group. The median number of oocytes retrieved was

higher in the standard group (9 vs 4).

Of the 74 cycles in the reduced LA group, 45 culminated in ETs. Seventeen patients had poor fertilization, 2 were at risk of ovarian hyperstimulation syndrome and deferred transfer, 5 had premature luteinization and retrieval was canceled, and 5 had inadequate endometrial lining (<8mm)

Table 1 - Comparison of IVF-ET outcome for older women by stimulation protocol used

	<i>Micro-flare (n=74)</i>	<i>Short-flare (n=61)</i>
<i>Age*</i>	<i>(40-49) 42</i>	<i>(40-48) 41</i>
Baseline bloods (day 2 of cycle)*		
E2 (pg/mL)	(3-69) 20.0	(10-242) 24
P (ng/mL)	(.1-29.0) .2	(.1-2.1) .4
LH (mIU/mL)	(1-32) 4	(.1-25.0) 4.0
FSH (mIU/mL)	(1-37) 7	(2-18) 7
Mid-cycle bloods (day of hCG)*		
E2 (pg/mL)	(204-6912) 1137	(209-5803) 1396
P (ng/mL)	(0.0-6.4) .7	(.1-6.2) .7
LH (mIU/mL)	(1-10) 5.6	(.6-8.0) 5.0
FSH (mIU/mL)	(2-47) 21	(10-40) 21.0
Stimulation response		
No. follicles	(1-28) 7	(2-47) 8
No. oocytes retrieved	(1-27) 5	(1-26) 9
Fertilization rate	(0-100) 50.0	(0-100) 57.0
No. of deferred transfers	29	13
Risk of OHSS	2	2
Pre-mature luteinization	5	1
Thin endometrial lining	5	3
Poor fertilization	17	7
No. of embryo transfer cycles	45	(1-6)4
No. of embryos transferred*	48	(1-7)4
Clinical pregnancy rates/retrieval	21.6% (16/74)	22.9% (14/61)
Clinical pregnancy rates/transfer	35.5% (16/45)	29.2% (14/48)
Implantation rates	14.4% (22/153)	11.6% (22/190)
Frozen ET cycles		
No. transfers	8	12
Pregnancy rates	50.0% (4/8)	25.0% (3/12)
Implantation rates	23.5% (8/34)	10.4% (5/48)

* Data presented as (minimum-maximum) median

and deferred transfer. In the standard group, 48 out of the 61 cycles culminated with ET. In 7 cycles, there was poor fertilization; 2 transfers were deferred because the patient was at risk of ovarian hyperstimulation syndrome, 1 had premature luteinization and 3 had poor endometrial linings.

The outcome of the IVF-ET cycles is summarized in Table 1. In both groups the median number of embryos transferred was 4. In the reduced LA group, the viable PR per transfer was 35.5% with an implantation rate of 14.4%. In the standard group, the PR per transfer was 29.2% with an implantation rate of 11.6%.

Within the time framework of the study, there were 8 frozen ETs in the reduced LA group and 12 frozen ET cycles in the standard group. The resultant PRs and implantation rates were respectively 50% and 23.5% in the reduced group and 25.0% and 10.4% in the standard group.

Conclusions

The data presented here suggest that improvements in IVF technology have resulted in marked improvement in PRs and implantation rates for women age 40 and over. It should be noted that this study did not exclude women with elevated baseline serum FSH levels so the results could have been even higher if this poor risk group was excluded.

Though the numbers were small, it would appear that embryos from older patients also withstand the rigors of embryo freezing and thawing.

Overall only 30 of 93 (32.2%) cycles did not have immediate ET related to poor fertilization or premature luteinization. Some of these patients who failed to go to transfer on the retrieval cycle still had some embryos cryopreserved for future transfers.

References

- [1] BOPP BL, ALPER MM, THOMPSON IE, MORTOLA J. Success rates with gamete intrafallopian transfer and in vitro fertilization in women of advanced maternal age. *Fertil Steril* 63:1278-83, 1995.
- [2] KARLSTROM PO, BERGH T, FORSBERG AS, SANDKUIST U, WIKLAND M. Prognostic factors for the success rate of embryo freezing. *Hum Reprod* 12:1263-6, 1997.
- [3] CHECK JH, HOOVER L, NAZARI A, O'SHAUGHNESSY A, SUMMERS D. The effect of assisted hatching on pregnancy rates after frozen embryo transfer. *Fertil Steril* 65:254-7, 1996.
- [4] BAKER AF, CHECK JH, HOURANI CL. Survival and pregnancy rates of pronuclear stage human embryos cryopreserved and thawed using a single step addition and removal of cryoprotectant. *Hum Reprod Update* 2, (CD-ROM) item 12, 1997.

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