

AGE AS A PREDICTOR OF ASSISTED REPRODUCTIVE TECHNIQUES OUTCOME

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ABSTRACT

Objective: This study evaluated the effect of age on ovarian response to gonadotropin stimulation and the success of IVF & ICSI cycles.

Methodology: In this retrospective analytic study, 280 women undergoing first IVF & ICSI cycles were collected. Patients were divided in three groups: <35 years old, 35 - 39 years and e" 40 years old. Stimulation protocol for all patients was long standard protocol.

Results: There were significant decrease in the number of follicles, oocytes retrieved and embryos obtained with increasing age ($p < 0.05$). Fertilization rate did not differ significantly with increasing age ($P > 0.05$). Clinical pregnancy rate were 21.8% in patients < 35, 13.2% in patients 35-39 and 5.9% in e" 40 ($p = 0.157$) and live birth rate were 14.2% in patients < 35, 7.9% in 35-39 and 5.9% in e" 40 years old. ($p = 0.50$)

Conclusions: Clinical pregnancy rate & live birth rate diminished with increasing age.

KEY WORDS: IVF, ICSI, Clinical pregnancy, Live birth.

Pak J Med Sci April - June 2008 (Part-II) Vol. 24 No. 3 378-381

How to cite this article:

Karimzadeh MA, Ghandi S, Tabibnejad N. age as a predictor of assisted reproductive techniques outcome. Pak J Med Sci 2008;24(3):378-81.

INTRODUCTION

Virtually all clinicians are aware of the age – related diminution in reproduction potential of women. As women become older, their

chances of becoming pregnant decline.¹ On the other hand, current demographic trends towards delayed childbearing due to career or financial pressures, together with a rising divorce rate, have combined to produce an epidemic of infertility in women aged over 35 years. The age-related decline in reproductive potential is the principal factor contributing to the increase in the prevalence of infertility in Western society.² Recent extensive data link the age-related change in reproductive potential to follicular depletion and also diminished oocyte quality, factors which in aggregated are referred to as diminished ovarian reserve.^{2,3} A classic report on the effect of female age on fertility found that the percentage of women not using contraception who remained childless rose steadily according to their age at marriage.⁴ A sharp decline in pregnancy rate with advancing female age is noted with donor insemination studies⁵ and with associated repro-

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- * Received for Publication: February 8, 2008
- * Revision Received: February 11, 2008
- * Revision Accepted: March 18, 2008

ductive technologies (ART) including in vitro fertilization (IVF). The risk of spontaneous abortion increases with female age.⁶ Also, the percentage of clinical pregnancies that failed to result in a live birth rose according to the woman's age.⁷ The available evidence indicates that both the age-related decline in female fertility and the increase in risk of spontaneous miscarriage can be attributed to progressive follicular depletion and a high incidence of abnormalities in aging oocytes. Evidence derived from detailed cytogenetic analysis of oocytes retrieved for IVF that failed to fertilize, suggests that the global rate of oocyte aneuploidy increases with advancing age.⁸ Many infertile women will finally undergo assisted reproduction treatments for their infertility. Implicit in these techniques is the recruitment and development of multiple ovarian follicles in response to stimulation with exogenous gonadotropins. The ovarian ability to respond to gonadotropin stimulation by the recruitment of a cohort of follicles is central to success with treatments such as IVF & ICSI. The response achieved is a direct reflection of ovarian potential or ovarian reserve and is a function of the size of the pool of primordial follicles.^{9,10} This retrospective study is an attempt to assess the effect of age as a predictor of response to ovarian stimulation & pregnancy in assisted reproductive program.

METHODOLOGY

Study population: In the retrospective analytic study, 280 women undergoing IVF / ICSI cycles in our unit were collected between February 2003 to March 2006. Only women with first IVF & ICSI cycles were selected. Patients with a history of pelvic surgery, endometrioma larger than two cm in vaginal sonography and patients with severe endometriosis at laparoscopy were excluded from this study. Patients were divided in three groups: < 35 years old, 35 – 39 and ≥40 years old.

The number of follicles >15mm on the day of hCG administration, the number of retrieved oocytes, good quality oocytes, fertilized oocytes, embryos obtained, fertilization rate, clinical

pregnancy, live birth, abortion and cancellation rates were compared between these groups. Age was calculated as complete years on the day of starting ovarian stimulation.

Stimulation protocol: All patients were stimulated using long GnRH – a protocol with subcutaneous buserelin (Hoechst, Germany) that was started at a dose of 0.5cc daily from the day 21 of previous cycle and continued 0.25cc per day after the start of menses. Ovarian stimulation was performed using hMG (Menogon, Ferring, Germany) 150 – 375 IU per day from day two of treatment cycle. When at least three follicles e"18mm was observed by vaginal sonography, hCG (Daroupakhsh, Iran) 10,000 IU was administered and transvaginal oocyte retrieval was performed 36h later. Embryo transfer in all patients was performed in a similar fashion. Luteal phase was supported by using progesterone in oil 100mg per day for 14 days. Clinical pregnancy per treatment cycles was defined as the presence of fetal cardiac activity in sonography three weeks after embryos transferred. Cancelled cycles were defined as the cycles with no ovarian response. The cycles that was resulted to ovum pick up was defined as a normal cycles. Abortion was defined as the pregnancies ending before 24 weeks of gestation.

