Article

Age and ovarian reserve are distinct predictive factors of cycle outcome in low responders

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Abstract

The respective roles of age and ovarian reserve in predicting IVF outcome do not seem to be equivalent, as a high pregnancy rate seems to be preserved in the youngest women, despite low ovarian recruitment. The purpose of this study was to analyse the outcome of IVF/intracytoplasmic sperm injection (ICSI) procedures according to both age and ovarian reserve of patients with a low ovarian response to stimulation. A total of 163 IVF/ICSI cycles selected by a low response were analysed. The IVF outcome differed according to the women's age, with a cut-off value at 36 years. While the number of transferred embryos was similar, the pregnancy rate (PR) was 14.6% in younger patients but 4.9% ($P < 0.04$) in older ones. An elevated FSH was constantly associated with a poor cycle outcome. In contrast, when the FSH was normal, PR was significantly higher ($P < 0.05$) in women aged <36 (23.8%) than in women aged ≥36 (6.5%). This study shows that assisted reproduction outcome in women with a low ovarian response is primarily dependent on the ovarian status. The negative influence of age is relevant in patients with normal FSH. Therefore, even if the ovarian response to stimulation is low, patients aged <36 years with a normal FSH should proceed to oocyte retrieval.

Keywords: *IVF outcome, low responders, ovarian reserve, prognostic factors, women's age*

Introduction

A low follicular recruitment following ovarian stimulation may be observed in 9–24% of the IVF cycles (Keay *et al*., 1997) and is usually associated with a poor outcome related to the low number of retrieved oocytes and transferred embryos. Two factors have been previously demonstrated as predictive factors for the ovarian response to stimulation: age and ovarian reserve. However, the respective role of these factors in the poor prognosis usually associated with a low ovarian response is still uncertain. While a diminished ovarian reserve attested by an elevated FSH is constantly associated with a poor success rate, the role of age has been recently challenged. Indeed, a high pregnancy rate seems to be preserved in younger women even in presence of a low ovarian response (Roest *et al*., 1996; Hanoch *et al*., 1998; Lashen *et al*., 1999; Biljan *et al*., 2000). This observation could be explained by a higher quality of the oocytes retrieved from younger patients because the incidence of oocyte aneuploidy is age-related (Wu *et al*., 2000). Therefore, it has been assumed that, in contrast to older women, young women may be protected from the negative impact of a low ovarian response upon pregnancy rate. However, the cut-off values for age greatly differ between studies and range from 30 to 40 years (Roest *et al*., 1996; Hanoch *et al*., 1998; Lashen *et al*., 1999; Biljan *et al*., 2000). This discrepancy between studies may be partly explained by the large heterogeneity in the definition of the low ovarian response.

In the present study, a low ovarian response to ovarian stimulation was defined according to the number of growing follicles observed before human chorionic gonadotrophin (HCG) administration. This approach aims to more closely mimic clinical practice, where physicians facing this issue have to decide to cancel the cycle or to eventually proceed to oocyte retrieval. The predictive values of age and ovarian reserve were assessed in this clinical situation.

Materials and methods

Selection of patients

Data of IVF/intracytoplasmic sperm injection (ICSI) cycles performed from February 1996 to November 2001 in the reproductive unit were reviewed. For this retrospective analysis, records of women considered as low responders were selected. A low ovarian response to ovarian stimulation was defined by two simultaneous criteria: presence of fewer than five follicles ≥14 mm and plasma oestradiol value lower than 1000 pg/ml at the time of HCG administration. In this subgroup of patients, IVF/ICSI cycles were performed for tubal, male, unexplained or mixed infertility. The exclusion criteria for this analysis were: women with a single ovary or whose oocyte retrieval was registered as technically difficult, women with known uterine pathology.

