Revisiting the management of recurrent implantation failure through freeze-all policy


a IVF Laboratory, Al-Yasmeen Fertility and Gynecology Center, Benha; b IVF Laboratory, Nile Badrawi Hospital, Cairo; c Department of Obstetrics and Gynecology, Faculty of Medicine, Kafrelsheikh University, Kafr El-Sheikh; d Obstetrics and Gynecology Department, Faculty of Medicine, Benha University, Benha; e Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo; and f Department of Community Medicine, Faculty of Medicine, Benha University, Benha, Egypt

Objective: To determine whether a freeze-all policy for in vitro human blastocysts improves the ongoing pregnancy rate in patients with recurrent implantation failure (RIF).

Design: Prospective cohort study.

Setting: Single private center.

Patient(s): A total of 171 women with RIF divided into two groups: freeze-all policy group (n = 81) and fresh embryo transfer (ET) group (n = 90).

Intervention(s): Freeze-all policy.

Main Outcome Measure(s): Ongoing pregnancy rate.

Result(s): The clinical pregnancy rate (52% vs. 28%; odds ratio [OR] 1.86; 95% confidence interval [CI], 1.29–2.68) and ongoing pregnancy rate (44% vs. 20%; OR 2.2; 95% CI, 1.04–3.45) were statistically significantly higher in the freeze-all group than the fresh ET group, respectively. The implantation rate was also statistically significant (freeze-all group 44.2% vs. fresh ET group 15.8%; OR 2.80; 95% CI, 2.00–3.92).

Conclusion(s): The freeze-all policy statistically significantly improved the ongoing pregnancy and implantation rates. Thus, a freeze-all policy is likely to be the new key to helping open the black box of RIF. These findings also are useful for further investigating the adverse effect of controlled ovarian stimulation on in vitro fertilization outcomes. (Fertil Steril © 2017; ■ ■ ■ ■ © 2017 by American Society for Reproductive Medicine.)

Key Words: Freeze all policy, recurrent implantation failure

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Recurrent implantation failure (RIF), a distressing clinical problem that affects about 10% of intracytoplasmic sperm injection (ICSI) cycles (1), refers to the failure in a woman younger than 40 years to achieve a clinical pregnancy within three or more consecutive embryo transfer (ET) cycles in which four good-quality embryos are transferred (2). Recurrent implantation failure may be attributed to multiple or interlinked causes, such as defective embryonic quality, inadequate endometrial receptivity, or both (3).

Various approaches have been used to improve ICSI outcomes in cases of RIF, such as attempts to improve the quality of embryos, the receptivity of the endometrium, or the interaction between embryos and endometrium (4, 5). Randomized, controlled studies have indicated that blastocyst transfer and salpingectomy may improve clinical outcomes in couples with RIF (2). Hysteroscopy in the preceding cycle has been reported to improve pregnancy outcomes in couples with three or more failed ET cycles (6), but this evidence has recently been contradicted by a multicenter, randomized controlled trial that showed hysteroscopy to be of no value in RIF (7). Furthermore, other techniques such as assisted hatching are still considered controversial in RIF patients (8), and the same debates...
continue with zygote intrafallopian transfer, cocultures, and preimplantation genetic screening (2, 3, 9).

Embryo implantation, a highly regulated process influenced by ovarian hormones, requires a receptive endometrium, a functional blastocyst, and reciprocal blastocyst–endometrium interaction (10). Supraphysiologic hormone levels during the follicular phase (11) of controlled ovarian stimulation (COS) may result in reduced endometrial receptivity and an impaired uterine environment, which in turn lowers the implantation rate in ICSI cycles and decreases the probability of pregnancy (12). In attempts to provide a more physiologic environment for ET and improve implantation, many studies have suggested a freeze-all policy in which the entire cohort of embryos is electrolytically cryopreserved for transfer in a consecutive frozen-thawed cycle. Freeze-all may improve implantation as well as pregnancy when compared with fresh ET after ICSI (13–15).

We are not aware of any published studies to date that have evaluated whether a freeze-all policy can improve implantation and pregnancy in patients with RIF. Therefore, in hopes of establishing a new approach for RIF management, we investigated whether a freeze-all policy improves ongoing pregnancy rates in women with RIF.

