

# Outcome of Assisted Reproductive Technology in Women Aged 40 Years and Older: An Analytic Study from Life Clinic Lahore Pakistan

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## ABSTRACT:

**Objective:** To find out the impact of woman's age on the number of retrieved oocytes, embryos obtained, embryo's transferred, pregnancy, abortion and cancellation per cycle.

**Materials and Methods:** In this study in-vitro fertilization(IVF) or intracytoplasmic sperm injection (ICSI) cycles were completed. Number of oocytes retrieved, embryos obtained and transferred were observed along with rates of cancellation, pregnancy and abortion per cycle.

**Results:** The study was performed on 75 women undergoing ART cycles. Patients age was divided into five categories 40 years (n=45) 60.0 %, 41 (n=4) 5.30%, 42 (n= 9) 12.0%, 43 (n=6) 8.0% and =44years (n=11) 14.7%. The mean age of these women was 41.17±1.67. The mean number of retrieved oocytes per cycle was 5.69±4.78; embryos obtained per cycle were 2.71±3.96; No of transferred embryos was 1.16±1.01. The overall pregnancy rate was 6.0% (7/75) per cycle. The abortion rate was found in 5.86% (7/75) and the overall cancellation rate was 9.6% per oocytes retrieval.

**Conclusion:** Aged women yield lesser number of oocytes as well as embryos. Pregnancy rates and delivery rates are also decreased. So the women of age more than 40 years must be counseled thoroughly before enrolling them in the ART programs.

**Keywords:** Women, Age, Impact, Oocytes, Assisted reproduction, Technology, Outcome

## INTRODUCTION:

As the women grow old natural fertility decline and it is important to note that this decline in fertility is dependent on a number of factors. Every woman has a different diagnostic profile and it is quite well known that the effect of age on the reduction of fertility is different in different women, similar to the fact that women reach menopause in different ages. Thus reproductive capacity of female is gauged by the count and quality of oocytes they have in their ovaries. It is termed as ovarian reserve.<sup>1</sup> When a female is born the

ovaries have a specific number of oocytes which decrease as the age of the female increases.<sup>2</sup> This is known as ovarian aging. Ovarian aging is an individual process which varies in different women and so is the pace of this process.<sup>3</sup>

Number as well as quality of oocytes decays gradually and end result is the menopause. So fertility declines as the number and good quality oocytes decrease which is marked by rise in FSH levels and fall in levels of anti-Mullerian hormone.<sup>4</sup>

Clinical relevance of measuring the ovarian reserve of the females is linked with diagnosis of subfertility. Forecasting about the response to COH as well as the outcome of assisted reproduction is also possible by monitoring of the ovarian reserve and estimation of the hormones mentioned above.<sup>5</sup>

Reproductive ability of the women decreases as they grow old. It is a well-known fact which is substantiated by academic and scientific evidence.<sup>6</sup> Availability of reliable methods of contraception gave control to the women over their lives and they started living according to their wishes and decided to give up the traditional roles of motherhood.<sup>7,8</sup> This developed into a new trend of delaying pregnancy and parenthood.<sup>9</sup> The women chose to attain higher education and benefit themselves from the opportunities open for them. Modern social trends have brought a huge change in the life of women. Independence bestowed by education and liberty to choose financially better careers have made women confident and self-assured.<sup>10</sup> Modern women became interested in jobs and the concept of sole bread winner of the family was replaced by two earners in the family.<sup>11,12</sup> As the age of pregnancy highly increased due to new social trends it entered into lesser fertile or subfertile period. This happened mostly in the Europe and some areas of USA.<sup>13,14,15</sup> Delay in marriage and pregnancy may be due to career pressure but rise in the tendency of divorce have complicated the situation and has been incriminated for the epidemic of subfertility

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in the women in the third decade of their life.<sup>16</sup> Social trends are changing the life of the women all over the world.<sup>17</sup> The numbers of over age 30 mothers are on the rise as well as over age 35 mothers. Number of younger mothers is decreasing. Fertility rate of females with respect to age has changed with time. Previously highest pregnancy rate was found in females whose age was 25-29; in comparison to lately it has climbed to 30-34. Whenever clinicians decide to embark on the idea of assisted reproduction as a treatment for a couple they have to think about the expected chances of success in this decision.<sup>18</sup>

Only if the chances are bright they start thinking about the best treatment modality for the couple in question.<sup>5</sup> Age is one single factor that can affect the chances of success. A study has documented that as the age advances pregnancy rates after assisted reproduction decrease that is 12.2 % in women 25-39 years age, 7.3 % women 40-43 years age and 1.7 % in women 44-45 years age. Advanced age in women has been correlated with poor treatment outcomes due to decreased number of oocytes, fertilized oocytes, embryos transferred, embryos implanted and pregnancy rate.<sup>19</sup> Assisted reproduction with donated oocytes in women of higher age group have shown a fall in implantation rate and pregnancy rates.<sup>20</sup>

Advancing age thus negatively affects the outcome of any treatment modality of assisted reproductive technology. As the women grow old natural fertility decline and this is important to note that this decline in fertility is dependent on a number of factors. Every woman has a different diagnostic profile and it is quite well known that the effect of age on the reduction of fertility is different in different women, similarly as the women reach menopause in different ages.<sup>21</sup> Predictability of age as a prognostic factor about the outcome of the treatment may have a limited value and may need other factors to be taken into account. This has immense importance as treatment is expensive, long, tiresome and painful for the patient who is hopeful and during the counseling sessions constantly questions about the efficacy of the treatment.

