Article

Assisted reproduction in women over 40 years of age: how old is too old?

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Abstract

Women's fertility progressively declines with advanced age due to depletion of the ovarian follicular reserve and poorer oocyte quality. However, many women of advanced age are eager to conceive from their own ova. The aim of the present study was to evaluate the outcome of IVF cycles among older patients. All IVF retrievals performed in the unit in patients ≥42 years old between 1998 and 2006 were retrospectively analysed. Data were compared with patients <35 years old treated in the unit during the same time period. A total of 843 IVF retrievals in 459 patients ≥42 years old were assessed. Clinical pregnancy rates per cycle were 7.7%, 5.4% and 1.9% for 42, 43 and 44 years old, respectively. Only one IVF cycle in patients aged 44 years resulted in delivery. None of the 54 cycles performed in women of 45 years or older resulted in a pregnancy. A marked decline in clinical pregnancy and delivery rates, accompanied by an increase in spontaneous abortion rates, was found in patients ≥42 years old. In view of these results and as the option of egg donation is a promising alternative with delivery rates close to 50%, it appears that IVF treatment should be limited to patients not older than 43 years old with adequate ovarian response.

Keywords: autologous oocytes, advanced age, cost effectiveness, IVF

Introduction

Advanced maternal age is one of the most challenging fields in reproductive medicine. In most western countries, the average women's age at marriage and child bearing is ever increasing. Moreover, many single women, mostly around their 40s are now seeking assisted procreation treatments in order to conceive.

Currently, in our centre, over 45% of the IVF cycles are performed in women over 35 years of age. Since natural fecundity also declines dramatically after this age, assisted reproduction in women over 40 years of age raises major medical, moral and social issues.

The progressive decline in female reproductive performance becomes more acute during the fourth decade of life. The hallmark of this decline in fertility is shortening of the menstrual cycle with concomitant increase in basal FSH concentrations. Consequently, assisted reproduction patients with advanced age demonstrate higher degrees of ovarian resistance to trophic hormone administration, decreased pregnancy rates, higher rates of pregnancy loss and higher rates of perinatal genetic anomalies in comparison with younger patient populations (Hull *et al*., 1996; Dor *et al*., 1997; Márquez *et al*., 2000; Dal Prato *et al*., 2005).

In Israel, infertility treatments including IVF are covered by the state until the age of 45. On the other hand, other countries prohibit IVF practice even at a lower age limit.

The goal of the present study was to evaluate IVF outcome during a period of almost 8 years in patient popula-

tions over 40 years of age, and to help to define new guidelines and policy for infertility treatments in these age groups.

Materials and methods

The research protocol was approved by the local internal review board. Medical records of all IVF female patients ≥42 years of age and less than 35, treated between January 1998 and July 2006 (8.5 year period), were analysed retrospectively. Only cycles with fresh embryo transfer using autologous oocytes were included in the study. A control group of women <35 years old was chosen, as fertility rates decrease with increasing age of women and this age is a milestone in the literature.

Three different stimulation protocols were used for the induction of follicular growth, as previously described (Elizur *et al.*, 2005; Hourvitz *et al.*, 2006). In brief, 51.7% ($n = 2960$) of the patients underwent a long protocol of gonadotrophin-releasing hormone analogue (GnRHa) followed by recombinant FSH (rFSH) or menotropins. In all, 34.6% ($n = 1981$) of the women underwent a suppression protocol using GnRH antagonists, and 12.3% ($n = 704$) underwent ovarian stimulation using the flare-up protocol. In 1.3% ($n = 81$) of cases, a spontaneous cycle was used. Human chorionic gonadotrophin (HCG) was administered when at least two follicles of 17 mm average diameter were observed by transvaginal ultrasound. Oocytes were harvested by transvaginal ultrasound-guided follicular puncture approximately 35–36 h after HCG administration. Conventional insemination or intracytoplasmic sperm injection (ICSI) were performed as indicated. Transfer of two to four of the best cleaved embryos was performed on day 3. In some cases when embryo quality was poor, more than four embryos were transferred after detailed discussion with the couple of the risks of multiple pregnancies. Only fresh embryo transfers were included. Progesterone supplementation was given to all women from 1 day after oocyte retrieval.

Positive pregnancy was defined as a serum HCG concentration of ≥10 IU/l on day 12 after transfer. A clinical pregnancy was defined as the presence of a gestational sac and visualization of fetal heart beat by ultrasound 2 weeks later. Implantation rate was defined as the ratio between the total number of fetal sacs and the total number of embryos replaced.

Data were collected using the Statistics Package for Social Sciences (SPSS) version 11 for windows program (SPSS, Inc., Chicago, IL, USA). Chi-squared or the Fisher's exact tests for categorical variables and the unpaired two-way Student's *t*-test for continuous factors were used as appropriate. A *P*-value of <0.05 was considered significant.

Results

During the period from January 1998 to July 2006, a total of 9081 treatment cycles were performed in the unit. The study group consisted of 843 (9.3%) treatment cycles that were performed in 459 patients aged 42–47 years old. Patients' basic characteristics and data concerning the relevant oocyte retrieval cycle were similar for all patients aged 42–44 years old (with no difference between women in the different year groups).

Patients' characteristics are shown in **Table 1**. The older patients had a significantly longer period of infertility, more previous IVF cycles, and a higher mean basal FSH than the younger group (all *P* < 0.001). The cancellation rate and gonadotrophin consumption were significantly higher in the older group, with a lower number of oocytes retrieved and fertilized (all *P* < 0.001; **Table 2**). Reasons for cycle cancellation were early lutealization, no ovarian response, no ova during retrieval and no fertilization.

Table 3 describes the characteristics of the treatment cycles among patients ≥42 years old according to the woman's age. No differences were found for any of the parameters between the 42, 43 and 44 years age groups. Therefore, the data concerning these patients could be grouped together. The overall clinical pregnancy rate per retrieval in the 42–47 years old group was 5.3%, with a steep decline from 7.7% at the age of 42 to no clinical pregnancies in women of 45 years and older (**Table 4**). Out of five women (3.2%) at the age of 44 years who conceived (positive HCG), only one woman (0.6%) delivered. None of the 54 cycles performed in patients aged 45 years or older resulted in a pregnancy. Although the number of embryos transferred was similar for the two age groups (**Table 2**), clinical pregnancy rates were dramatically reduced in patients ≥42 years old, with higher rates of biochemical pregnancies and spontaneous abortion (**Table 4**).

Discussion

The data show a significant decline in the ovarian response of the study group (≥42 years old) and live birth rates. This

Table 1. Patient characteristics in the two age groups.

	Age group (No. of cycles)		
	<35 years (4883)	*≥42 years (843)*	*P-value*
Mean age	29.6 ± 3.1	43.9 ± 1.0	<0.001
No. of previous cycles	4.4 ± 3.8	9.7 ± 5.7	<0.001
Duration of infertility (years)	5.2 ± 6.6	8.2 ± 9.9	<0.001
Basal FSH (IU/l)	7.5 ± 4.9	9.7 ± 5.6	<0.001