MATERIALS AND METHODS
Patient Selection and Study Design
This prospective cohort study was conducted at a specialized fertility and gynecology center from April 2014 to October 2016. The research ethics committee of the center in which the study was conducted approved the protocol. On the day of oocyte retrieval and before the retrieval procedure, all couples were asked to sign informed consent forms with all of the details of the study written out and explained.

Women were eligible for the study if they were younger than 38 years, had no uterine abnormalities as assessed by a transvaginal ultrasound, had no post-ICSI pregnancies after three fresh ET cycles with ≥4 high-quality embryos transferred, had unexplained implantation failure, and agreed to participate and signed an informed consent form. High-quality embryos were defined as [1] cleaved—seven to eight cells on day 3, with symmetrical blastomeres and no or less than 10% fragmentation by volume according to Istanbul consensus (16); or [2] blastocyst stage—AA, AB, and BA embryos that reached stage 3, 4, or 5 of blastocoelic expansion on day 5 of culture according to the Gardner and Schoolcraft grading system (17). The study design also included midluteal pituitary down-regulation COS cycles, only fresh semen samples, and women with ≥8 mm endometrial thickness at the day of the human chorionic gonadotropin trigger shot. All ICSI cycles that did not result in day-5 blastocysts were excluded.

A total of 171 women with RIF were randomly assigned on the day of oocyte retrieval by use of a computer-based Microsoft Excel spreadsheet into two groups: the freeze-all group, which included 81 women who underwent the freeze-all protocol on day 5 after ICSI followed by a consecutive frozen-thawed embryo transfer (FET); and the fresh ET group (comparison group), which included 90 women who underwent a conventional ICSI followed by day-5 fresh ET. Assigning the participants into the freeze-all or fresh ET protocols was performed through an Excel table, where the first woman was assigned to the freeze-all group and the second woman assigned to the fresh ET; this sequence continued consecutively throughout the study. This study limited the treatment to only one cycle per participant. No hysteroscopies or saline sonograms were performed during in the treatment cycles for the enrolled patients.

COS and Oocyte Retrieval
Pituitary down-regulation was achieved by starting gonadotropin–releasing hormone agonists (Lucrin; Abbot) on day 21 of the preceding cycle, and it was continued throughout the treatment cycle. On treatment cycle day 2, recombinant follicle-stimulating hormone (FSH, Gonal-F; Serono) and/or human menopausal gonadotropin (Menogon; Ferring) and/or human menopausal gonadotropin (Menogon; Ferring) were initiated after laboratory and ultrasound confirmation of down-regulation. The dosage of FSH and/or human menopausal gonadotropin was individualized at 150–450 IU daily, according to patient age, body mass index, antral follicle count, and response to ovarian stimulation. When three or more follicles were ≥18 mm and the mean diameter of the main cohort was 14–15 mm, ovulation was induced by injection of 250 µg/0.5 mL of recombinant human chorionic gonadotropin (Ovitrelle; Serono). Oocyte retrieval was performed 36 hours after the recombinant human chorionic gonadotropin trigger under transvaginal ultrasound guidance.

Semen Sample Processing, Oocyte Denudation, and ICSI
In all patients, ICSI was performed using fresh sperm ejaculates. The semen samples were collected by masturbation after an abstinence period of 3 to 5 days. Semen samples were prepared using a discontinuous sperm gradient centrifugation (ISolate; Irvine Scientific).

Oocytes were denuded 4 hours after retrieval using 40 µL of hyaluronidase (Irvine Scientific) for 30–60 seconds with mechanical aid pipetting. The metaphase-II oocytes were inseminated by ICSI at ×400 original magnification. Groups of three injected oocytes per droplet were cultured in oil-covered (Irvine Scientific) droplets of 50 µL of Single Step Medium (Irvine Scientific) with 10% Serum Substitute Supplement protein (Irvine Scientific). The injected oocytes were then cultured in a gas phase of 6% CO2, 5% O2, 89% N2 inside an incubator chamber at 37°C, which was continued throughout the 5 days of culture (same gas phase and temperature).

