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Original Article

Outcomes of anti-Müllerian hormone-tailored ovarian stimulation protocols in *in vitro* fertilization/intracytoplasmic sperm injection cycles in women of advanced age

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ABSTRACT

Objective: We aimed to compare the outcomes of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatments in women of advanced age (>40 years) using anti-Müllerian hormone (AMH)-tailored ovarian stimulation protocols versus conventional protocols based on antral follicle count (AFC).
Materials and Methods: We retrospectively reviewed 210 women who underwent IVF/ICSI cycles: 116 women underwent stimulation protocols that were tailored to their AMH levels, whereas 94 women received treatment using conventional stimulation protocols based on AFC as the ovarian reserve marker.
Results: The following parameters were significantly higher in the AMH-tailored group than in the conventional group: initial and total doses (IU) of recombinant follicle-stimulating hormone (rFSH) used for stimulation (514.2 ± 137.9 vs. 452.3 ± 135.3, $p = 0.001$; 4713.8 ± 1618.8 vs. 4047.2 ± 1366.0, $p = 0.007$, respectively), ovum pick-up rate (OPU; 88.8% vs. 75.5%, $p = 0.016$), serum estradiol (E2) level on the day of human chorionic gonadotropin (hCG) administration (1818.5 ± 1422.4 vs. 1394.0 ± 929.0 pg/mL, $p = 0.028$), number of oocytes retrieved (7.4 ± 5.1 vs. 5.5 ± 3.4, $p = 0.007$), number of embryos per case (4.2 ± 3.2 vs. 3.3 ± 2.5, $p = 0.048$), clinical pregnancy rates (22.4% vs. 8.5%, $p = 0.008$), implantation rates (13.1% vs. 3.9%, $p = 0.001$), and live birth rates per cycle (15.5% vs. 6.4%, $p = 0.049$).
Conclusion: Individualized controlled ovarian stimulation (COS) protocols tailored to patients' AMH levels may improve the pregnancy rate, implantation rate, and live birth rate in women of advanced age undergoing IVF/ICSI compared with those receiving conventional stimulation protocols.

Introduction

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein produced by the granulosa cells of preantral and antral ovarian follicles. In the past, AMH has played a significant role in infertility assessment and treatment because it is a more accurate marker for predicting ovarian response to controlled ovarian stimulation (COS) than age or levels of Day 3 follicle-stimulating hormone (FSH), estradiol (E2), and inhibin B [1–3]. Before *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatments are initiated, AMH levels can help guide clinicians in counseling their patients about the risks and benefits of treatment and the likelihood of success, as well as allowing them to individualize treatment strategy according to the anticipated ovarian reserve. AMH levels are also correlated with the onset of menopause; however, its value is much more limited in the accurate prediction of the age of menopause [4]. In several reviews and meta-analyses, AMH measurement prior to ovarian stimulation has been associated with accurate prediction of ovarian over-response; therefore, choosing a

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stimulation strategy and adjusting the FSH dose according to the patient's serum AMH level may help reduce the incidence of ovarian hyperstimulation syndrome (OHSS) [1–3,5,6]. However, the utility of AMH levels for predicting poor ovarian response has been questioned, and evidence supporting the role of AMH in predicting pregnancy outcomes is scarce [5–7]. Thus, the aim of this study was to compare the outcomes of IVF/ICSI between women of advanced age using AMH-tailored stimulation protocols and conventional stimulation protocols based on antral follicle count (AFC) as the ovarian reserve marker.

Material and methods

Study participants

We retrospectively reviewed and analyzed the medical records of all patients aged > 40 years who received IVF/ICSI treatment at the Infertility Division of the Department of Obstetrics and Gynecology at MacKay Memorial Hospital in Taipei, Taiwan, between January 1, 2006 and September 30, 2011. The study protocol was approved by the Institutional Review Board of MacKay Memorial Hospital. The inclusion criteria for the reference population were patients who underwent a cycle of IVF, with or without ICSI, using fresh embryos, during the study period. The exclusion criteria were the presence of any of the following conditions: (1) infertility due to a uterine factor (e.g., thin endometrium, endometrial synechiae); (2) cancer; and (3) systemic disease (e.g., diabetes mellitus, thyroid disease, autoimmune disease).

Study design

Participants were divided into two groups according to the availability of AMH data. The control group comprised women who were treated with a conventional protocol of ovarian stimulation using chronological age and AFC as markers of the ovarian reserve, because AMH data was not obtained prior to beginning ovarian stimulation. The starting dose of gonadotropins for the control group was determined according to AFC with a baseline dose of 450 IU if AFC $\leq$ 5 or decrease dose to 150 IU if AFC > 15.

