Pregnancy Rates in Older Poor Responders Who Achieve Embryo Transfer in Long Down-Regulated ART Cycles Are Comparable to Those in Younger Poor Responders

Tevfik Yoldemir, MD,[1,2] Ian S. Fraser, MD[1]

[1]Fertility Unit, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia

[2]Marmara University, School of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey

Abstract

Objective: To determine whether older women with a poor response to follicular stimulation achieve pregnancy results that are comparable to those of younger poor responders.

Methods: Two hundred five women undergoing in vitro fertilization treatment at the Fertility Unit in the Royal Prince Alfred Hospital in Sydney, Australia were selected for retrospective cohort analysis. The outcomes in women > 38 years of age with < 5 oocytes retrieved were compared with those in women ≤ 38 years who also had < 5 oocytes retrieved. Clinical and ongoing pregnancy rates were compared.

Results: Implantation rates (21.01 ± 0.38 % vs. 12.82 ± 0.27%, *P* = 0.11) and clinical pregnancy rates (25.71 ± 0.44% vs. 20.21 ± 0.40%, *P* = 0.41) were similar in the two groups following cleavage stage embryo transfer. The same was true for blastocyst stage embryo transfer (implantation rates 16.67 ± 0.33% vs. 13.89 ± 0.33%, *P* = 0.80, and clinical pregnancy rates 23.81 ± 0.44% vs. 16.67 ± 0.38%, *P* = 0.59). Ongoing pregnancies beyond the 12th week of gestation were also comparable between cleavage stage (24.28 ± 0.43% vs. 16.84 ± 0.34%, *P* = 0.24) and blastocyst stage embryo transfers (23.81 ± 0.44% vs. 11.11 ± 0.32%, *P* = 0.32).

Conclusion: If older poor responders reach the stage of embryo transfer, they can achieve pregnancy rates similar to those of younger poor responders when matched numbers of embryos are transferred.

Key Words: Poor responder, age, pregnancy, embryo transfer

Competing Interests: None declared.

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Résumé

Objectif : Déterminer si les femmes âgées qui réagissent faiblement à la stimulation folliculaire obtiennent des résultats de grossesse comparables à ceux des femmes qui réagissent tout aussi faiblement à cette stimulation, mais qui sont plus jeunes.

Méthodes : Deux cent cinq femmes subissant un traitement de fécondation *in vitro* au sein de la *Fertility Unit* du *Royal Prince Alfred Hospital* à Sydney, en Australie, ont été sélectionnées en vue d'une analyse de cohorte rétrospective. Les issues chez des femmes de plus de 38 ans comptant moins de cinq ovocytes récupérés ont été comparées à celles qui ont été constatées chez des femmes de 38 ans ou moins qui comptaient également moins de cinq ovocytes récupérés. Les taux de grossesse clinique et en cours ont été comparés.

Résultats : Les taux d'implantation (21,01 ± 0,38 % vs 12,82 ± 0,27 %, P = 0,11) et les taux de grossesse clinique (25,71 ± 0,44 % vs 20,21 ± 0,40 %, P = 0,41) étaient semblables dans les deux groupes à la suite du transfert d'embryons en étant au stade de la segmentation. Cela était également vrai pour ce qui est du transfert d'embryons en étant au stade du blastocyste (taux d'implantation 16,67 ± 0,33 % vs 13,89 ± 0,33 %, P = 0,80, et taux de grossesse clinique 23,81 ± 0,44 % vs 16,67 ± 0,38 %, P = 0,59). Les grossesses en cours se situant au-delà de la 12e semaine de gestation étaient également similaires lorsque l'on a comparé les transferts d'embryons en étant au stade de la segmentation (24,28 ± 0,43 % vs 16,84 ± 0,34 %, P = 0,24) et les transferts d'embryons en étant au stade du blastocyste (23,81 ± 0,44 % vs 11,11 ± 0,32 %, P = 0,32).

Conclusion : Lorsque le nombre d'embryons transférés est le même et que les femmes âgées qui réagissent faiblement à la stimulation folliculaire atteignent l'étape du transfert d'embryons, ces femmes peuvent obtenir des taux de grossesse semblables à ceux que l'on constate chez les femmes qui réagissent tout aussi faiblement à cette stimulation, mais qui sont plus jeunes.