Zygote and Blastocyst Morphology Assessment
The fertilization check was performed 17 ± 1 hours after ICSI, and oocytes with two pronuclei were considered normally fertilized. The morphologic features of the blastocysts were assessed according to the Gardner and Schoolcraft criteria (17). Three different parameters were used for grading blastocysts: expansion and hatching stage, and grades of inner cell mass and trophectoderm. Grade A blastocysts included expansion and hatching of 4–6 and inner cell mass/trophectoderm of AA, AB, and BA. Grade B blastocysts included
expansion of 3 and inner cell mass/trophocid of AA, AB, and BA. Grade C blastocysts included grade 3 except for AA, AB, and BA.

**Blastocyst Freezing and Thawing**

All blastocysts were vitrified on day 5 using a vitrification kit (Vitkit-Freeze; Irvine Scientific) according to a previously described protocol (18). Blastocysts were thawed using a thaw kit (Vitkit-Thaw; Irvine Scientific) according to the manufacturer’s instructions. The thawed blastocysts were rinsed and incubated in pre-equilibrated Single Step Medium supplemented with 20% Serum Substitute Supplement overlaid with oil. Only reexpanded blastocysts with no morphologic signs of apoptosis were graded and transferred 4 hours after thawing.

**Endometrial Preparation, Luteal Phase Support, and ET**

In the freeze-all group, patients were prepared for FET by use of the natural cycle with modified luteal support, in which the endometrium was monitored by transvaginal ultrasound and the serum levels of estradiol and progesterone were measured on cycle day 10, 11, or 12. When the endometrium reached or exceeded 8 mm and a dominant follicle of 18–22 mm was monitored, progesterone was administered, and cryopreserved blastocysts were transferred 5 days later.

In the fresh ET group, progesterone was initiated on the day of fertilization. In the freeze-all group, the women were not prescribed progesterone during this cycle; they only received it during the planned frozen/thawed transfer cycles. In both groups, twice daily progesterone vaginal suppositories (Cyclogest; Actavis) at doses of 400 mg were used for ≥14 days; if a pregnancy occurred, progesterone was continued up to 8 weeks of gestation.

All transfers occurred only on day 5 of the blastocyst stage. All transferred blastocysts underwent laser-assisted hatching before ET. The blastocysts were transferred using ET catheters (Labotect) under transabdominal ultrasound guidance.

**Outcomes**

The study’s primary outcome was the ongoing pregnancy rate, defined as the number of pregnancies after 20 weeks of gestation. The secondary outcomes included the rates of implantation (number of intrauterine gestational sacs over the total number of embryos transferred), clinical pregnancy (defined as the presence of fetal heartbeat on ultrasound 4 weeks or more after ET), and early pregnancy loss (unprovoked termination of pregnancy before 12 weeks of gestation).

**Sample Size Estimation**

We calculated that 158 patients were required to have an 80% chance of detecting at a 5% statistical significance level an increase in the ongoing pregnancy rate from 20% in the control group to 40% in the freeze-all group. The 20% was based on an analysis of the preceding cycles of RIF in the center in which the study was conducted.

**Statistical Analysis**

Baseline data and outcome data are summarized separately. Continuous variables are presented as mean and standard deviation (SD), and they were analyzed by Student’s t-test when distributed normally or near normally. Dichotomous variables were reported as proportions and were analyzed by chi-square test, Fisher’s exact test, or binomial logistic regression. Data are presented as odds ratio (OR), 95% confidence interval (CI), and P value whenever appropriate. The absolute differences between two groups were summarized using 95% CI.

The logistic regression analysis was used to verify whether the confounding variables would affect the study’s primary outcome. The variables included the woman’s age, body mass index, previous ICSI cycles, duration of infertility, baseline FSH level, antral follicle count, total gonadotropin dose, days of stimulation, cumulus–oocyte complexes retrieved, number of metaphase-II injected oocytes, rates of fertilization and blastulation, progesterone level, and progesterone exposure duration. All statistical analyses were performed using the computer program SPSS, version 20 (IBM, Inc.).

**RESULTS**

There were no statistically significant differences between the two groups in patients’ demographics or cycle characteristics with regard to age, body mass index, previous ICSI failures, duration of infertility, infertility diagnosis, antral follicle count, basal FSH level, total FSH/human menopausal gonadotropin dose, estradiol level, progesterone level, number of cumulus–oocyte complexes, or number of metaphase-II oocytes (Table 1). Both groups showed similarity in the rate of fertilization, blastocyst formation, number of blastocysts transferred, and blastocyst grading (see Table 1). The mean of the endometrial thickness on the day of ET was statistically significantly higher in the fresh ET group (11.1 mm) as compared with the freeze-all group (10.5 mm) (OR 0.60; 95% CI, 16–1.04; P = .008).

