

In-vitro fertilisation in women aged 40 years and above

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ABSTRACT

Introduction: To compare the results of in-vitro fertilisation (IVF) in women aged less than 40 years with those aged 40 years and above with baseline follicle-stimulating hormone (FSH) levels less than 15iu and using their own oocytes.

Methods: A total of 2179 fresh IVF cycles were started in KK Women's and Children's Hospital IVF Centre from 1997 to 2002, of which 247 cycles were done in women 40 to 45 years with FSH levels less than 15iu. The remaining 1932 cycles were performed in another group of women aged less than 40 years old. All couples were treated using our hospital's IVF protocol, and the same clinical and embryological team was involved in all treatments. The medical records of patient outcomes were retrospectively reviewed. The main outcomes measured were clinical pregnancy, miscarriage and delivery rates.

Results: The total number of fresh cycles performed in women over 40 years was 247 cycles. Of these, 186 (75.3 percent) cycles reached oocyte collection, and 179 (72.5 percent) cycles reached embryo transfer. The total number of pregnancies was 22 (12.3 percent). The number of cancelled cycles was 61 (24.7 percent). Women less than 40 years of age demonstrated higher rates in cycles reaching oocyte collection (89.2 percent), embryo transfer (84.6 percent), pregnancy rates (32.9 percent) and live-birth rates (24.0 percent). They also reported a lower miscarriage (36.1 percent) and cancellation rate (10.9 percent) as compared to the group of older women.

Conclusion: As older women seek IVF treatment, it is necessary for them to understand that chances of pregnancy decrease with increasing age. Our results show that as women exceed 40 years old, pregnancy and live-birth rates fall with concurrent rising miscarriage and cycle cancellation rates.

Keywords: delivery rate, follicle-stimulating hormone, in-vitro fertilisation outcomes, miscarriage rate, pregnancy

INTRODUCTION

As a woman ages, her fertility diminishes⁽¹⁻⁵⁾. Currently, more women are choosing to delay starting their family for various social reasons⁽⁶⁾. As more couples delay the commencement of child-rearing, the age of women seeking infertility treatment will inadvertently increase⁽⁷⁾. Although many women are fertile into their late 40s, most are not. However, the precise reasons for the loss of fertility are not well understood. There are thoughts to be due to a number of factors, including the decline in the frequency of intercourse⁽⁷⁾, decreasing number of primordial follicles⁽⁸⁾, poorer oocyte quality⁽⁹⁾, problems with the uterus⁽¹⁰⁾, and embryo loss resulting from chromosomal abnormalities⁽¹¹⁾.

In general, most women reach menopause by the early 50s. During this period, there will be a significant decline in the number of primordial follicles. This decline accelerates around the age of 37 years on average. Biological infertility is normal about 10-15 years before menopause^(12,13). Declining fertility in the 40s and thus poor ovulation response is an individual event that cannot be predicted accurately before an in-vitro fertilisation (IVF) cycle is undertaken. Questions thus remain with regard to the chances of a successful pregnancy and delivery in women aged 40 years or more using their own oocytes, and the maximum female age at which IVF may not be successful.

In Singapore, Ministry of Health regulations only allows IVF treatment in women up to 45 years of age. Our study summarises our experience with women aged 40 to 45 years who were treated in our IVF centre from 1997 to 2002. This will give a realistic assessment of IVF success rates for women in this age group and allow appropriate counselling for these women. At the same time, we also compared the data obtained from this group of women to a younger group (less than 40 years old) to allow better appreciation of IVF outcome rates.

METHODS

A total of 240 women aged 40 years and above was treated at the KK Women's and Children's Hospital (KKWCH) IVF centre from 1997 to 2002. A total of

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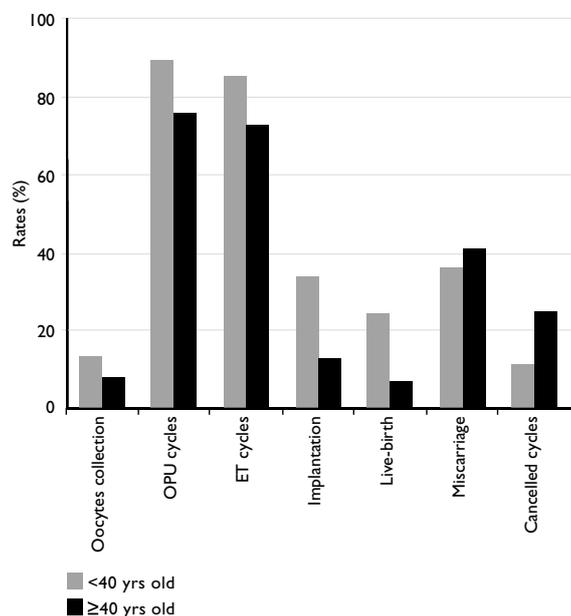
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Table I. Comparison of IVF outcomes in women aged 40 years or more with women aged less than 40 years.