There is a need to educate the public about the decreasing reproductive potential of aging females who may be having older partners to think and plan about making early decisions if they want to have a family.<sup>22</sup> Women of age 50 have been able to carry out a successful pregnancy; the oocytes were donated by younger women. So ovarian aging evidenced by lesser number of oocytes and fertilized oocytes as well lesser numbers of embryos transferred is different from uterine aging which has the capacity to gestate with donor eggs.<sup>23</sup>

#### **MATERIALS AND METHODS:**

This retrospective study was performed on 75 women undergoing ART cycles with age= 40 years in Hameed Latif Hospital in Lahore from January 2015 to December 2015. After getting approval from Institutional ethical committee data collection was started. A specially designed questionnaire was used for data collection

which was validated by the biostatisticians of Lahore Institute of Fertility and Endocrinology (LIFE) research cell. Informed consent forms were signed by the couples after reading the information leaflet. Sampling method was non-probability consecutive.

Controlled ovarian stimulation in ART cycles was done using long down-regulation or short flare-up protocols with gonadotropin-releasing hormone (GnRH) agonist and HMG/r-FSH or GnRH antagonist with HMG/r-FSH or only HMG protocols. When at least two follicles or dominant follicle reached a mean diameter of 18 mm, using transvaginal ultrasonography, 10000 IU HCG was administered. Oocytes pick-up was performed 34-36 hours after HCG injection and conventional IVF or ICSI were done as appropriately.

On the day 2 or 3 after oocytes retrieval embryo transfer was performed with using a Labotect catheter (Labotect, Gottingen Germany) based on the number and quality of obtained embryos. Luteal phase support with 100 mg of intramuscular progesterone in oil (progesterone, Aburaihan Co., Tehran, Iran) or 400 mg of vaginal progesterone (Cyclogest®; Actavis, Branstaple, UK) was started from the day of oocytes pick-up and was continued until the negative pregnancy test or the end of the first trimester of pregnancy. Follow-up of ART outcomes was done based on clinical pregnancy, abortion, and cycle cancellation. Clinical pregnancy was considered as the observation of fetal heart activity by transvaginal ultrasonography, 3 weeks after positive beta-HCG. Spontaneous abortion was defined as loss of fetus with gestational age <20 weeks. Cycle cancellation was identified when no embryo was transferred because of no oocyte retrieval or no obtained embryo. Statistical analysis was performed using the statistical package for the social science version 15.0 for windows (SPSS, Inc., Chicago, IL). Chi-square was used as appropriate. P value of less than 0.05 was considered statistically significant.

#### **RESULTS:**

The study was performed on 75 women undergoing ART cycles. Women who enrolled in the study were aged with the range of 40-45 years. The patients were stratified into five groups by age. The frequency and percentages are given in Table 1. Patients age was divided into five categories 40 years (n=45) 60.0 %, 41 (n=4) 5.30%, 42 (n= 9) 12.0%, 43 (n=6) 8.0% and =44years (n=11) 14.7%.

The mean age of these women was 41.17±1.67. The mean number of retrieved oocytes per cycle was 5.69±4.78. The mean number of per cycle obtained embryos was 2.71±3.96 and the mean number of transferred embryos was 1.16±1.01 Table 2. The overall pregnancy rate was 6.0% (7/75) per cycle. The abortion rate was found in 5.86% (7/75) and the overall cancelation rate was 9.6% per oocytes retrieval Table 3. In our results, there is no significant association between age with respect to pregnancy outcome, parity, cycle cancellation and embryos transferred (p-value=0.429, 0.550, 1.000, 0.316 respectively).

Table :1  
Number and Percentages of women in different age group

Age (years)	No. of patients	Percentage of patients
40	45	60.0%
41	4	5.30%
42	9	12.0%
43	6	8.0%
≥44	11	14.7%

Table: 2  
Cycle response based on women's age

Age(years)	No. of retrieved oocytes	No. of obtained embryos	No.of transferred embryos
40	7.98±5.04	4.15±3.24	1.78±1.06
41	3.75±1.71	1.75±2.22	1.00±0.82
42	5.55±5.66	2.67±3.61	1.00±1.00
43	6.33±5.43	2.17±3.92	1.00±1.26
≥44	4.82±6.06	2.82±5.49	1.00±0.89
Total	5.69±4.78	2.71±3.96	1.16±1.01

