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CLINICAL ARTICLE

Reproductive potential of mature oocytes after conventional ovarian hyperstimulation for in vitro fertilization

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ABSTRACT

Objective: To compare cumulative live birth rate according to the rate of use of metaphase II (MII) oocytes in conventional ovarian stimulation protocols for in vitro fertilization (IVF) or intracytoplasmic sperm injection. **Methods:** In a cohort study, patients aged 18–38 years undergoing their first IVF treatment at one US center were enrolled between February 1, 2009, and August 31, 2013. Ovarian response was categorized by the yield of MII oocytes (low: 1–2; intermediate: 3–6; high: ≥ 7). The main outcome measure was cumulative live birth rate over a 6-month period. **Results:** Among 250 participants, 3240 oocytes (mean \pm SEM 12.96 \pm 0.50) were retrieved and there were 152 (60.8%) live births. Overall, 172 (68.8%) participants had a high oocyte yield, 61 (24.4%) an intermediate yield, and 17 (6.8%) a low yield. The cumulative live birth rate was 58.8% (10/17) in the low-yield group, 55.7% (34/61) in the intermediate-yield group, and 62.8% (108/172) in the high-yield group ($P = 0.35$). **Conclusion:** In conventional ovarian stimulation, live birth rate is not affected by the ovarian response. Whether oocytes produced from a low ovarian response are biologically more effective than oocytes obtained from a high ovarian response remains to be determined.

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1. Introduction

Conventional in vitro fertilization (IVF) using high doses of gonadotropins has several advantages [1,2], including the production of a high number of oocytes that can be retrieved to allow the formation of more embryos, potentially leading to high rates of pregnancy [2–4]. Outcome measures for IVF treatment commonly include live birth rate per IVF cycle and live birth rate per embryo transfer; however, live birth rate per number of retrieved mature oocytes can provide additional useful information, particularly because use of oocyte cryopreservation is increasingly widespread [5–8].

Oocyte cryopreservation allows women to electively prolong their reproductive life for family planning and provides fertility preservation for patients with cancer [7]. Outcomes after oocyte cryopreservation are good; as a result, the number of centers performing oocyte cryopreservation is growing. Thus, it would be valuable to assess the reproductive efficiency of human oocytes fertilized in vitro on the basis of oocyte yield [9]. In one study of women aged 23–43 years [9], it was reported that the live birth rate per mature oocyte retrieved—the oocyte utilization rate (OUR)—was approximately 5% for women aged 37 years or younger, 3.8% for women aged 38 years, and 0.8% for women aged 43 years.

The aim of the present study was to determine the metaphase II (MII) oocyte efficiency, as represented by cumulative live birth rate, among fairly young women with normal ovarian reserve who underwent conventional ovarian hyperstimulation for IVF with single or double embryo transfer.

2. Materials and methods

In a cohort study, women aged 18–38 years with normal menstrual cycles who underwent a first conventional IVF treatment at the New Hope Fertility Center, New York, NY, USA, between February 1, 2009, and August 31, 2013, were enrolled. The inclusion criteria were infertility due to unexplained, male, and tubal factors. Women with pre-existing medical conditions and those with a body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) of less than 18.5 or more than 32 were excluded. In addition, participants who had a baseline cycle day-3 follicle-stimulating hormone (FSH) level of 13 mIU/mL or higher were excluded because of potentially diminished ovarian reserve. The study was approved by the Institutional Review Board of New York Downtown Hospital (IRB approval reference no.: JZ-09-08) and the Biomedical Research Alliance of New York (BRANY). Informed consent was obtained from each participant before enrollment.

Conventional ovarian hyperstimulation was performed by the long gonadotropin-releasing hormone (GnRH) agonist protocol using leuprolide acetate (Teva, Sellersville, PA, USA), which was started at

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the mid-luteal phase to achieve ovulation suppression. Ovarian stimulation was achieved with injections of high-dose gonadotropins, including Bravelle and/or Menopur (Ferring, Parsippany, NJ, USA), Follistim (Merck, White House Station, NJ, USA), or Gonal F (EMD Serono, Rockland, MA, USA), at a starting dose of 150–300 IU daily depending on the age and ovarian reserve of the participant. The GnRH agonist was administered daily, along with the gonadotropin injections. During ovarian stimulation, participants were closely monitored by transvaginal ultrasonography and measurements of serum estradiol, progesterone, and luteinizing hormone.

When at least two follicles reached a diameter of 18 mm or greater, oocyte maturation was induced with human chorionic gonadotropins, such as Novarel (Ferring), Pregnyl (Merck), or Ovidrel (EMD Serono). The retrieved oocytes were fertilized by either conventional IVF or intracytoplasmic sperm injection [10]. All embryos were subsequently cultured until the blastocyst stage, and one or two blastocysts were transferred in a fresh cycle. The remaining surplus blastocysts were frozen by vitrification. The frozen embryos were then thawed and subsequently transferred in a natural or artificial cycle with oral Estrace (Actavis Pharma, Parsippany, NJ, USA) within 6 months of oocyte retrieval.

The participants were subdivided into three subgroups according to the yield of mature MII oocytes after oocyte retrieval: “low” represented a yield of 1–2 oocytes, “intermediate” a yield of 3–6 oocytes, and “high” a yield of 7 or more oocytes. Patients who had no oocytes retrieved were excluded from the data analysis.

The main outcome measure was cumulative live birth rate over a 6-month period, which was calculated as the number of births divided by the total number of participants in each subgroup. The likelihood of live birth was expressed as an odds ratio (OR) with 95% confidence intervals (CIs).

