

In vitro fertilization versus conversion to intrauterine insemination in the setting of three or fewer follicles: how should patients proceed when follicular response falls short of expectation?

David E. Reichman, M.D.,^a Vinay Gunnala, M.D.,^b Laura Meyer, M.D.,^a Steven Spandorfer, M.D.,^a Glenn Schattman, M.D.,^a Owen K. Davis, M.D.,^a and Zev Rosenwaks, M.D.^a

^a Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine and ^b Weill Cornell Medical Center, New York, New York

Objective: To determine whether in vitro fertilization (IVF) cycles with suboptimal response should be converted to intrauterine insemination (IUI) or proceed to oocyte retrieval (OR).

Design: Retrospective cohort.

Setting: Academic medical center.

Patient(s): All patients initiating IVF from January 2004 through December 2011.

Intervention(s): OR versus conversion to IUI.

Main Outcome Measure(s): A total of 1,098 patients were identified whose IVF cycles were characterized by recruitment of three or fewer follicles, excluding patients with bilateral tubal disease or severe male factor. Cycles with three follicles were defined as those with three follicles ≥ 14 mm with no fourth follicle ≥ 10 mm. Cycles with two or fewer follicles were similarly defined. Outcomes were compared for patients proceeding with OR ($n = 624$) versus converting to IUI ($n = 474$). Age-adjusted relative risks for pregnancy were calculated, stratifying for number of follicles.

Result(s): The likelihood of retrieving at least one mature oocyte (82.9% vs. 94.8% vs. 96.2%), having at least one zygote (61.9% vs. 76.8% vs. 84.2%), and undergoing transfer (57.1% vs. 73.0% vs. 83.3%) increased significantly with increasing follicle number. Patients with three or fewer follicles were 2.6 times more likely to achieve a live birth with IVF versus IUI (9.3% vs. 3.4%). This benefit was only apparent when at least two follicles were present. No benefit was gained by performing OR in the setting of one follicle.

Conclusion(s): IVF compared with IUI presents superior pregnancy rates in the setting of two or more follicles. Assisted reproduction programs may benefit their patients by pursuing IVF in this scenario. (Fertil Steril® 2013;100:94–9. ©2013 by American Society for Reproductive Medicine.)

Key Words: IVF, IUI, conversion, poor responders

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Reprint requests: Zev Rosenwaks, M.D., Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical Center, 1305 York Avenue, New York, New York 10021 (E-mail: zrosenw@med.cornell.edu).

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The recruitment and development of multiple follicles in response to gonadotropins is a principle component of controlled ovarian hyperstimulation for IVF. The presence of four or more large follicles in response to stimulation is frequently used as a criterion for proceeding with oocyte retrieval (OR) (1–6); those

patients with recruitment of three or fewer follicles are often counseled for conversion to intrauterine insemination (IUI), except in those cases in which bilateral tubal occlusion or severe male factor infertility render IUI futile. The decision to proceed with OR, convert to IUI, or cancel the cycle altogether is a difficult choice for patients and physicians alike, informed by relatively few published studies (5–13).

A significant proportion of patients at our center are poor responders who have failed numerous cycles (14). Some of these patients elect to undergo oocyte retrieval despite the recruitment of three or fewer follicles—patients we will refer to as “extremely poor responders.” Counseling such patients on the potential for failed retrieval (no oocytes retrieved), absence of normal fertilization, and the probability of live birth with IVF versus IUI is extremely challenging in the absence of robust clinical data. To that end, we reviewed all charts of patients undergoing IVF cycles where three or fewer follicles were recruited, and analyzed the likelihood of successful outcomes according to whether OR or conversion to IUI was pursued.

MATERIALS AND METHODS

Cycle Inclusion Criteria

This study was approved by the Weill Cornell Medical College Institutional Review Board. Cycles selected for inclusion were identified after review of all IVF cycles performed at the Weill Cornell Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine from January 2004 through December 2011. The inclusion criterion was any fresh IVF cycle characterized by three or fewer follicles present on ultrasound on the day of hCG administration. Cycles with one follicle were defined as those in which a single follicle >14 mm was present at trigger with no second follicle ≥ 10 mm. Cycles with two follicles had two follicles ≥ 14 mm present at trigger with no third follicle ≥ 10 mm. Cycles with three follicles had three follicles ≥ 14 mm at trigger with no fourth follicle ≥ 10 mm. All ultrasound examinations were performed by attending physicians. Patients with bilateral tubal occlusion, hydrosalpinges, or couples with severe male factor infertility (characterized by <1 million total motile sperm) were excluded from analysis. A total of 19,474 IVF cycles were analyzed for inclusion.