	Women aged ≥ 40 years	Women aged < 40 years
Total number of fresh cycles	247	1932
No. of cancelled cycles (%)	61 (24.7)	212 (10.9)*
No. of cycles reaching OPU (%)	186 (75.3)	1720 (89.2)*
No. of cycles reaching ET (%)	179 (72.5)	1634 (84.6)**
No. of implantations (%)	22 (12.3)	539 (32.9)**
No. of live-births (%)	12 (6.7)	399 (24.0)**
No. of miscarriages (%)	10 (40.9)	144 (36.1)**
Total number of oocytes collected	1413	22628***
Average number of oocytes collected/cycle	7.59	13.15***

* $p < 0.01$ ** $p < 0.05$ *** p not significant**Table II. IVF outcomes comparing individual age groups from 40 years to more than 44 years old, as compared to the age group less than 40 years old.**

Age groups (in years)	No. of fresh cycles	No. of cancelled cycles (%fresh cycles)	No. of oocytes collected (oocytes/fresh cycle)	No. of cycles reaching OPU (%fresh cycles)	No. of cycles with ET (%fresh cycles)	No. of pregnancies (%ET cycles)	No. of livebirths (%ET cycles)	No. of miscarriages (%pregnancies)
Subgroups								
40	100	31 (31)	674 (9.77)	69 (69)	68 (68)	9 (13.2)	5 (7.4)	3 (33.3)
41	60	15 (25)	348 (7.73)	45 (75)	45 (75)	6 (13.3)	2 (4.4)	4 (66.7)
42	24	6 (25)	94 (5.22)	18 (75)	15 (62.5)	3 (20.0)	3 (20.0)	0 (0)
43	41	6 (14.6)	193 (5.51)	35 (85.4)	32 (78.0)	4 (12.5)	1 (3.1)	3 (75.0)
>44	22	3 (13.6)	104 (5.47)	19 (86.4)	19 (86.4)	1 (5.3)	1 (5.2)	0 (0)
Total (≥ 40)	247	61 (24.7)	1413 (7.59)	186 (75.3)	179 (72.5)	22 (12.3)	12 (6.7)	10 (45.5)
<40	1932	212 (10.9)	22628 (13.15)	1720 (89.2)	1634 (84.6)	539 (32.9)	399 (24)	144 (26.78)

Fig. I Comparison of IVF outcomes in women aged 40 years or more with women less than 40 years.

2179 fresh IVF cycles were started in the KKWCH IVF Centre during this period, of which 247 cycles were done in women 40 years and above (11.3%). The remaining 1932 cycles were performed in another group of women aged less than 40 years. The causes of subfertility in couples seen at our IVF centre are male factor, tubal disease, ovulatory disorder, endometriosis, failed intrauterine insemination, previous tubal ligation, premature menopause and unexplained subfertility.

The indications for IVF in the two groups of patients are similar and there was no selection bias in both groups. All the couples were treated using our centre's IVF protocol, and the same clinical and embryological team was involved in all treatments. Follicle-stimulating hormone (FSH) levels were measured immediately in the proliferative phase before treatment. Women whose FSH levels were consistently >15 mIU/ml were excluded from this study,

as a raised FSH level would already indicate diminished ovarian response. All the women had menstrual cycles with no clinical signs of menopause detected.

A retrospective review of all 247 fresh cycles performed in women 40 years and above was done. The indices reviewed were the rate of cancelled cycles before ovum pick-up (OPU), the rates of cycles with OPU but no embryo transfer, the rates of cycles with embryo transfer, pregnancies rates, live-birth rates and miscarriage rates. These indices were then compared to the other group of younger women aged less than 40 years. The X^2 test and Student's t-test for unpaired data were used to test for statistical differences between the two groups of women. P-value of less than 0.05 was deemed significant.