A total of 287 blastocysts were cryopreserved. Of these, 188 were thawed, 183 survived post-thawing (97.3% survival rate), and 173 were transferred to 81 women of the freeze-all group (Table 2).

Despite the similar number and grade of the blastocysts transferred (see Table 1), there was a statistically significantly higher pregnancy rate (overall) in freeze-all group (48 of 81; 59.3%) than in the fresh ET group (31 of 90; 34.4%; OR 2.77; 95% CI, 1.49–5.15; P = .001). Similarly, the implantation rate was statistically significantly improved in the freeze-all group (69 of 173; 39.9%) compared with the fresh ET group (33 of 207; 15.9%; OR 3.50; 95% CI, 2.16–5.66; P = .001). The clinical pregnancy rate was also higher in the freeze-all group (42 of 81; 51.9%) compared with the fresh ET group (26 of 90; 28.9%; OR 2.65; 95% CI, 1.41–4.98; P = .001). Furthermore, the ongoing pregnancy rate was higher in the freeze-all group (33 of 81; 40.7%) compared with the fresh ET group (19 of 90; 21.1%; OR 2.57; 95% CI, 1.31–5.04; P = .001). Taking into account all cycles, including those that did not result in an ET, the results per stimulated cycles were similar, showing a statistically significant increase in the biochemical pregnancy, clinical pregnancy, and ongoing...
pregnancy rates for the freeze-all group as compared with the fresh ET group (Table 3).

Of note, the multiple pregnancy rate was favored in the freeze-all group (19 of 81; 23.5%) compared with the fresh ET group (8 of 90; 8.9%; OR 3.14; 95% CI, 1.29–7.0; P=.001). There was no statistically significant difference in early pregnancy loss when comparing the two groups.

The clinical pregnancy rate of the freeze-all group was independently tested using logistic regression to see whether it was associated with other variables. No correlation was found between clinical pregnancy and any other variables except the number of blastocysts transferred (OR 3.67; 95% CI, 1.92–7.0; P=.001).

**DISCUSSION**

A freeze-all policy is a newly developed approach in which cryopreservation of all embryos after a conventional ICSI cycle is performed followed by consecutive FET in hopes of improving the rate of implantation (19). To our knowledge, ours is the first study to evaluate the effectiveness of a freeze-all policy as compared with fresh ET in terms of clinical outcome measures in patients with RIF.