Clinical Protocols

Protocols for stimulation, OR, IVF, embryo culture, and embryo transfer (ET) were conducted according to previously described standard protocols (15). Briefly, patients either were down-regulated with the use of a GnRH agonist (Lupron; Abbott Pharmaceuticals) followed by stimulation with gonadotropins (Follistim, Merck;Gonal-F, EMD-Serono; and/or Menopur, Ferring) or were stimulated with gonadotropins until criteria were met for pituitary suppression with a GnRH antagonist (0.25 mg Ganirelix acetate, Organon; or 0.25 mg Cetrotide, EMD-Serono).

GnRH agonists were used in either “long” or “short” protocols as deemed clinically appropriate; this decision was based on earlier response and individual physician preference pending evaluation of the patient. Luteal suppression was begun with a GnRH agonist 8 days after an LH surge.

For GnRH antagonist-based cycles, patients were started on 0.25 mg Ganirelix or Cetrotide according to a flexible dosing schedule when either the lead follicle attained a mean diameter of 13 mm or the E₂ level exceeded 300 pg/mL. Patients receiving luteal suppression for antagonist-based cycles received E₂ patches starting 10 days after the LH surge. 10,000 IU hCG (Profasi, EMD-Serono; Novarel, Ferring Pharmaceuticals; or Pregnyl, Schering-Plough) was administered when one follicle measured ≥ 17 mm (1-follicle group), two follicles measured ≥ 17 mm (2- or 3-follicle group), or earlier/later as informed by previous IVF performance. Patients with three or fewer follicles were counseled regarding the risks and benefits of proceeding with IVF versus converting to IUI. In general, patients with three follicles were encouraged to undergo IVF whereas patients with one follicle were encouraged to undergo IUI, although each patient’s situation was evaluated on an individual clinical basis. Proceeding with IVF versus converting to IUI in the setting of only two follicles was a highly individualized decision after the couple and their attending physician had conferred, taking into account procedural invasiveness, financial cost to the patient, and the likelihood of persistently poor response during future treatments.

For those patients electing to undergo IUI, 10,000 IU hCG was administered in the evening, with IUI performed 36 hours later (16, 17). Follicular size criteria for trigger was the same as used for IVF. Semen specimens were prepared with the use of density-gradient isolation of motile spermatozoa. Vaginal progesterone suppositories (Endometrin; Ferring Pharmaceuticals) were begun 2 days following IUI in all cases.

For patients moving forward with IVF, retrieval was performed in the standard fashion under conscious sedation with propofol 35 hours after hCG administration. One day after OR, luteal progesterone supplementation was begun with the use of 25–50 mg intramuscular progesterone, depending on E₂ response. All patients meeting inclusion criteria underwent day-3 embryo transfer, which was performed with a Wallace catheter (Marlow/Cooper Surgical).

Outcome Variables Assessed

Demographic characteristics of patients undergoing IVF versus those choosing IUI were compared, including age, gravity, parity, body mass index (BMI), number of previous IVF attempts, day 3 FSH, and starting dose of gonadotropins. For those patients undergoing IVF, the number of harvested oocytes, metaphase II (MII) oocytes, 2-pronuclei (2PN) embryos, and day 3 embryos were analyzed according to number of follicles present at trigger. Clinical pregnancy and live-birth rates were tabulated according to whether IVF or IUI was performed, stratifying for the number of follicles present at trigger.

Fertilization rate was defined as the number of 2PN zygotes divided by the total number of mature oocytes inseminated for intracytoplasmic sperm injection cycles, or divided by the number of total oocytes retrieved in insemination cycles. Implantation rate was defined as the number of sacs detected by ultrasound at 5–6 weeks divided by the total number of embryos transferred. Clinical pregnancy rate was defined as the number of cycles with at least one viable fetus (as evidenced by ultrasound of fetal cardiac activity at 7 weeks) per retrieval. Live birth rate per retrieval was defined as the

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