Secondary outcomes were OUR, implantation rate, clinical pregnancy rate, number of blastocysts formed, total dose of gonadotropins used per cycle, number of fertilized oocytes, and number of days of stimulation (i.e. number of days during which the participants received gonadotropins). The implantation rate was defined as the number of gestational sacs observed on ultrasonography at 6 weeks of pregnancy divided by the number of blastocysts transferred. A clinical pregnancy was defined as at least one intrauterine sac at 6 weeks of gestation, and live birth was defined as a neonate born after 22 weeks of gestation and weighing at least 500 g. The cumulative clinical pregnancy rate over a 6-month period was calculated as the number of pregnancies divided by the total number of participants in each subgroup. The OUR was calculated as the number of live births over a 6-month period divided by number of MII oocytes produced after only one cycle of ovarian stimulation and oocyte retrieval.

Prism software (GraphPad, San Diego, CA, USA) was used to perform all data analyses. Power analysis indicated that 73 participants in each group would be needed to detect a 20% difference in live birth rate with 80% power and a one-tailed α value of 0.05.

Continuous variables were expressed as mean \pm SEM and compared by *t* test or analysis of variance (ANOVA) as appropriate. Categorical variables were expressed as number (percentage) and compared by χ^2 test. Multivariate logistic regression analyses were used to evaluate low, intermediate, and high ovarian responses as independent correlates of a live birth. To estimate the predictive ability of the number of MII oocytes and age (the strongest predictor of a subsequent live birth), receiver operating characteristic (ROC) curves were generated and the area under the ROC curve (AUC) was determined. $P < 0.05$ was considered statistically significant.

3. Results

During the study period, 250 participants enrolled in the study. The demographic and clinical characteristics of the participants are summarized in Table 1. Among all participants, 3240 total oocytes

Table 1
Demographic and baseline characteristics (n = 250).^a

Characteristic	Value
Age, y	32.02 \pm 0.26 (22–38)
Body mass index ^b	24.34 \pm 0.19 (18.6–30.7)
Baseline FSH, mIU/mL	8.37 \pm 0.15 (3–12)
Primary infertility	122 (48.8)
Nulliparous	200 (80.0)
Ethnic origin	
White	116 (46.4)
Black	58 (23.2)
Hispanic	44 (17.6)
Asian	24 (9.6)
Mixed/other	8 (3.2)
Infertility diagnosis	
Tubal	93 (37.2)
Unexplained	60 (24.0)
Male	43 (17.2)
Mixed male/female	23 (9.2)
Other	31 (12.4)

Abbreviation: FSH, follicle-stimulating hormone.

^a Values are expressed as mean \pm SEM (range) or number (percentage).

^b Calculated as weight in kilograms divided by the square of height in meters.

were retrieved (mean \pm SEM 12.96 \pm 0.50; range 1–43), of which 2525 were MII oocytes (10.1 \pm 0.42; range 1–38), yielding a maturity rate of 77.9%. Over a 6-month period, 152 live births occurred, giving a live birth rate of 60.8%. Three patients had no oocytes retrieved.

Most participants (172/250 [68.8%]) had a yield of seven MII oocytes or more. Only 17 (6.8%) participants had a low ovarian response, and 61 (24.4%) had an intermediate ovarian response. Women who had a high ovarian response produced significantly more fertilized oocytes and more blastocysts than did women who had an intermediate ovarian response ($P < 0.001$) (Table 2). In turn, women who had an intermediate ovarian response produced significantly more fertilized oocytes and more blastocysts than did women who had a low ovarian response ($P < 0.001$) (Table 2).

The implantation rate was highest for women with a low MII oocyte yield, followed by those with an intermediate MII oocyte yield, and then a high MII oocyte yield ($P < 0.001$) (Table 2, Fig. 1). The number of blastocysts transferred was significantly higher among participants with a high ovarian response than among those with an intermediate ovarian response ($P < 0.001$), and significantly higher among participants with an intermediate ovarian response than among those with a low ovarian response ($P < 0.001$) (Table 2). However, the rates of clinical pregnancy and live birth did not differ among the three groups (Table 2). The MII OUR was inversely related to ovarian response: it was 38.5% in the group with low ovarian yield, 12.2% in the intermediate-yield group, and 4.9% in the high-yield group ($P < 0.05$) (Fig. 1).

Among all participants, logistic regression showed that age was a negative predictor for achieving a live birth ($P = 0.018$). In multivariate logistic regression, after adjusting for day-3 FSH, day-3 estradiol, number of days of stimulation, and total dose of gonadotropins used per cycle, the number of MII oocytes retrieved (i.e. low, intermediate, or high) did not affect the likelihood of achieving a live birth (OR 0.99, 95% CI 0.96–1.04; $P = 0.088$) (Table 3).

In ROC curve analysis, the AUC for number of MII oocytes was 0.46 \pm 0.02 (95% CI 0.97–1.05; $P = 0.77$), and that for age was 0.61 \pm 0.31 (95% CI 0.86–0.98; $P = 0.01$) (Fig. 2). A threshold of eight or more mature oocytes produced the highest likelihood of achieving a live birth (positive likelihood ratio 1.15), but with poor sensitivity (61.5%) and specificity (46.5%).

4. Discussion

The present study has reported the efficiency of MII oocyte yield as reflected by cumulative live birth rate over a 6-month period among fairly young women with normal ovarian reserve who underwent

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