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Impact of laparoscopic ovarian drilling on the pregnancy rate in clomiphene-resistant polycystic ovarian syndrome patients undergoing in vitro fertilization: randomized controlled trial

Adel M. Nada*, Hala Abdelwahab, Hala Nabil and Reham A. Mohsen

Abstract

Background: The main objective of this randomized controlled trial was to study the impact of LOD on the pregnancy rate after ICSI-ET in PCOS.

Results: The study was conducted in Egypt in the period 2015–2017 and included 212 clomiphene-resistant PCOS patients, with at least 1-year infertility. The study group was the drilling group who underwent LOD and then ICSI-ET, while the control group did not undergo LOD but directly proceeded to ICSI-ET. The primary outcome was the clinical pregnancy rate per ET cycle. The baseline characteristics and hormonal profiles were comparable ($p > 0.05$) between the two groups. Ovarian stimulation days were ($p < 0.001$) higher in the drilling group. Endometrial thickness, estradiol at triggering day, and the number of oocytes retrieved were ($p < 0.001$) lower in the drilling group. The numbers of embryos transferred were not different ($p > 0.05$). The clinical pregnancy rate per ET cycle was higher in the drilling group (51%) than in the control group (37%) ($p = 0.046$). Multiple pregnancies were not significantly ($p = 0.265$) different between groups. The rate of OHSS was ($p = 0.046$) higher in the control group. Coasting was ($p < 0.001$) higher in the control group (18%) compared to the drilling group (2%).

Conclusion: Laparoscopic ovarian drilling for PCOS patients before ICSI-ET improves the clinical pregnancy rate with a reduction of OHSS.

Trial registration: Clinical Trial Registration: Pan African Clinical Trials Registry (PACTR), PACTR201604001567272, 5 April 2016.

Keywords: PCOS, clomiphene citrate resistant infertility, ICSI, Laparoscopy, Laparoscopic Ovarian Drilling (LOD)

Key message

The laparoscopic ovarian drilling for PCOS patients with clomiphene-resistant infertility improves ICSI-ET outcome, as it increases the clinical pregnancy rate with the reduction of the incidence of OHSS.

Background

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine disorder during the reproductive period [1]. According to the published literature, its prevalence range from 5 to 10% among women of this period [2–5]. However, when the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria is used, the prevalence is as high as 15–20% [6]. The most critical impact of PCOS resulted in ovulation dysfunction [1–6].

The management of PCOS is dependent upon the symptoms presented: androgen-related symptoms, menstruation-related symptoms, and infertility [7]. In PCOS patients with infertility, modification of lifestyle is the first-line approach in addition to the clomiphene-citrate (CC) and other selective

* Correspondence: dr.adel.nada@gmail.com
Department of Gynecology and Obstetrics, Faculty of Medicine, Cairo University, Al-Manyal St. Giza, Cairo 11433, Egypt

estrogen receptor modulators (SERMs) [3]. However, CC resistance was seen in 20% of patients with unsuccessful induction of ovulation [8]. The second-line of treatment is the gonadotropin therapy with its higher risks of ovarian hyper-stimulation syndrome (OHSS) and the consequent multiple pregnancies [9].

Laparoscopic ovarian drilling (LOD), using laser or electrocautery to make 4–10 holes in ovarian surface and stroma, is indicated for the management of infertility in patients with PCOS resistant to CC (Thessaloniki ESHRE/ASRM, 2008). One study showed the reestablishment of ovulatory menstrual cycles in the majority of cases and pregnancy in more than 50% [10]. However, there is a lack of consensus on the effectiveness of LOD for ovulation induction [7, 11]. Also, the addition of LOD to gonadotropins for ovulation induction is advocated as a second-line option by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) [12].

A third-line therapy for those patients with CC-resistant infertility is the intra-cytoplasmic sperm injection/embryo transfer (ICSI-ET) [13].

However, the effect of LOD on ICSI-ET outcomes in PCOS patients is still controversial. Thus, the rationale intended for this parallel randomized controlled study was to study the impact of LOD on the pregnancy rates of ICSI-ET in PCOS patients with clomiphene-resistant infertility.

Methods

This parallel randomized controlled trial was conducted in the Obstetrics & Gynecology Department, Cairo University Hospital, and in Obstetrics and Gynecology Department, Beni-Suif University Hospital, during the period from January 2015 to January 2017. This study followed the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and was approved by the medical ethical review committee of Cairo University on December 14, 2014, with registration number no: OG-5-14-12-2014. The purpose of this study was clearly explained in the Arabic language to all subjects before their enrollment to the study, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited patients attending infertility unit in the two centers with age between 20 and 35 years old, history of at least 1-year infertility, and no response to CC for at least three cycles. Patients diagnosed with PCOS according to Rotterdam consensus. To consider a patient as a PCOS patient, two criteria out of three should be present. Criteria are oligo/or anovulation, hyperandrogenism, and polycystic ovarian morphology by transvaginal ultrasound.

