

Outcomes in, and characteristics of, patients who undergo intrauterine insemination immediately after failed oocyte retrieval

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Objective: To describe the patient and cycle characteristics of women who undergo intrauterine insemination (IUI) immediately after an unsuccessful oocyte retrieval.

Design: Retrospective case series.

Setting: University-affiliated center.

Patient(s): Women who underwent an oocyte retrieval procedure in which no oocytes were retrieved followed by an IUI on the same morning.

Intervention(s): None.

Main Outcome Measure(s): Live birth rate, subsequent live birth rate.

Result(s): From 2011 to 2019, 63 cycles in 57 patients were identified. The mean (SD) age was 39.6 (4.6) years, and diminished ovarian reserve (94.7%) was the most common diagnosis. The median (IQR) number of previous IVF cycles in this cohort was 3 (1–7), with 56.1% having had at least one previous canceled IVF cycle. The majority of patients had undergone either controlled ovarian hyperstimulation (COH) (64.9%) or modified natural cycles (21.1%). The mean (SD) number of follicles >14 mm at the time of trigger was 1.9 (1.4), with 38.9% of patients manifesting a drop in their estradiol levels after the trigger. One pregnancy resulting in a live birth was identified (1.8%). For patients who underwent subsequent IVF cycles, 60.7% had at least one subsequent cancelled cycle. Three patients went on to achieve a live birth using autologous oocytes (6.5%).

Conclusion(s): Same-day IUI for patients who have no oocytes retrieved is associated with a <2% chance of achieving a live birth. Of patients who attempt subsequent IVF cycles, nearly two thirds will go on to have at least one subsequent cancelled cycle. In this poor-prognosis cohort, fewer than 10% will ultimately achieve a live birth by the use of autologous oocytes. (Fertil Steril Rep® 2020;1: 239–42. ©2020 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, intrauterine insemination, oocyte retrieval, oocytes

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Nearly 1 out of every 20 patients undergoing controlled ovarian hyperstimulation (COH) fails to produce more than five mature follicles (1). The in-cycle management of poorly responding patients can entail conversion of the in vitro fertilization (IVF) cycle to intrauterine insemination (IUI), cycle cancellation, or continua-

tion with oocyte retrieval with the expectation of retrieving a limited number of oocytes. We have previously described cycle outcomes in patients undergoing IVF with three or fewer follicles who either underwent conversion to IUI or proceeded with IVF; these patients were 2.6 times more likely to achieve a live birth after IVF versus

IUI (9.3% vs. 3.4%), specifically when at least two follicles were present (2). Two other studies comparing outcomes of IVF with conversion to IUI in patients with poor ovarian response did not describe a similar benefit in proceeding with oocyte retrieval (3, 4).

As a tertiary center treating a significant number of infertility patients,

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our practice has routinely allowed patients with poor ovarian response to proceed with oocyte retrieval as an alternative to cycle cancellation or conversion to IUI. However, these patients are at an increased risk of having no oocytes at retrieval. In our prior study (2), patients with only a single follicle failed to have an oocyte retrieved in 8.6% of cases. In instances in which no oocytes are identified after follicle aspiration, we consider proceeding with IUI in patients with at least one (ipsilateral) patent fallopian tube and normal semen parameters, predicated on the possibility of tubal capture of an ovulated or “leaked” oocyte. Given that outcomes after this approach have not previously been reported, we sought to describe the potential utility of this strategy as well as the patient and cycle characteristics of women who undergo IUI immediately after a failed oocyte retrieval.

METHODS

Study Population and Design

All patients undergoing oocyte retrieval between January 1, 2011, and December 31, 2019, at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine were reviewed. Patients were included in this retrospective cohort if they underwent a COH cycle, a stimulated ovulation induction cycle, or a modified natural cycle at our center that culminated in an oocyte retrieval attempt yielding no oocytes, followed by an IUI on the same morning of the failed retrieval.

Clinical Protocols

Patients underwent COH with a flexible gonadotropin-releasing hormone (GnRH) antagonist or a GnRH agonist protocol, with protocol and dose selected according to patient age, weight, ovarian reserve, and prior response to stimulation (5, 6). Patients with diminished ovarian reserve either received estrogen priming in the midluteal phase of the prior cycle or were pretreated with a short course of oral contraceptives (7). Patients who underwent modified natural cycles or ovulation induction (clomiphene citrate or letrozole) were seen on day 2 of their menstrual cycle and returned periodically for cycle monitoring with assessment of serum hormones and transvaginal sonograms to monitor follicular growth. The decision to augment natural cycles with gonadotropins was made at the discretion of the treating physician. Oocyte maturation was triggered with either human chorionic gonadotropin (hCG) alone or a dual trigger with hCG and a GnRH agonist (leuprolide acetate) (8, 9). Oocyte retrieval was performed with the patient under conscious sedation by the use of transvaginal ultrasound guidance approximately 35 hours after the ovulatory trigger, with a 30-cm, 16-gauge oocyte aspiration needle with 80 mm Hg suction pressure.