RESULTS

A total of 247 fresh cycles were performed in the older group of women aged 40 years and above. There were 22 pregnancies, 12 live-births and 10 miscarriages in this group of patients. These observations translated to a pregnancy rate of 12.3%, live-birth rate of 6.7%, and miscarriage rate of 40.9%. In comparison, women less than 40 years old reported a higher pregnancy rate of 32.9%, live-birth rate of 24.0%, and a lower miscarriage rate of 36.1%

Of the 247 fresh cycles performed in the older group of women aged 40 years and above, 186 of these cycles reached the oocyte collection stage, while 179 cycles reached the embryo transfer stage. 61 cycles were cancelled in this group. In contrast, of the 1932 cycles performed in the younger group of women aged <40 years, 1720 cycles reached the oocyte collection phase and 1634 cycles reached the embryo transfer phase. The number of cancelled cycles in this group was 212. These results highlighted a lower rate of cycles reaching the oocyte collection (75.3%) and embryo transfer phase (72.5%) in the older women when compared to the younger women with higher rates of 89.2% and 84.6%, respectively. Older women also demonstrated a higher cancellation rate of 24.7%, compared to a lower cancellation rate in younger women of 10.9%.

The average number of oocytes collected per cycle was also noted to be lower in the group of older women, with a value of 7.59 as compared to the younger women less than 40 years old who reported 13.15 oocytes collected per cycle. These results are summarised in Table I and Fig. 1. Our results also analysed IVF outcomes in the individual age groups from 40 to more than 44 years old, as compared to the younger women less than 40 years of age (Table II). The indices looked at were the number of fresh cycles

Fig. 2 Comparison of IVF outcomes in women aged 40 years and above.

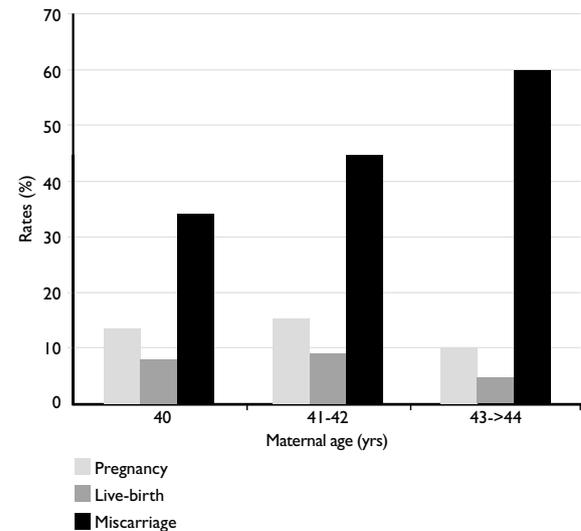
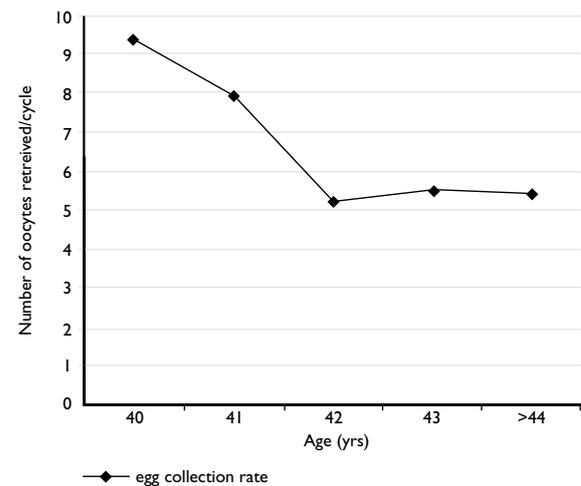


Fig. 3 Comparison of number of oocytes collected per cycle in women aged 40 years and above.



performed in each age group, rates of cancelled cycles, cycles reaching OPU, cycles reaching embryo transfer, pregnancy rates, live-birth rates, miscarriage rates, and the average number of oocytes collected per cycle.

The trends of the different IVF outcome rates as a woman exceeds 40 years of age are illustrated in Fig. 2. As we progress from the individual age groups of 40 years, 41 to 42 years, 43 to more than 44 years, a decreasing trend is noted for pregnancy and live-birth rates. Pregnancy rate decreased from 13.2% in the group of 40 years old to a lower 9.8% in the group aged 43 to more than 44 years old. Similarly, live-birth rates fell from 7.4% in the group aged 40 years old to a lower 3.9% in the group aged 43 to more than 44 years old. In contrast, a sharp increase is noted in miscarriage rates from 33.3% in the group aged 40 years to a high of 60.0% in the group aged 43 to more than 44 years old (Fig. 2).

Table III. Comparison of the rates of pregnancies and miscarriages in women aged over 40 years as the number of transferred embryos increase.