Many studies have attempted to standardize the definition of RIF (20, 21), but the definition still lacks of consistency (22). Most of published studies were not systematic reviews, and as such they were mainly based on opinion. Our study uses the definition found in the Coughlan et al. (2) review: RIF is a failure achieve a clinical pregnancy after at least three fresh or frozen cycles with a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Freeze-all group (n = 81)</th>
<th>Fresh ET group (n = 90)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean female age (y)</td>
<td>31.47 ± 2.55</td>
<td>31.18 ± 3.41</td>
<td>-0.29 (-1.21 to 0.63)</td>
</tr>
<tr>
<td>Mean female BMI (kg/m²)</td>
<td>27.11 ± 2.26</td>
<td>26.72 ± 2.19</td>
<td>-0.39 (-1.06 to 0.28)</td>
</tr>
<tr>
<td>Mean duration of infertility (y)</td>
<td>7.62 ± 2.14</td>
<td>6.97 ± 2.73</td>
<td>-0.65 (-1.40 to 0.10)</td>
</tr>
<tr>
<td>Previous negative ICSI cycles</td>
<td>3.89 ± 0.92</td>
<td>3.83 ± 1.13</td>
<td>-0.06 (-0.37 to 0.25)</td>
</tr>
<tr>
<td>Causes of infertility (%) Mean endometrial thickness (mm)</td>
<td>Basal FSH (mIU/mL)</td>
<td>AFC</td>
<td>Days of stimulation</td>
</tr>
<tr>
<td>Male factor</td>
<td>20 (24.7)</td>
<td>22 (24.4)</td>
<td>0.3 (-13.24 to 14.04)</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>4 (5)</td>
<td>3 (3.3)</td>
<td>1.7 (-5.37 to 9.40)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>6 (7.4)</td>
<td>9 (10)</td>
<td>2.6 (-7.03 to 11.97)</td>
</tr>
<tr>
<td>Ovarian factor</td>
<td>9 (11)</td>
<td>12 (13.3)</td>
<td>2.3 (-8.58 to 12.87)</td>
</tr>
<tr>
<td>Combined</td>
<td>17 (21)</td>
<td>15 (16.7)</td>
<td>4.3 (-8.16 to 16.92)</td>
</tr>
<tr>
<td>Unexplained</td>
<td>25 (30.9)</td>
<td>29 (32.2)</td>
<td>1.3 (-13.40 to 15.79)</td>
</tr>
<tr>
<td>Basal FSH (mIU/mL)</td>
<td>6.51 ± 0.75</td>
<td>6.44 ± 0.751</td>
<td>-0.07 (-0.30 to 0.16)</td>
</tr>
<tr>
<td>AFC</td>
<td>12.4 ± 4.2</td>
<td>13.0 ± 4.3</td>
<td>0.6 (-0.69 to 1.89)</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>11.17 ± 0.86</td>
<td>10.93 ± 0.82</td>
<td>-0.24 (-0.49 to 0.01)</td>
</tr>
<tr>
<td>Total dose of gonadotropin (IU)</td>
<td>2,689.44 ± 355.22</td>
<td>2,516.06 ± 77.7</td>
<td>-173.38 (-355.22 to 8.46)</td>
</tr>
<tr>
<td>E₂ trigger (pg/mL)</td>
<td>2,654.82 ± 212.43</td>
<td>2,732.52 ± 367.83</td>
<td>77.7 (-212.439 to 367.83)</td>
</tr>
<tr>
<td>P₄ trigger (ng/mL)</td>
<td>1.10 ± 0.22</td>
<td>1.07 ± 0.19</td>
<td>-0.03 (-0.09 to 0.032)</td>
</tr>
<tr>
<td>COC retrieved</td>
<td>13.47 ± 3.40</td>
<td>14.84 ± 6.70</td>
<td>1.37 (-0.26 to 3.0)</td>
</tr>
<tr>
<td>MIJ injected</td>
<td>12.30 ± 3.04</td>
<td>13.23 ± 5.93</td>
<td>0.93 (-0.52 to 2.38)</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>(715/996) 71.8%</td>
<td>(828/1,191) 69.5%</td>
<td>2.3% (-12.16 to 16.49)</td>
</tr>
<tr>
<td>Blastulation rate per fertilized oocyte (%)</td>
<td>(315/715) 44%</td>
<td>(349/828) 42%</td>
<td>2% (-13.48 to 17.44)</td>
</tr>
<tr>
<td>Mean no. of embryos transferred</td>
<td>2.14 ± 0.56</td>
<td>2.3 ± 0.56</td>
<td>0.16 (-0.01 to 0.33)</td>
</tr>
</tbody>
</table>

Note: Values are mean ± standard deviation or percentages unless otherwise indicated. AFC = antral follicle count; BMI = body mass index; CI = confidence interval; COC = cumulus corona cell oocyte complexes; E₂ = estradiol; ET = embryo transfer; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; MIJ = metaphase II; P₄ = progesterone.

cumulative transfer of at least four good-quality embryos in a woman under 40 years of age. However, weonly included cases with three previous fresh ET cycles. Improvements in vitrification protocols can now offer an alternative option for patients undergoing ICSI (23). In our study, vitrification was the method of choice for cryopreserving blastocysts. The application of vitrification techniques to human blastocysts has resulted in higher postwarming survival, implantation, and pregnancy rates as compared with other cryopreservation techniques (24, 25). We have had high blastocyst survival rates after warming (97.3%), which is in accordance with previous studies (18, 26).

Various studies have tried to eliminate the adverse effects of COS and improve implantation via elective FET (a freeze-all policy). These studies suggested that a freeze-all policy improved endometrial receptivity and decreased uterine contractility (27–30) when compared with fresh ET after ICSI. In our study of women with RIF, despite the statistically significantly higher endometrial thickness in the fresh ET group, the freeze-all policy culminated in a statistically significantly higher implantation rate of 39.9% compared with 15.9% in the fresh ET group. Our results are in agreement with previous findings in which cryopreservation of all viable blastocysts after ICSI followed by a subsequent FET cycle improved implantation when compared with fresh ET (13, 31, 32). The statistically significant difference in endometrial thickness might not be an important factor in light of studies that have found no correlation between endometrial thickness >10 mm and assisted reproduction outcomes (33).