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INTRODUCTION

In the context of in vitro fertilization, there is no consistent definition of a "poor responder." The definition is usually based on the outcome of previous ovarian stimulation cycles but varies among parameters; these include measurements of serum estradiol, the number and size of follicles, and the dosage of follicle-stimulating hormone required to stimulate follicular growth.[1] The incidence of poor response to ovarian stimulation has been reported to vary from 9% to 24%.[2–4] Garcia et al.[5] described lower pregnancy rates in poor responders, compared with normal responders, following a standard ovarian stimulation protocol using human menopausal gonadotropins. Poor ovarian response has been shown to be a first sign of ovarian aging (early ovarian failure or early menopause).[6–8]

Numerous criteria have been used to characterize poor response. The number of developed follicles and/or number of oocytes retrieved after a standard-dose ovarian stimulation protocol are the most important criteria for defining poor ovarian response. The proposed number varies among authors, and ranges from fewer than three to fewer than five dominant follicles on the day of hCG administration,[9–11] and/or fewer than three to fewer than five retrieved oocytes.[12–14]

The lack of a uniform definition of "poor response" makes it difficult to compare treatment outcomes.[2] Since the number of embryos available for transfer directly influences IVF success rates,[15] a poor ovarian response reduces pregnancy rates.[16] Even though increasing the gonadotropin dose may increase follicular recruitment, this may not lead to higher pregnancy rates.[9,17] Lamazou et al.[18] defined poor prognostic criteria as follows: patient age > 38 years, antral follicle count < 10 on cycle day 3, and day 3 serum FSH levels > 10 IU/L. Accordingly, we decided to compare the pregnancy outcomes of women aged ≤ 38 years who develop fewer than five follicles following ovarian stimulation with those in women aged > 38 years who also developed fewer than five follicles.

ABBREVIATIONS

E_2	estradiol
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
hMG	human menopausal gonadotropin
ICSI	intracytoplasmic sperm injection
LH	luteinizing hormone
rFSH	recombinant follicle-stimulating hormone

MATERIAL AND METHODS

Two hundred five women undergoing in vitro fertilization treatment at the Fertility Unit in the Royal Prince Alfred Hospital in Sydney, Australia were selected for retrospective cohort analysis. All poor responder cycles (i.e., resulting in fewer than 5 oocytes retrieved) in a five-year period (1998 to 2002) that resulted in embryo transfer were included. The cohort was divided into two groups: women ≤ 38 years of age and women > 38 years of age. Exclusion criteria were irregular menstrual periods, cycle day 3 serum FSH level > 12 IU/L, endometriosis (other than minimal), BMI > 28 kg/m^2, the presence of only one ovary or previous ovarian surgery, a basal antral follicle count > 7, polycystic ovary syndrome or other endocrine disorder, ultrasound evidence of polycystic ovaries, exposure to study drugs within three months of participation in the study, and cycles in which no embryos were transferred.

All women undergoing ovulation induction for IVF or intracytoplasmic sperm injection had routine pituitary down-regulation with nafarelin acetate (Synarel nasal spray, Searle, Monsanto Australia Ltd, Melbourne, Australia) three puffs/day, starting from the 21st day of the preceding cycle in the long down regulation protocol.[19] The nafarelin dose was lowered to two puffs/day once gonadotropin injections began and continued to the day of hCG administration. After two weeks of nafarelin therapy, serum levels of E_2, progesterone, and luteinizing hormone were measured to confirm pituitary down-regulation before ovulation induction began. Daily subcutaneous injections of 150 to 300 IU recombinant follicle-stimulating hormone (Puregon, Organon Schering-Plough Pty. Ltd, North Ryde, Australia) were given. The initial daily gonadotropin dose was 150 IU rFSH for women younger than 25, 200 IU for women between 25 and 35, and 300 IU for women over the age of 35. The gonadotropin dose remained constant during stimulation. When one or two follicles of at least 18 mm mean diameter were identified during ultrasound scanning, 5000 IU hCG (Profasi, Serono Lab. Ltd., Sydney, Australia) was administered. At 36 hours after hCG administration, oocytes were retrieved under transvaginal ultrasound guidance. Aspiration of follicles was performed with the patient in a sedated but conversant state.

The sperm and oocytes were prepared for fertilization in vitro, either naturally or using ICSI. The fertilized eggs were cultured in small-chamber bench-top "mini" incubators (K-MINC-1000, Cook IVF, Eight Mile Plains, Australia), together with a proprietary culture medium (SIVF culture medium, Cook IVF, Australia). Cleavage occurred in a medium supported by pyruvate, but with zero or low glucose concentrations and with a continuous

flow of 6% carbon dioxide and 5% oxygen in nitrogen. Embryos for extended culture were transferred to 10 μL microdrops of SIVF blastocyst culture medium covered by 0.5 mL mineral oil on the third day after retrieval.

