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Original Article

Age is a major prognosticator in extremely low oocyte retrieval cycles

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ABSTRACT

Objective: Clinical prognosis appears to be varied in females with poor ovarian response (POR), and poor responders defined by the Bologna criteria might not be sufficiently homogeneous. The aim of this study was to determine the major predictor of reproductive outcomes in extremely low oocyte retrieval cycles.
Materials and Methods: A cohort of fresh *in vitro* fertilization/intracytoplasmic sperm injection cycles ($n = 858$) was analyzed from January 2001 to September 2014. Females from whom zero, one, two, or three oocytes were retrieved following ovarian stimulation were examined. Univariate analyses were performed to determine the association of pregnancy rate with potential confounding variables. Multiple logistic regression analysis was subsequently performed to identify factors that affected the occurrence of pregnancy.
Results: The clinical pregnancy rate was higher in women aged < 40 years, long protocol, and high embryo score in univariate analysis. After adjusting for confounding factors in multivariate analysis, the maternal age [odds ratio (OR) = 0.91], primary or secondary infertility (OR = 1.99), number of matured oocytes retrieved (OR = 0.64), and score of embryos transferred (OR = 1.39) were significantly associated with the clinical pregnancy rate per cycle and per transfer. In the age subgroup analysis, POR females aged < 35 years significantly demonstrated the highest number of matured oocytes, embryo scores, and clinical pregnancy rates compared with POR females aged 35–40 years and ≥ 40 years.
Conclusion: This study highlights the predictive value of maternal age and embryo quality on the probability of pregnancy in females with extremely low oocyte retrieval cycles. Young females with few eggs collected can still achieve acceptable pregnancy probability as long as they have good-quality embryos. Future randomized control trials for POR using the Bologna criteria should first stratify patients into different age groups.

Introduction

Controlled ovarian hyperstimulation (COH) employs exogenous gonadotropin administration to recruit a large number of oocytes for *in vitro* fertilization (IVF), such that high-quality embryos can be selected for transfer. However, patient response to ovarian stimulation can be highly variable, and this response is a major determinant of treatment outcome. Females with oocyte counts < 5 have a significantly lower cumulative conception pregnancy rate than those with normal responses (> 5 oocytes retrieved) [1].

Reliable predictors of pregnancy outcome would provide physicians with valuable information for counseling patients on whether to start a cycle. The most common tests for predicting ovarian reserve are anti-Mullerian hormone (AMH) and antral follicle counts. These tests have demonstrated a correlation to ovarian response in IVF even though the prediction of successful pregnancy remains controversial [2–4]. Moreover, there is apparently no solid link between the quantity and quality of oocytes.

Despite the unfavorable prognosis of females with poor ovarian response (POR), some studies have reported a reasonable pregnancy rate for such women [5,6]. Thus, it appears that the prognosis varies among poor responders after COH for IVF/intracytoplasmic sperm injection (ICSI) [7]. It is possible that the characteristics or treatments of specific females may provide them with an acceptable prognosis, although they produce an extremely low number of oocytes in the current cycle.

The management of POR has been a major challenge for clinicians because it is difficult to compare different treatments due to the use of different definitions of POR over the past 2 decades. In an effort to standardize the terminology, the European Society of

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Human Reproduction and Embryology (ESHRE) published the Bologna criteria in 2011 to define POR [8]. According to these criteria, at least two of the following three features must be present: (1) advanced maternal age (≥ 40 years) or any other risk factor for POR; (2) previous experience of POR (≤ 3 oocytes with a conventional stimulation protocol); and (3) abnormal ovarian reserve tests (ORTs) result (i.e., antral follicle count of 5–7 or AMH level of 0.5–1.1 ng/mL). However, recent research studies have suggested that females classified as having POR by these criteria are highly heterogeneous [9], and thus, the adoption of these criteria is still debated [10,11].

The aim of present study was to identify significant predictor variables for pregnancy in females from whom an extremely low number of oocytes were collected. On the basis of the results of our analysis, we aimed to determine whether there is a prognosis difference in POR using the Bologna criteria.

Materials and Methods

Participants

This retrospective cohort study reviewed the medical records of infertile couples that underwent IVF/ICSI from 2001 to 2014 at our institution. All females who obtained zero, one, two, or three oocytes at retrieval were included. Cycles in which ovarian stimulation employed clomiphene, gonadotropin, and gonadotropin-releasing agonist/antagonist were examined. Cycles with the administration of Corifollitropin alfa (Elonva; NV Organon, Oss, the Netherlands), frozen–thawed embryo cycles, and donor egg cycles were excluded. To reflect routine clinical practice in which poor responders may be present, there were no other exclusion criteria.