Table 3:  
ART outcomes based on women's age (N, %)

Age(years)	Pregnancy per cycle	Abortion per positive pregnancy	Cycle cancelation per oocyte retrieval
40	6(13.3)	5(11.1)	5(11.1)
41	0	0	0
42	0	0	1(11.1)
43	1(16.7)	0	1(16.7)
≥44	0	2(18.2)	1(9.1)
Total	7(6.0%)	7(5.86%)	8(9.6%)

## DISCUSSION:

Social trends are changing the life of the women all over the world.<sup>17</sup>In 1991 one out of 4583 women were aged 45 or more whereas in 2004 the trend changed one out of 1159 women was aged 45 or more.<sup>24,25</sup> In Australia the women of age 40 who underwent ART cycles constituted 11.2 in 2002 whereas in 2004 this percentage changed to 20.80%. Similarly in the UK the age 40 or more who underwent ART cycles constituted the percentage of 9.10 % changed to 15.70 % in 2006.<sup>26</sup> While thinking of using assisted reproductive technology in women of age 45 or more one needs to consider the chances of success of treatment as outcome in the shape of live healthy birth.<sup>27</sup>

In our study 75 women were included who were between the ages 40 and 45. These women were distributed according to ages 40, 41, 42, 43 and >44years with respective frequencies 60.0 % (45), 41 5.30% (4), 12.0% (9), 8.0% (6) and 14.7% (11). Mean age of these women was 41.17±1.67 years. Mean number of oocytes retrieved was 5.69±4.78. Mean number of embryos obtained was 2.71±3.96 and mean number of embryos transferred was 1.16±1.01. Overall pregnancy rate per cycle was 6.0%. Age with parity, cycle cancellation and embryos transferred, pregnancy outcome, was found to be insignificantly associated.

Ron in 2000 analyzed the outcome of ART in women

who were 41 years old or more. There was no pregnancy in women aged 45 or more and delivery in women aged 44 or more.<sup>28</sup>In a retrospective study conducted by Lass and his colleagues in London, UK, 471 females aged 40 or more were analyzed for 1087 ART cycles. It was found that 77.50% had oocyte retrieval and 64.60% had embryos transferred. Pregnancy rate for women aged less than 40 years of age was 28.20% in comparison to 11.30% for women aged more than 40 years of age.<sup>29</sup>In a study published by Pantos it was shown that frequency of blastocysts formation, implantation and achieving pregnancy significantly decreased in women undergoing ART at the age of 40 or more.<sup>30</sup>While thinking of using assisted reproductive technology in women of age 45 or more one needs to consider the chances of success of treatment as outcome in the shape of live healthy birth.<sup>27</sup> In an interesting study done by Spandorfer in 2007 it was concluded that ART was a good choice in females aged 45 who had a normal ovarian reserve and were able to produce five oocytes.<sup>31</sup> Serour and his colleagues analyzed 2,386 consecutive IVF/ ICSI cycles in females whose age was 40 years or above. Autologous oocytes were used in these IVF/ ICSI cycles. Overall Live birth rate per cycles was calculated to be 6.7 %. This rate was significantly higher in women aged less than 43 years. In women below 43 years of age live birth rate per cycle was higher (7.4%) which



was statistically significant. In women above 43 years of age live birth rate per cycle was significantly lower (1.1%).<sup>32</sup> Navot in 1994 tried to explore the contribution of the uterus to the reproductive failure due to female aging. In this study two groups of women, below and above the age of 40, were studied with respect to ova received, ova fertilized and embryos transferred. Women received ova from the donors. Interestingly no significant difference was noted among these two groups in the parameters mentioned above. The study concluded that uterus may not be responsible for age related decline in the capacity of conception or gestation.<sup>24</sup>

The frequency of obstetric complications rises with increase in the age of the female undergoing assisted reproduction. Advanced age may combine with medical comorbidities and reduced adaptability to physical stress to affect the outcome and may result in increased perinatal morbidity and mortality.<sup>33</sup>

Tsafir has published a retrospective analysis of IVF 1217 treatment cycles performed on females of forty years of age or more. This study included all 381 women were treated during 1995-2004 at the fertility center in a university hospital at Jerusalem in Israel. Embryo transfer was successful in 62.6 percent of the cycles. In women aged 40 pregnancy rates were 13.9% and 9.1% women delivered; in women aged 45 pregnancy rates were 2.8% and 0.7% women delivered.<sup>34</sup> Advancing age increases cycle cancellation rate. A study has reported 52.9% which was found to be statistically significant.<sup>6</sup> Serour has reported cancellation rate per initiated cycle to be 16 %, while Tsafir has reported as 16.6% and Klipstein as 19.9%.<sup>32,34,35</sup>

## CONCLUSION:

Aged women have lesser ovarian reserve so when they undergo ART they usually yield lesser number of oocytes as well as embryos. Pregnancy rates and delivery rates are also decreased with advancing age. Aged women must be counseled thoroughly before enrolling them in ART programs.

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