If it was determined that no oocytes were retrieved after follicle aspiration, in the setting of normal semen parameters and at least one patent fallopian tube, we offered patients the option of proceeding with an IUI that morning in an attempt to “salvage” the treatment cycle. All patients received vaginal progesterone supplementation after IUI. Serum hCG testing was performed 14 days after IUI.

This study was approved by the Weill Cornell Medical College Institutional Review Board, study protocol number 19-06020283.

RESULTS

Over a 9-year period, 63 cycles in 57 patients were identified in which an IUI was performed immediately after an unsuccessful oocyte retrieval. Of these 57 patients, there was an 8.8% risk of recurrent failure to retrieve oocytes: four patients underwent a second unsuccessful oocyte retrieval, and one patient underwent a third. Our analysis focuses on the first failed oocyte retrieval in this cohort.

The mean (SD) age of these patients was 39.6 (4.6) years, and the most common infertility diagnosis was diminished ovarian reserve (94.7%), followed by male-factor infertility (24.6%). The mean (SD) anti-müllerian hormone level was 0.5 (0.9) ng/mL. Most of these patients had previously undergone IUI (median: 4, IQR: 2–6) or IVF cycles (median: 3, IQR: 1–7). Of the patients who had undergone previous IVF cycles at our center, 56.1% (n=33) had at least one previous canceled cycle for poor response, estradiol drop prior to ovulatory trigger, or premature ovulation. Patient characteristics are summarized in Table 1.

The majority of patients who had no oocytes retrieved had undergone COH (64.9%), followed by modified natural cycle (21.1%), natural cycle (8.8%), ovulation induction converted to COH (3.5%), and ovulation induction (1.8%). The mean (SD) antral follicle count was 4.2 (3.1), and 19.6% had a dominant follicle >10 mm at cycle start. One in three women had an ovarian cyst at cycle start (32.1%). The average cycle length was 13 (9–16) days with a mean (SD) total

TABLE 1

| Characteristic | Study cohort (n = 57) |
|---|-----------------------|
| Patient characteristics. | |
| Age, years, mean (SD) | 39.7 (4.6) |
| Gravidity, median (IQR) | 1 (0–2) |
| Parity, median (IQR) | 0 (0–1) |
| BMI (kg/m ²), mean (SD) | 24.5 (8.7) |
| Ethnicity, n (%) | |
| Other | 26 (45.6) |
| White | 24 (42.1) |
| Asian | 7 (12.3) |
| Infertility diagnosis, n (%) | |
| Diminished ovarian reserve | 54 (94.7) |
| Male factor | 14 (24.6) |
| Tubal factor | 13 (22.8) |
| Uterine factor | 11 (19.3) |
| Anovulatory/PCO | 1 (1.8) |
| Endometriosis | 6 (10.5) |
| Idiopathic | 1 (1.8) |
| AMH ng/mL, mean (SD) | 0.5 (0.9) |
| Antral follicle count, mean (SD) | 4.2 (3.1) |
| Previous IUI cycles, median (IQR) | 4 (2–6) |
| Previous IVF cycles, median (IQR) | 3 (1–7) |
| History of previously cancelled IVF cycles, n (%) | 33 (73.3) |

AMH = anti-müllerian hormone; BMI = body mass index; IQR = interquartile ratio; IUI = intrauterine insemination; IVF = in vitro fertilization; PCO = polycystic ovary; SD = standard deviation.

Bortoletto. IUI after failed oocyte retrieval. *Fertil Steril Rep* 2020.

gonadotropin dose of 3,411.3 (2,845.2). The mean (SD) follicular size on the day of trigger was 19.8 (2.7) mm with a mean of 1.9 (1.4) total follicles >14 mm in size. Nearly all (n=49, 86.0%) patients received an hCG- only ovulatory trigger, with appropriate subsequent (next-morning) serum hCG levels (mean: 217 mIU/mL, SD: 200.6). Thirteen percent of patients experienced an estradiol drop prior to trigger, with a median (IQR) of -8.0% (-18.8 to -0.9). One in three patients (38.9%) had a drop in estradiol following the ovulatory trigger, with a median (IQR) of -12.7% (-27.1 to -8.0). Of the 57 patients with no oocytes retrieved, 61.4% (n=35) had no apparent reason for retrieval failure, 35.1% (n=20) showed evidence of premature ovulation, and 3.5% (n=2) were secondary to an inability to access the ovary for oocyte retrieval. Cycle characteristics are displayed in Table 2.

Of the 57 patients who underwent IUI, only one became pregnant and went on to deliver a term live birth (1.8%). Forty-six patients had at least one subsequent ART cycle (IUI, IVF, or modified natural cycle). Of the subsequent IVF attempts (n=28) available for analysis at our center, 60.7% (n=17) had at least one subsequent cancelled cycle. Of patient who underwent subsequent ART treatment (IUI, IVF, or modifier natural) at our center (n=46), three patients went on to achieve a live birth using autologous oocytes (6.5%). Subsequent reproductive outcomes are displayed in Table 3.