	No. of embryos transferred				Total
	1	2	3	4	
No. of initiated cycles	38 (%)	32 (%)	97 (%)	12 (%)	179 (%)
No. of clinical pregnancies	4 (10.5)	5 (15.6)	12 (12.3)	1 (8.3)	22 (12.3)
No. of miscarriages	3 (7.9)	3 (9.4)	4* (4.1)	0 (0)	10* (45.5)

*Includes one case of ectopic pregnancy

DISCUSSION

The Human Fertilisation and Embryology Authority (HFEA) database has permitted a detailed analysis of the characteristics of patients that affect the outcome of IVF treatment. Duration of fertility, previous pregnancy, previous unsuccessful IVF attempts⁽¹⁴⁾ are just some of the various ways of prognosticating ovarian response, but none of these could predict the outcome of IVF accurately. The age of the women is well known to be an important factor influencing the outcome of IVF⁽¹⁵⁻¹⁷⁾. Other studies have previously described that the effect of age can be overcome by the use of donated eggs⁽¹⁸⁾. However, even in women who received donated eggs, the pregnancy rate is still lower in women aged 40 years and above⁽¹⁹⁾.

In our study, women above the age of 40 have an overall pregnancy rate of 12.3%. Data from HFEA⁽¹⁴⁾ reported a live-birth rate of 8.1% per embryo transfer in women aged 40-44 years. Our study reported a rate of 6.7% (12/179) per treatment cycle. This is in concordance with our national policy of not allowing IVF treatment for women aged 45 years and above, as women in this age group have very poor results from IVF treatment. It is important for society to recognise that it might be preferable for childbearing to take place by 33 to 35 years of age, or else women will increasingly encounter unexpected difficulties, which may or may not be overcome by IVF treatment.

We noted earlier that both pregnancy and live-birth rates fell with increasing age from 40 years onwards. A similar downward trend was also observed for the number of oocytes collected per cycle (Fig. 3). This finding is consistent with the fact that as a woman ages, her ovarian reserves diminishes^(8,12,13), resulting in the loss of primordial follicles and fertility. In the counselling of women with diminished ovarian reserve in our centre, in conjunction with the use of FSH levels, the use of ultrasound antral follicular count, baseline ovarian stromal blood flow

and ovarian volume help us prognosticate and predict IVF outcomes.

In IVF treatment of women aged 40 years and above, our study showed that the rate of pregnancy (implantation) did not correlate with an increasing number of embryos transferred. In this group of women, a pregnancy rate of 10.5% was noted when one embryo was transferred. Pregnancy rates of 15.6%, 12.3% and 8.3%, respectively, were obtained when the number of embryos increased to a maximum of four (more embryos were transferred as there were smaller number of cycles in this age group and there were poorer quality of embryos overall). The rate of miscarriages did not show any definite trend as the number of transferred embryos increased (Table III).

Despite the higher number of embryos transferred, there was no case of multiple pregnancies reported in IVF treatment of women in this age group. This may be due to the effect of age on endometrial receptivity; among women who received donated eggs, the pregnancy rates were found to be lower in older women⁽¹⁴⁾. These findings are consistent with those reported by Yaron et al⁽¹⁹⁾. Despite this, there is still continuing controversy about the sustained fertility of older women⁽²⁰⁾.

As an increasing number of older women seek IVF treatment, these results show that it is a reasonable form of treatment for women 40 years and above. But one must note that the success of IVF treatment is much lower in women above 40 years compared with those below 40 years (12.3% vs 32.9%). IVF pregnancies in women aged 40 years and above have a lower implantation rate, higher cancelled cycles, less oocytes recovered and more miscarriages, compared with IVF in women aged less than 40 years. The number of embryos transferred in this age group does not increase pregnancy rates. It is therefore necessary for women to know that with increasing age, the number of oocytes retrieved decreases and the success of embryo transfer also decreases. Therefore, the chances of a successful pregnancy is lower.

In the counselling of these women undergoing IVF treatment, they must realise that there will be increased cancellation rates, which may result in increased cost either from drugs or from repeated cycles. They must also be made aware of the fact that if they do succeed in their IVF treatment, they may experience a higher rate of miscarriages and also associated aged-related pregnancy complications. Foetal abnormality, risk of gestational diabetes, and pre-eclampsia are just a few of the problems associated with advanced maternal age pregnancy. In summary, women above the age of 40 years should expect some increased

risk in pregnancy-related issues. We recommend that all women in this age group seek professional assistance early so that they can be counselled suitably as to what their potential risks can be.

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