Luteal phase support was provided by 150 mg vaginal progesterone pessaries (USP, Sigma, St Louis, MO) starting three days after oocyte retrieval. Fresh embryo transfer was carried out on either the third or fifth day after retrieval. Day three embryos with > 7 cells and grade 0–1 fragmentation, and cavitating blastocysts with a discrete, compact inner cell mass and good trophectoderm cell numbers were considered to be the optimal quality embryos for transfer. All embryo transfers were performed using a standard embryo transfer catheter (K-JETS-6019-SIVF, Cook, Australia).

Serum levels of E_2, progesterone, FSH, LH, and hCG were measured by an ACS180 chemoluminescent immunoassay system (Bayer Diagnostics, North Ryde, Australia). Pregnancy was confirmed by assay of serum hCG 12 days after the embryo transfer. The implantation rate was determined by the number of gestational sacs seen on ultrasound examination. Clinical pregnancy was defined as the presence of fetal heart activity on vaginal ultrasound seven weeks after embryo transfer. Implantation rates and clinical and ongoing pregnancy rates per transfer were calculated for cleavage stage and blastocyst stage transfer cycles in the ≤ 38 years and > 38 years groups.

All statistical analyses were performed using StataSE 9.2 software (Statacorp, College Station, TX). For the whole group statistical evaluation, the Student *t* test was used; $P < 0.05$ was considered significant. The skewness–kurtosis normality test was used to check data for normal distribution. The skewness was between zero and +½, indicating that the distribution of data was approximately symmetric. Multivariable logistic regression modelling was used to compute the odds ratios of variables predictive of clinical and ongoing pregnancies. The independent variables were age, serum E_2 level on the day of hCG administration, duration of stimulation, total FSH dose for ovarian stimulation, number of oocytes collected, and number of embryos transferred. We calculated that in order to detect a difference of 15% in clinical pregnancy rates between the groups, 92 patients were needed in each group, accepting a type I error as 0.05 with power of 70%.

Patients gave written consent to follow-up and publication of aggregate data. Ethical approval for this study was not required and has not been included because there were no interventions that are not a part of standard care. All practices and protocols conformed to ethical requirements for assisted reproductive technology programs stipulated by the National Health and Medical Research Council of Australia.

RESULTS

There were 113 women in the > 38 years group and 92 women in the ≤ 38 years group. No woman was included more than once in the cohort. In the > 38 years group, 64 IVF cycles and 28 ICSI cycles were completed. In the ≤ 38 years group, there were 79 IVF cycles and 34 ICSI cycles. In the > 38 years group the causes of infertility were male factor (28%), tubal factor (17%), minimal endometriosis (10%), ovulatory factor (7%), or unexplained (27%). The corresponding proportions in the ≤ 38 years group were 28%, 21%, 6%, 6%, and 28%. The duration of stimulation and the mean serum E_2 levels on the day of hCG administration were similar between the groups. The mean total FSH used for ovarian stimulation was higher in the > 38 years group than in the ≤ 38 years group (3758 ± 1165 IU vs. 2929 ± 1247 IU; $P < 0.001$). The mean number of oocytes retrieved was higher in the ≤ 38 years group than in the > 38 years group (3.21 ± 0.84 vs. 2.65 ± 1.05; $P = 0.02$), and the mean number of fertilized oocytes in the ≤ 38 years group was also higher (2.21 ± 0.95 vs. 1.78 ± 0.78; $P < 0.005$) (Table 1).

The mean number of embryos transferred on either day 3 or day 5 did not differ between groups (Table 1). Implantation and clinical pregnancy rates were similar between the groups when cleavage stage embryo and blastocyst transfers were compared. Ongoing pregnancies beyond the 12th week of gestation were also similar (Table 2). The clinical pregnancies that did not continue were all miscarriages.