DISCUSSION

In this cohort of 57 women undergoing same-day IUI following follicle aspiration procedures in which no oocytes were retrieved, only one successful pregnancy was achieved following the ensuing IUI, for a live birth rate of 1.8%. Our

TABLE 2

| Cycle characteristics. | |
|--|-----------------------|
| Characteristic | Study cohort (n = 57) |
| Cycle type, n (%) | |
| COH | 37 (64.9) |
| Natural cycle converted to COH | 12 (21.1) |
| Natural cycle | 5 (8.8) |
| Ovulation induction converted to COH | 2 (3.5) |
| Ovulation induction | 1 (1.8) |
| Days of stimulation median (IQR) | 13 (9–16) |
| Total gonadotropin dose (IU), mean (SD) | 3,411.3 (2,845.2) |
| Size of leading follicle at time of trigger, mean (SD) | 19.8 (2.7) |
| No. of follicles >14 mm at time of trigger, mean (SD) | 1.9 (1.4) |
| Trigger type, n (%) | |
| hCG only | 49 (86.0) |
| hCG + GnRH agonist | 8 (14.0) |
| Post-trigger LH mIU/mL, mean (SD) | 48.6 (51.5) |
| Post-trigger hCG mIU/mL, mean (SD) | 217.1 (200.6) |

COH = controlled ovarian hyperstimulation; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; IQR = interquartile ratio; LH = luteinizing hormone.

Bortoletto. IUI after failed oocyte retrieval. Fertil Steril Rep 2020.

TABLE 3

Subsequent reproductive outcomes.

| Outcome | Study cohort |
|---|--------------|
| Subsequent treatment, n (%) | |
| Donor oocytes | 6 (10.5) |
| Autologous IVF | 28 (49.1) |
| Intrauterine insemination | 32 (56.1) |
| Of patients who pursued autologous IVF, n (%) | |
| Recurrent no oocytes retrieved | 5 (17.9) |
| Recurrent canceled IVF cycles | 17 (60.7) |
| Subsequent live birth, n (%) | |
| Donor oocytes | 4 (66.7) |
| Autologous IVF | 3 (6.5) |

IVF = in vitro fertilization.

Bortoletto. IUI after failed oocyte retrieval. Fertil Steril Rep 2020.

data do not support routine use of this treatment strategy as an attempt to salvage cycles in which no oocytes are retrieved. Furthermore, in this particularly poor-prognosis cohort of women, largely of advanced age and with severely diminished ovarian reserve, nearly two-thirds will experience at least one subsequent canceled IVF cycle with a 17.9% risk of at least one recurrent cycle in which no oocytes are retrieved.

Regardless of the potential reasons for unsuccessful recovery of oocytes, the common theme noted in this series of 57 women was significantly diminished ovarian reserve. The mean (SD) age was 39.6 (4.6) years, with a mean anti-müllerian hormone of 0.5 (0.9) ng/mL and a mean of 1.9 (1.4) total follicles >14 mm at the time of the preretrieval trigger. Most patients had previously undergone several IVF attempts (median, 3; IQR, 1–7), with the majority having undergone at least one previously canceled IVF cycle owing to poor ovarian response. Our group has previously identified a diagnosis of diminished ovarian reserve as a specific risk factor for GnRH antagonist failure resulting in premature LH surges/premature ovulation in IVF cycles, as was the case in one out of three women in our current cohort (10).

Whereas our data demonstrate the low likelihood of success of same-day IUI, we believe that understanding the subsequent reproductive outcomes in this patient population is important for counseling. A third of patients demonstrated evidence of premature ovulation, allowing physicians to tailor subsequent cycles to allow for more aggressive GnRH antagonist administration or earlier administration of ovulatory trigger. Of the patients (n = 28) who pursued additional IVF cycles at our center, 60.7% (n = 17) had at least one recurrent cycle cancellation, and 17.9% of patients (n = 5) had a subsequent cycle in which no oocytes were retrieved. When patients (n = 46) who underwent subsequent IUI, IVF, or modified natural cycle at our center are considered, three patients went on to achieve a live birth with the use of autologous oocytes (6.5%).

In summary, the likelihood of failed oocyte retrieval after an adequate preretrieval hCG (or agonist) trigger is heightened in patients with a poor and especially unifollicular response. A “salvage” strategy of same-day IUI for these patients is associated with a <20% chance of achieving a live

birth in that cycle. Of patients who undergo further IVF attempts, nearly two thirds will have a subsequent cancelled cycle, and fewer than 10% will ultimately achieve a live birth with the use of autologous oocytes. These patients warrant individualized counseling regarding their future reproductive potential with the use of autologous oocytes.

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