The progesterone exposure period also differed between the freeze-all and fresh ET groups (5 vs. 6 days, respectively). However, this difference fell within a range observed in previous studies which addressed that no optimum progesterone exposure duration is still scheduled; it should only to be not less than 5 days after ovulation (34, 35). Furthermore, our logistic regression analyses showed that the duration of progesterone exposure was not independently associated with the outcome.

Although our study showed better outcomes for clinical and ongoing pregnancy within the freeze-all group, and this agreed with a handful of studies (13, 36), these findings need further validation by a large, multicenter, randomized controlled trial. However, our novel findings suggest that a freeze-all protocol should be kept in mind when approaching the RIF subgroup of patients.

In this study, we showed a positive correlation between the transfer of multiple blastocysts and implantation, and hence clinical pregnancy. In the freeze-all group, the transfer of multiple blastocysts led to a higher rate of multiple gestations, which is a major drawback. Our findings showed 23.5% multiple pregnancies in the freeze-all arm compared with 8.9% in fresh ET group. Such a high rate of multiple pregnancies in the freeze-all group may be related to the transfer of ≥2 blastocysts and possibly enhanced endometrial receptivity. Therefore, using elective single ET to reduce the rate of multiple pregnancies without compromising the overall success of a freeze-all policy could be a valuable option for patients who have failed to conceive in three or more ET cycles.

In conclusion, our study shows that a freeze-all policy is a potentially effective paradigm to improve RIF outcomes, in particular the rates of implantation and clinical and ongoing pregnancy. However, freeze-all policies require further validation for safety, efficacy, and practicality in a variety of laboratories and populations, as well as further studies of prenatal outcomes and offspring health. Hence, a large multicenter, prospective, randomized clinical trial would be required.

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REFERENCES


TABLE 3

Clinical outcomes of fresh ET group and freeze-all group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Freeze-all group (n = 81)</th>
<th>Fresh ET group (n = 90)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation rate</td>
<td>69/173 (40)</td>
<td>33/207 (16)</td>
<td>3.49 (2.16–5.66)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No. of biochemical pregnancies</td>
<td>48/86 (56)</td>
<td>31/92 (34)</td>
<td>2.49 (1.36–4.56)</td>
<td>.003</td>
</tr>
<tr>
<td>per stimulated cycles</td>
<td></td>
<td></td>
<td>2.77 (1.49–5.15)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of clinical pregnancies</td>
<td>48/81 (59)</td>
<td>31/90 (34.4)</td>
<td>2.42 (1.30–4.51)</td>
<td>.005</td>
</tr>
<tr>
<td>per ET</td>
<td></td>
<td></td>
<td>2.65 (1.41–4.98)</td>
<td>.002</td>
</tr>
<tr>
<td>No. of clinical pregnancies</td>
<td>42/86 (48.8)</td>
<td>26/92 (28.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>per stimulated cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ongoing pregnancies</td>
<td>42/81 (51.9)</td>
<td>26/90 (28.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>per ET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ongoing pregnancies</td>
<td>33/86 (38.4)</td>
<td>19/92 (20.7)</td>
<td>2.39 (1.23–4.66)</td>
<td>.009</td>
</tr>
<tr>
<td>per stimulated cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancy rate</td>
<td>33/81 (40.7)</td>
<td>19/90 (21.1)</td>
<td>2.57 (1.31–5.04)</td>
<td>.005</td>
</tr>
<tr>
<td>Early pregnancy loss</td>
<td>19/81 (23.5)</td>
<td>8/90 (8.9)</td>
<td>3.14 (1.29–7.65)</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>9/81 (11.1)</td>
<td>7/90 (7.8)</td>
<td>1.48 (0.53–4.18)</td>
<td>.46</td>
</tr>
</tbody>
</table>

Note: Values are mean ± standard deviation. Values in parentheses are percentages. P< .05 was considered statistically significant when compared with the fresh ET control group. CI — confidence interval.

ORIGINAL ARTICLE: ASSISTED REPRODUCTION


