Egg production predicts a doubling of in vitro fertilization pregnancy rates even within defined age and ovarian reserve categories

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Objective: To examine the age-independent association of ovarian response and IVF outcome in women with normal and abnormal ovarian reserve.
Design: Retrospective analysis.
Setting: Academic IVF center.
Patient(s): Four thousand eight hundred sixty-two consecutive IVF cycles.
Intervention(s): None.
Main Outcome Measure(s): Outcome of IVF was analyzed as a function of ovarian response to controlled ovarian hyperstimulation and ovarian reserve.
Result(s): The mean patient age was 36.2 ± 4.5 years. Younger patients and patients with normal ovarian reserve were found to have better implantation and clinical pregnancy rates. Patients with normal ovarian reserve had a higher number of oocytes retrieved, mature oocytes, two-pronuclei embryos, and embryos transferred. A greater number of embryos were transferred for patients with higher ovarian response. Higher clinical pregnancy rates were seen in those patients who had more oocytes retrieved for all patients, regardless of age and ovarian reserve. In fact, clinical pregnancy rates more than doubled for specific patient groups.
Conclusion(s): In an age-independent fashion, ovarian response is highly predictive of IVF outcome in women with normal and abnormal ovarian reserve. These findings highlight the importance of not solely relying on age when presenting and discussing IVF outcome data and are useful information when helping patients interpret their IVF cycle response. (Fertil Steril® 2005;83:24–9. ©2005 by American Society for Reproductive Medicine.)

Key Words: IVF outcome, ovarian response, age independent

Maternal age is the major determinant in predicting IVF outcome. Fecundity decreases with advancing maternal age (1, 2). This decline is also reflected in older women undergoing assisted reproduction, such as IVF (3). In addition, IVF success is modified by ovarian reserve. Elevated FSH levels have been associated with poor performance during IVF and are a reflection of a diminished ovarian reserve (4).

Ovarian response has also been suggested as a predictor of IVF treatment (4). Patients who have a good response to controlled ovarian hyperstimulation (COH) have been found to have a better prognosis for IVF treatment. One previous study has suggested that a cutoff of fewer than three follicles during ovarian stimulation should be used as a guideline for cycle cancellation (6). It has been proposed that response to COH may be used independently to predict successful IVF outcome.

In this study, we attempted to define how ovarian response coupled with ovarian reserve can predict age-independent IVF outcome in a large cohort of patients.

MATERIALS AND METHODS

From 1996 to 2000, 4,862 consecutive IVF cycles from The Center of Reproductive Medicine and Infertility at the Weill Medical College of Cornell were retrospectively reviewed. The study was approved by the Institutional Ethics and Research Committee.

Cycles using donor oocytes, transfer of frozen embryos, natural cycle, experimental protocols, or blastocysts were excluded. On the basis of day 3 FSH levels, patients were labeled as having either normal or poor ovarian reserve. By using an RIA (Quantitative FSH Assay; Solid Phase Inc., Portland, ME), a cutoff of 20 mIU/mL was considered as an indicator of abnormal ovarian reserve. Normal ovarian reserve patients were those patients who had a day 3 FSH level

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of <20 mIU/mL. Poor ovarian reserve patients were defined as those patients who had a day 3 FSH level of 20–22 mIU/mL and/or a day 3 estradiol (E_2) level of >70 pg/mL and/or who had a history of poor response in previous protocols (i.e., estrogen levels <500 pg/mL, follicle numbers ≤3).

At our center, patients with an FSH of > 22 mIU/mL had a pregnancy rate close to 0, and hence this number has been used as our cutoff for IVF treatment.

An IVF cycle was canceled if no more than five follicles were present, and E_2 level was <1,000 pg/mL.

Normal ovarian reserve patients were treated with a standard ovulation induction protocol and underwent IVF as described elsewhere (7). In brief, patients were started with luteal phase leuprolide acetate (GnRH-a, Lupron; TAP Pharmaceuticals, Deerfield, IL; 0.5–1 mg SC daily) until ovarian suppression was achieved. Poor ovarian reserve patients began stimulation on day 2 of their treatment cycle. These patients were placed on a flare based, clomiphene citrate based, or no-lupron protocol.