Data Analysis: The Statistical Package for the Social Sciences 15.0 software was used to analyse data of all patients. For the non-normal distribution of the data, Anova and X² tests were used when appropriate, for the small number of cases, Fisher's exact test was used for the comparison of frequencies. A p<0.05 was considered statistically significant.

RESULTS

In this analysis 280 women undergoing IVF/ ICSI were studied. Overall, clinical pregnancy rate was 19.6%, live birth rate was 12.9%, abortion rate was 25.4% and cancellation rate was 3.2%.

The mean number of follicles >15mm, retrieved oocytes, good quality oocytes, fertilized oocytes and embryos obtained decreased

significantly with increasing age ($p < 0.001$). Fertilization rate ($p = 0.635$) did not differ significantly between these groups. Cancellation rate increased significantly with increasing age ($p < 0.001$). Clinical pregnancy ($p = 0.157$) and live birth rate ($p = 0.504$) decreased with increasing age. The difference was not significant ($p > 0.05$).

Only one pregnancy occurred in age groups of ≥ 40 years old which was resulted in live birth and five pregnancies occurred in age groups of 35–39 years old that resulted in three live birth. Forty nine pregnancies occurred in age groups of < 35 years old that resulted in thirty two live birth and fourteen abortions. There was no significant differences in abortion rates between groups ($p = 0.502$). The total dose of gonadotropins required increased significantly with increasing age ($p < 0.001$).

In group one age less than 35 years live birth accounted for 14.2% while pregnancy rate was 21.8%. In group two age 35 – 39 years the live birth was 7.9% while pregnancy rate was 13.2%. In the third group age more than forty years, live birth as well as pregnancy both accounted for 5.9% each.

DISCUSSION

Woman’s age is considered as a prognostic factor when assisted reproduction treatment is proposed to infertile couples as a marked decline in success rate is observed as age increased.^{3,11,12} Oocyte donation has demon-

strated that age - related decline in female fecundity is due predominantly to ovarian rather than uterine factors, presumably due to a decrease in ovarian reserve.^{2,12} Success rates achieved with ART decline as age increases. The number of oocytes retrieved and embryos available are lower, embryo fragmentation rates are higher and implantation rates are lowering in older than younger women.^{13,14}

In our study the number of oocytes retrieved, good quality oocytes, oocytes fertilized and embryos obtained were significantly decreased with increasing age (Reflecting a reduction in follicular pool). Whereas the number of remaining ovarian follicles decline with increasing age, more rapidly after approximately age 37, observations in stimulated cycles suggest that aging follicles also become progressively less sensitive to gonadotropins. As age increases, the total dose and duration of treatment required to stimulate multiple follicular development increase. Thus the quality and quantity of oocytes decreases with increasing age. With increasing age ovarian follicles pool reduces, reflecting the smaller cohorts of follicles that can be recruited to respond.¹⁵

In our study like the studies mentioned above, the total dose of gonadotropins increased significantly with increasing age and the number of follicles > 15 mm on the day of hCG decreased significantly with increasing age. Clinical pregnancy and live birth rate

Table-I: The characteristics of women under investigation regarding their age

≥ 40 age (n=17)	of 35-39 age (n=38)	< 35 age (n=225)	Variables
4.45±38.88	2.18±32.16	24.66±3.42	Total dose of gonadotropins (Ampoules)
3.07± 3.29	3.38± 7.16	10.66 ± 5.09	Number of follicles > 15 mm
2.24± 2.61	3.04± 5.05	8.14 ± 4.29	Number of oocytes retrieved
1.41±2.18	2.60± 2.97	4.83 ± 3.14	Number of good quality oocytes
1.76±2.43	1.74±3.24	5.46 ± 3.07	Number of oocytes fertilized
1.76±2.43	1.73±3.16	5.31 ± 3.02	Number of embryos obtained
40.05±70.00	24.49±72.48	70.75 ± 21.96	Fertilization rate (%)
5.9 (1/17)	13.2 (5/38)	21.8(49/225)	Clinical pregnancy rate (%)
5.9 (1/17)	7.9 (3/38)	14.2 (32/225)	Live birth rate (%)
52.9 (9/17)	0	0	Cancellation rate (%)
0	0	28.5	Abortion rate (%)

decreased with increasing age. The differences were not significant because of small sample size. By using exclusion criteria as mentioned at first, we had limited cases. Cancellation rate significantly increased with increasing age. One half of the treatment cycles in women ≥ 40 years old were cancelled. This shows poor prognosis in this age group. The lower pregnancy rates seen in older women seem to be due partly to a worsening response to superovulation and in spite of increased dosage of gonadotropins older women generally yield fewer oocytes and have higher cycle cancellation rates.¹⁶ All the abortions occurred in age group of < 35 years old, because the majority of pregnancies occurred in this age group. Only six pregnancies occurred in age group of 35 - 39 and ≥ 40 years old. In our study there were no obvious differences in fertilization rate among all groups. It is believed that the fertilization rate is predominantly determined by the male factor rather than the ovarian factor.¹⁷

CONCLUSIONS

In conclusion, in ART programs, older women produce less oocytes, embryos and have lower clinical pregnancy and live birth rate, reflecting the small size and the impaired quality of their follicles pool. Therefore this group of patients should be carefully counseled about their lower chances of conception when undergoing ART treatments.

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