The multivariate analysis showed no association between the rate of clinical pregnancy and age (OR 0.94; 95% CI 0.85 to 1.04, $P = 0.22$), serum E_2 level on the day of hCG administration (OR 0.99; 95% CI 0.99 to 1.00, $P = 0.17$), duration of stimulation (OR 1.13; 95% CI 0.92 to 1.39, $P = 0.23$), total dose of FSH used (OR 0.99; 95% CI 0.99 to 1.00, $P = 0.81$), number of oocytes retrieved (OR 1.24; 95% CI 0.72 to 2.14, $P = 0.43$), or number of blastocysts transferred (OR 1.33; 95% CI 0.25 to 7.15, $P = 0.74$). There was no association between the rate of ongoing pregnancy and age (OR 0.91; 95% CI 0.83 to 1.00, $P = 0.07$), serum E_2 level on the day of hCG administration (OR 0.99; 95% CI 0.99 to 1.00, $P = 0.33$), duration of stimulation (OR 1.11; 95% CI 0.91 to 1.37, $P = 0.30$), total dose of FSH used (OR 1.00; 95% CI 0.99 to 1.00, $P = 0.81$), number of oocytes retrieved (OR 1.09; 95% CI 0.63 to 1.90, $P = 0.74$), or the number of blastocysts transferred (OR 3.22; 95% CI 0.36 to 28.57, $P = 0.29$) (Table 3).

Table 1. The characteristics of the study groups

	Women ≤ 38 years (n = 92)	Women > 38 years (n = 113)	*P*
Mean age, years	33.9 ± 3.8 (33.1 to 34.7)	41.7 ± 1.8 (41.4 to 42.0)	< 0.001
Day 3 FSH, IU/L	5.90 ± 1.57 (5.56 to 6.23)	7.12 ± 2.81 (6.60 to 7.65)	< 0.001
BMI, kg/m^2	26.03 ± 6.26 (24.82 to 27.25)	26.66 ± 6.81 (24.82 to 27.25)	0.46
IVF cycles, n	64	79	
ICSI cycles, n	28	34	
Duration of stimulation, days	12.1 ± 2.5 (11.6 to 12.6)	12.0 ± 2.0 (11.6 to 12.3)	0.67
Mean serum E_2 level on day of hCG administration, pmol/L	2898 ± 1742 (2520 to 3276)	2850 ± 2042 (2457 to 3243)	0.86
Total dose of FSH, IU	2929 ± 1247 (2667 to 3192)	3758 ± 1165 (3535 to 3981)	< 0.001
Mean number of oocytes retrieved	3.21 ± 0.84 (3.03 to 3.38)	2.65 ± 1.05 (2.46 to 2.85)	< 0.001
Mean number of fertilized oocyte per retrieval	2.21 ± 0.95 (1.92 to 2.32)	1.78 ± 0.78 (1.63 to 1.92)	0.005
Mean number of embryos transferred at cleavage stage	1.64 ± 0.51 (1.52 to 1.76)	1.58 ± 0.62 (1.45 to 1.71)	0.51
Mean number of embryos transferred at blastocyst stage	1.57 ± 0.51 (1.34 to 1.80)	1.61 ± 0.70 (1.26 to 1.96)	0.84

Most values are given as mean ± standard deviation (95% CI).

DISCUSSION

A poor ovarian response to gonadotropin stimulation has been associated with a reduced chance of pregnancy in the current treatment cycle, as well as in subsequent cycles, and may be indicative of ovarian reserve in both the quantitative and the qualitative senses.[20] The number of oocytes[21] and of embryos available for transfer directly influence IVF success rates.[22] In studies of poor ovarian response to stimulation, different numbers of follicles identified at the time of oocyte retrieval have been used to quantify a poor ovarian response; some investigators have used fewer than three follicles,[9] some fewer than four follicles,[11] and others fewer than five follicles.[13] We found that older women in whom fewer than five oocytes were retrieved had similar pregnancy rates to younger poor responders, provided that embryo transfer could be performed.

Previous studies have found no differences in the number of oocytes retrieved[13,23] and pregnancy rates[9,24] between women requiring higher doses of gonadotropins for an ovarian response and women requiring lower doses. Shulman et al.[24] reviewed a total of 813 ovarian stimulation cycles in poor responders, grouped according to the total dose of hMG used. Although fertilization rates were similar among these groups, the number of oocytes retrieved and pregnancy rates were significantly lower in women receiving > 5775 IU of hMG. Karande et al.[25] concluded that high-dose FSH stimulation at the onset of the menstrual cycle did not improve the IVF outcome in low-responder patients. In our study, even though the total FSH dose was higher in the older poor responders, the mean number of oocytes retrieved was lower than in the younger women. Similarly, rates of clinical and ongoing pregnancies were lower in the older group, but the difference was not statistically significant.