For both normal and poor ovarian reserve patients, ovarian stimulation was effected with a combination of gonadotropins (hMG) and/or FSH; Pergonal or Metrodin; Serono, Waltham, MA), employing a step-down protocol. Human chorionic gonadotropin (3,300 to 10,000 IU) was administered when at least two follicles of 17-mm diameter were observed by transvaginal ultrasound. Oocytes were harvested by transvaginal ultrasound-guided follicular puncture approximately 35 hours after hCG administration.

Conventional oocyte insemination or micromanipulation was performed as indicated. Morphologically normal embryos were transferred into the uterine cavity approximately 72-hours after retrieval. As per our standard protocol, the number of embryos transferred was dependent on maternal age. In general, women under 34 years of age, between 35 to 39 years, and aged 40 years and over underwent a transfer of three, four, and five embryos, respectively.

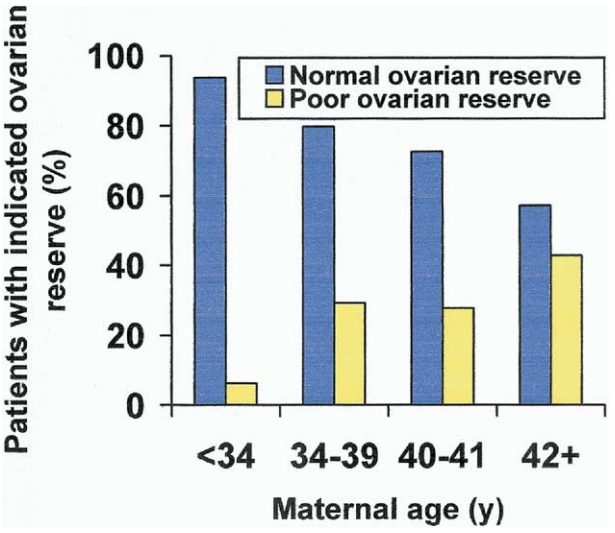
Methylprednisolone (16 mg/d) and tetracycline (250 mg every 6 hours) were administered for 4 days to all patients, commencing on the day of oocyte retrieval. Progesterone supplementation was initiated on the 3rd day after hCG administration (25–50 mg IM daily) and was continued until sonographic assessment of the pregnancy at 47–51 days of gestation, as determined by the day of oocyte insemination (day 14).

Data were collected regarding outcome of IVF cycle. A clinical pregnancy was defined as the presence of a fetal heartbeat at the 7-week sonogram. Implantation rate was defined as number of fetal hearts per the number of embryos transferred.

Patient data is analyzed with respect to maternal age, ovarian reserve, and number of oocytes at the time of retrieval. Data is collected using the Stat View program. Chi-square analysis and nonparametric *t* tests were performed. A *P* value of <.05 was considered significant.

FIGURE 1

Distribution of patients with normal vs. poor ovarian reserve, by maternal age (y). Blue bars, normal ovarian reserve. Yellow bars, poor ovarian reserve.



Yih. Egg production predicts IVF pregnancy rates. Fertil Steril 2005.

RESULTS

Four thousand eight hundred sixty-two consecutive IVF cycles were studied over a 4-year period (1996–2000). The mean (± SD) maternal age was 36.3 (±4.5) years. Overall, clinical pregnancy rate per retrieval and implantation rate per retrieval were 46.9% and 22.1%, respectively.

Effect of Age

Maternal age was found to be an important factor in predicting implantation and clinical pregnancy rates. Younger patients had significantly higher implantation and clinical pregnancy rates (for patients aged <34, 34–39, 40–41, and ≥42 years of age, the implantation rates were 33.7%, 22.2%, 12.2%, and 6.3%, and the clinical pregnancy rates were 58.2%, 48.9%, 39.5%, and 25.7%, respectively; *P*<.0001).

Effect of Ovarian Reserve

Eighty percent (3,881 of 4,862 patients) of the total number of patients were defined as having normal ovarian reserve, whereas 20% (981 of 4,862 patients) had poor ovarian reserve. Patients with a normal ovarian reserve were younger than patients with an abnormal ovarian reserve (35.6 ± 4.5 vs. 38.7 ± 3.8 years, *P*<.0001). Not surprisingly, as maternal age increased, the percentage of patients with poor ovarian reserve also increased (See Fig. 1). Patients with a