Protocols

Cycles stimulated according to a gonadotrophin-releasing hormone (GnRH) agonist protocol (triptorelin, Decapeptyl 0.1 mg; Ipsen/Biotech, Paris, France) were selected for this analysis. Ovarian stimulation was performed by using gonadotrophins available at the time of treatment [human menopausal gonadotrophin (HMG; Pergonal, Serono SA, Boulogne, France), urinary (u) FSH (Metrodin HP, Serono SA) or recombinant (r) FSH (Gonal F, Serono SA; Puregon, Organon, Puteaux, France)]. The starting dose was chosen according to women's age, assessment of ovarian function and body mass index. Cycles were monitored from day 6 by simultaneous determinations of plasma oestradiol, LH and progesterone concentrations and by transvaginal ultrasonographic scanning of the ovaries on alternate day. In the vast majority of patients, follicular assessment was performed by ultrasound on the day of HCG. When US scanning was performed on the day before HCG, the criteria for follicular measurement was adjusted on the basis of a daily growth of 1.7 mm (van Santbrink *et al*., 1995).

Human chorionic gonadotrophin (10,000 IU Gonadotrophines Chorioniques Endo 5000; Organon) was administered when at least two follicles reached a diameter of 17 mm. Oocyte retrieval was performed 36 h later. Transvaginal ultrasound-guided follicular aspiration was carried out under local or general anaesthesia. Oocytes were inseminated or micro-injected and one to three viable embryos were transferred to patients 48 or 72 h after fertilization. The luteal phase was supported with micronized progesterone supplementation (Utrogestan; Besins International, Montrouge, France) and additional doses of HCG. Pregnancy was diagnosed by measuring serum βHCG dosage 10–12 days after embryo transfer, and later confirmed by ultrasonography.

Assessment of ovarian reserve

Ovarian reserve was assessed by measuring plasma FSH at cycle day 3 within 6 months prior to stimulation. According to the normal range of hormonal parameters in the IVF unit, ovarian reserve was classified as diminished if plasma FSH value was >12 IU/l.

Assessment of the cut-off value for age

To assess the cut-off value for age, an observational analysis of the age of women who got pregnant was firstly performed. The observed cut-off value was subsequently tested using a Student's *t*-test.

Statistical analysis

For statistical analysis, the chi-squared test, Student's *t*-test, and analysis of variance (ANOVA) test were carried out. The data are expressed as means ± SD. A *P*-value <0.05 was considered as statistically significant.

Results

A total of 163 cycles with a low ovarian response to ovarian stimulation were analysed. The main characteristics and indications for IVF/ICSI of the overall population are shown in **Table 1**.

The results of the ovarian parameters and cycle outcome for the overall population are presented in **Table 2**. In this population, selected for a low ovarian response, the numbers of retrieved, mature and fertilized oocytes, transferred embryos as well as the overall pregnancy and the take home baby rates were low as compared with those currently observed in normal responders.

Analysis of the cycle outcome according to the women's age

The distribution of ongoing pregnancies and spontaneous miscarriages was firstly analysed according to women's age. The vast majority of the pregnant women were aged below 36. Therefore, the age of 36 years was considered as the cut-off value for subsequent statistical analyses. As shown in **Table 2**, a significantly higher ($P < 0.05$) number of follicles and oocytes was recruited in the subgroup of women aged <36 years (81/163) than in the subgroup of women aged >36 years (82/163). However, the numbers of total and transferred

Table 1. Main characteristics and indication of IVF/ICSI in the overall population ($n = 163$). Figures in parentheses are percentages.

Age (years)	35.5 ± 4.8
BMI (kg/m^2)	24.0 ± 4.7
Duration of infertility (years)	4.4 ± 3.2
Assisted reproduction procedure	
IVF	86 (52.7)
ICSI	77 (47.3)
Mean no. of previous attempts	2.4 ± 1.7
Indications of IVF/ICSI	
Tubal factor	49 (30.1)
Endometriosis	6 (3.7)
Male factor	67 (41.1)
Unexplained	11 (6.7)
Mixed	30 (18.4)