The characteristics of all patients were evaluated, including age, body mass index, family history, risk factors of POR (chronic smoking, drinking, previous ovarian surgery, previous chemotherapy), primary or secondary infertility, cause of infertility, hormone levels [basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2) on cycle Day 3 and AMH]. We do not refuse treatment solely based on ultralow AMH levels or higher basal FSH levels [12,13]. Treatment characteristics, such as protocol, IVF or ICSI, and adjuvant r-LH supplement, were analyzed. Follicle size on human chorionic gonadotropin (hCG) day and number of mature oocytes at retrieval were used as determinants of ovarian response. Gonadotropin dose adjustments may affect the response; thus, total gonadotropin dose used during the cycle was also used as a determinant of ovarian response. For the change in IVF practice during a long period of 14 years, the treatment period was considered (2001–2005, 2006–2010, 2011–2014). The score of the embryo transferred was also used as variables to predict clinical pregnancy.

The Institutional Review Board and the Ethics Committee of Chang Gung Memorial Hospital (Kaohsiung, Taiwan) approved this study (CGMF IRB No.: 104-8485C).

Controlled ovarian stimulation

The ovarian stimulation protocols included gonadotropin-releasing hormone (GnRH) agonist long, GnRH agonist short, and GnRH antagonist protocols, all of which were performed following standard clinical practice. The protocol for each patient was selected according to the ovarian reserve, which assessed the patient's age, baseline serum FSH concentration, previous ovarian response to gonadotropins, and the preference of each clinician. Each patient was administered an initial dose of 150–300 IU human menopausal gonadotropin or FSH (purified or recombinant), and dose adjustments during the cycle were determined individually based on the response to gonadotropin as assessed by serum E_2 concentration and sonographic monitoring of follicular growth. In addition, r-LH (Luveris; Serono) was administered in females with poor responses in a previous cycle or suboptimal follicular progression in a current cycle, starting on Day 1 or Day 6 of FSH stimulation at a daily fixed dose of 75 IU throughout the treatment period. Females undergoing the GnRH antagonist protocol that had at least one leading follicle measuring > 14 mm in diameter received an additional 0.25 mg/day GnRH (Cetrotide, Merk Serono) until the day of hCG injection. When two more follicles had matured (follicle diameter ≥ 16 mm), a 6500 IU dose of hCG (Ovidrel, Merk Serono) was administered, and oocyte retrieval was performed 36–38 hours later by transvaginal aspiration under ultrasound guidance. Standard IVF or ICSI procedures were used for oocyte fertilization, as previously described [14].

The choice between Day 3 embryo transfer and extended culture to blastocyst and transfer on Day 5 was based on embryo quality and number. The luteal phase was supported by intravaginal administration of progesterone (90 mg) vaginal gel once daily (Crinone 8%, Serono Pharmaceuticals Ltd.) or micronized progesterone vaginal capsules (200 mg) four times daily (Ultrogestan, Laboratories Besins International), starting on the day after oocyte retrieval.

Hormone measurements

FSH and LH levels were measured on Day 3 of the menstrual cycle before gonadotropin administration. Serum concentrations of progesterone and E_2 were measured on the day of hCG administration during each IVF cycle, where progesterone is expressed as ng/mL and E2 as pg/mL. Serum concentrations of E_2 and progesterone were determined using standard immunoassay systems (ADVIA Centaur ® XP, Siemens, USA). The intra- and inter-assay coefficients of variation were 5.0% and 4.1% for E_2 and 5.2% and 3.5% for progesterone.

Oocyte grading

According to nuclear maturation grading, the oocytes were classified into categories, metaphase II (mature) or non-metaphase II. The latter category included oocytes at the metaphase I and prophase I stages. For IVF, the retrieved oocyte–corona–cumulus complexes were immediately classified according to their maturity. For ICSI, the oocyte–corona–cumulus complexes were denuded and assessed shortly after retrieval. The denuded oocytes were cultured in an M2 culture medium (Medicult, Denmark) for 3–8 hours and were subsequently examined for the presence of the first polar body. After confirmation of the first polar body, ICSI was performed. The oocytes that did not develop to metaphase II after 8 hours of incubation were discarded. The oocyte preparation has been previously described in detail [14].

Assessment of fertilization, embryo culture, and zygote and embryo grading

ICSI and conventional IVF were performed according to standard procedures. Briefly, oocyte–corona–cumulus complexes were cultured in IVF Medium (Medicult, Denmark) for 4–6 hours, and the oocytes were inseminated with approximately 10^5 motile spermatozoa/mL in 1 mL of IVF medium. The oocytes were transferred from the insemination medium to fresh IVF medium and cultured. Our ICSI procedure has been previously described in detail [14].

Fertilization was evaluated after 16–18 hours. Normal fertilization was defined by the formation of zygotes with two pronuclei.