The average time required to receive AMH level test results in our hospital is 2 weeks; therefore, AMH data for women in the control group was usually not obtained due to the time constraints of patients who live far away from the hospital or abroad, or who did not have a chance to obtain an AMH-level test prior to initiating treatment. The study group consisted of women whose basal AMH levels were measured within 3 months prior to treatment, and whose starting dose of gonadotropins was tailored to their serum levels of AMH of those < 1.0 receiving a 600-IU dose of FSH, those $\geq$ 1.0 and < 1.2 receiving a 525-IU dose of FSH, those $\geq$ 1.2 and < 1.5 receiving a 450-IU dose of FSH, those $\geq$ 1.5 and < 2 receiving a 300-IU dose of FSH, those $\geq$ 2 and < 5 receiving a dose of 225-IU, and those $\geq$ 5 receiving a dose of 150 IU.

Poor response to ovarian stimulation, which resulted in cycle cancelation, was defined as a serum E2 level of $\leq$ 500 pg/mL and $\leq$ two follicles > 16 mm seen on transvaginal ultrasonography on the day of human chorionic gonadotropin (hCG) administration. The main outcomes compared included the initial dose of recombinant FSH (rFSH), total dose of rFSH, duration of stimulation, serum E2 level on hCG day, ovum pick-up (OPU) rate, number of oocytes retrieved, number of embryos per case, embryo transfer (ET) rate, number of embryos transferred, clinical pregnancy rate, implantation rate, live birth rate, and abortion rate of women receiving AMH-tailored stimulation protocols and those undergoing conventional stimulation protocols.

COS

Pelvic ultrasonography was used to check for pelvic cavity abnormalities, including ovarian tumors, on Day 2–3 of the menstrual cycle. Patients underwent IVF treatment using a long down-regulation or short flare-up protocol with a gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist protocol. In the GnRH agonist protocol, pituitary suppression was initiated with 1 mg subcutaneous leuprolide acetate (Takeda Pharma GmbH, Stolberg, Germany) beginning on Day 21 of the previous menstrual cycle until the serum levels of E2 fell below 30 pg/mL, and thereafter 0.5 mg leuprolide acetate until hCG day. In the GnRH antagonist protocol, 0.25 mg subcutaneous cetrorelix (Cetrotide; Serono, Baxter Oncology GmbH, Halle, Germany) or 0.25 mg ganirelix acetate (Orgalutran; Schering-Plough, Whitehouse Station, NJ, USA) was administered daily when the follicles were > 14 mm in diameter until hCG day. All patients received rFSH (Gonal-F; Serono Laboratories, Aubonne, Switzerland) and/or human menopausal gonadotropin (Menopur; Ferring GmbH, Kiel, Germany). The dosage of gonadotropin was determined by the age of the patient and the AFC or the AMH levels. The dosage was then adjusted every 2–3 days in accordance with follicle growth. When a leading follicle $\geq$ 18 mm in diameter was detected by ultrasonography, 10,000 IU of hCG (Pregnyl; Schering-Plough, Kenilworth, NJ, USA) or 250 μg of choriogonadotropin-alfa (Ovidrel; Serono, Rome, Italy) was administered, and oocyte retrieval was performed 34–36 hours later. We performed IVF or ICSI with either ejaculated sperm or surgically retrieved sperm. Up to four embryos were transferred into the uterine cavity on Day 2–3 after oocyte retrieval according to the embryo number and quality. Clinical pregnancy was defined as the presence of an intrauterine gestational sac by ultrasonography at approximately 5 weeks of pregnancy.

Serum AMH measurement

AMH levels were measured by enzyme-linked immunosorbent assay kit (Diagnostic Systems Laboratories, Webster, TX, USA). The detection range of the assay was 0.025–15 ng/mL, with the detection limit at 0.017 ng/mL. Values below the detection limit were considered zero. The intra-assay and interassay variation coefficients were 4.6% and 8.0%, respectively. Samples from all participants were obtained via venipuncture and analyzed by the same laboratory (Department of Immunoassay, MacKay Memorial Hospital, Taipei, Taiwan). The samples were processed according to the manufacturer instructions by centrifuging at 1400*g* for 10 minutes to separate cellular contents and debris; the serum was then transferred to sterile polypropylene tubes to be preserved at −70°C until the assay.

Statistical analysis

The main outcome measures were compared using the Chi-square test or Fisher exact test for comparing percentages and a *t* test for comparing mean values. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). A p value $\leq$ 0.05 was considered statistically significant for all measures.

Results

After applying inclusion and exclusion criteria, 210 patients were included; of them, 116 patients comprised the study group (i.e., the AMH-tailored group), whereas 94 patients comprised the control group (i.e., the conventional stimulation group). Table 1 summarizes their characteristics.