Although age is a significant predictor of success in fertility treatments,[26] Lashen et al.[27] reported similar cumulative pregnancy rates in their comparison between older (> 35 years) and younger (≤ 35 years) poor responders. The total gonadotropin dose administered, however, in older women was significantly higher despite a similar duration of stimulation. Our study confirms the conclusion of these authors that older women undergoing IVF should receive higher gonadotropin doses than younger women.

Since the number of embryos transferred was similar between the groups in our study, comparable pregnancy

Table 2. Clinical and ongoing pregnancy outcomes in groups

	Women ≤ 38 years (n = 92)	Women > 38 years (n = 113)	*P*
Number of cleavage stage embryo transfers	71	94	
Number of blastocyst stage embryo transfers	21	19	
Clinical pregnancy per cleavage stage transfer, n (%)	26 (25.71 ± 0.44)	19 (20.21 ± 0.40)	0.41
Clinical pregnancy per blastocyst stage transfer, n (%)	6 (23.81 ± 0.44)	3 (16.67 ± 0.38)	0.59
Implantation per cleavage stage transfer, n (%)	25 (21.01 ± 0.38)	21 (12.82 ± 0.27)	0.11
Implantation per blastocyst stage transfer, n (%)	6 (16.67 ± 0.33)	3 (13.89 ± 0.33)	0.80
Ongoing pregnancy per cleavage stage transfer, n (%)	23 (24.28 ± 0.43)	17 (16.84 ± 0.38)	0.24
Ongoing pregnancy per blastocyst stage transfer, n (%)	6 (23.81 ± 0.44)	2 (11.11 ± 0.32)	0.32

Percentages in parentheses are mean ± standard deviation.

Table 3. Multivariate analysis

	OR	*P*	95% CI
Clinical pregnancy rate			
Age	0.94	0.22	0.85 to 1.04
Serum E_2 level on hCG day	0.99	0.17	0.99 to 1.00
Duration of stimulation	1.13	0.23	0.92 to 1.39
Total dose of FSH used	0.99	0.81	0.99 to 1.00
Number of oocytes retrieved	1.24	0.43	0.72 to 2.14
Number of blastocysts transferred	1.33	0.74	0.25 to 7.15
Number of cleavage stage embryos transferred	3.38	0.004	1.46 to 7.84
Number of grade 1 embryos transferred	1.68	0.08	0.94 to 3.01
Ongoing pregnancy rate			
Age	0.91	0.07	0.83 to 1.00
Serum E_2 level on hCG day	0.99	0.33	0.99 to 1.00
Duration of stimulation	1.11	0.30	0.91 to 1.37
Total dose of FSH used	1.00	0.81	0.99 to 1.00
Number of oocytes retrieved	1.09	0.74	0.63 to 1.90
Number of blastocysts transferred	3.22	0.29	0.36 to 28.57
Number of cleavage stage embryos transferred	2.99	0.01	1.27 to 7.03
Number of grade 1 embryos transferred	1.58	0.13	0.87 to 2.86

rates could be achieved regardless of age, whether embryos are transferred at the cleavage stage or the blastocyst stage. Even though the mean number of fertilized oocytes was higher in the younger group, the mean number of embryos transferred either on day 3 or day 5 did not differ. Two previous studies showed that the number of embryos produced correlated with pregnancy rates in women > 40 years of age.[28,29] Roest et al.[29] compared cycles in women > 40 years of age and found that "good" ovarian response cycles yielded higher numbers of oocytes and pregnancy rates than "poor" ovarian response cycles. Although the older women in our study had fewer oocytes retrieved, the number of embryos transferred was similar to that in younger women. Hence we observed a trend towards diminished implantation and pregnancy rates, although the difference was not significant for comparable embryo transfers.

A limitation of our study was the cohort size and consequent limited statistical power. We considered a 15% difference in pregnancy rates clinically significant; however, demonstrating a 10% difference in rate (25% vs. 15%) would have required 270 women in each arm, accepting a type I error as 0.05 with the power of 80%. As a result, our findings need to be supported with future studies using greater sample sizes.

CONCLUSION

Older women who are poor responders to ovarian stimulation but who undergo embryo transfer after long protocol IVF treatment have pregnancy outcomes that are comparable to those of younger poor responders. Although we identified a trend towards higher rates of implantation, clinical pregnancy, and ongoing pregnancy in younger poor responders, the difference between the two groups did not reach statistical significance.

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