Exclusion criteria included the following: women with any other cause of oligomenorrhea and hyperandrogenism were excluded. Furthermore, patients with the following criteria were excluded: history of previous ICSI-ET, chronic diseases such as thyroid disorders and diabetes mellitus; women who received hormones or drugs for major medical diseases; women who presented ovarian tumors; patients who underwent LOD outside our institute; severe endometriosis, uterine anomalies, or hydrosalpinx documented by hystero-salpingeography, ultrasound, or hysteroscopy and infertility due to severe male factor (azoospermia).

Randomization and blinding

For the allocation of the participants, a computer-generated list of random numbers was used. Block randomization with a block size of 4 was used with 1:1 ratio of drilling and control group. The allocation sequence was concealed from the researchers enrolling and assessing participants. The study was assessor-blinded.

Participants were randomly allocated to the study group and the control group. The study group underwent LOD and then proceeded into one ICSI-ET cycle. The control group proceeded directly into one ICSI-ET cycle without LOD. Neither the researcher allocating the participants nor the assessing person knew the decoding of the groups in its relation to the allocation sequence. However, the physicians who did the ICSI-ET were not blinded.

Procedures: Laparoscopic ovarian drilling

Laparoscopic ovarian drilling (LOD) was done in the two institutes using the standard routine procedure done in Cairo University Hospitals under general anesthesia. Inflation was made by CO_2 up to 14 mmHg. Three ports were done one at the umbilicus for the camera, and two side ports for manipulating and holding the ovary. Fifty-watt current (coagulation mode) was used making four holes each lasting 4 s at a depth of 3–4 mm to both ovaries. The time interval between the drilling and IVF was 1–3 cycles.

Procedures: ICSI

After the explanation of the whole procedure and before starting the ovarian stimulation, fasting blood samples from all eligible women, for basal early follicular phase serum AMH, FSH, LH, prolactin, TSH, and preceding ICSI cycle. All patients underwent baseline transvaginal sonography on day 2 of the menstrual cycle to check for antral follicle count (AFC) and endometrial thickness and to rule out the presence of an ovarian cyst.

AFC was done at day 2 of the cycle next to that of drilling counting all follicles from 4–9 mm. Ovarian

stimulation was started on day 2 of the cycle by injection of gonadotropins (Merional-IBSA, Switzerland) (150–300 IU daily) according to AFC, anti-Mullerian hormone (AMH), and BMI; and the dose is adjusted according to follicular development. We continued the same dose if there was an adequate response (fixed dosage protocol). In some patients, we needed to increase the dose (step-up) or decrease the dose (step-down dosage protocol). Cetrorelix acetate (Cetrotide-Merck-Serono, Germany) 0.25 mg s/c treatment was started when the leading follicle reached a diameter of 14 mm and/or the estradiol levels were > 400 pg/ml. Treatment with merional and antagonist was continued till the day of the final oocyte maturation trigger. When three or more follicles of size 18 mm or more were seen, the final oocyte maturation trigger was given with Choriomon (IBSA, Switzerland) injection HCG 5000 IU intramuscular. We did not trigger ovulation by Gn RH agonist as it may reduce the clinical pregnancy rate. Transvaginal ultrasound-guided oocyte aspiration (OPU) was performed approximately 35–36 h after hCG injection under general anesthesia. Conventional ICSI was performed. Fertilization was defined as the presence of pronuclei 16–18 h post/injection. Embryo grading was done by standard morphology assessment. Embryo transfer was done on day 3 following oocyte retrieval. Luteal phase support with 800 mg of micronized progesterone (Prontogest, Marcyrl Co., Egypt) was initiated on the same day of oocyte retrieval. One cycle only was made for each patient in both groups.

Pregnancy was assessed by serum hCG assay after 15 days from embryo transfer and then confirmed when a gestational sac with positive fetal pulsation was visualized at the vaginal US after two further weeks later. Only cases with US confirmation of pregnancy were counted in the calculation of pregnancy and implantation rates, whereas biochemical pregnancies were not considered.

Outcome measures

The primary outcome measure was the clinical pregnancy rate per ET cycle. The clinical pregnancy was defined as the presence of a gestational sac with the detection of fetal heartbeat detection at 6–7 weeks of gestation.

Secondary outcome measures were the live birth rate, the occurrence of OHSS, total dose of gonadotropins, E2 concentration on the day of hCG administration, cycle cancellation rate, number of cumulus oocyte complexes (COCs) retrieved, number of metaphase I and II oocytes, and fertilization rates, embryo grade classified as grade (1, 2, 3).

Statistical analysis and sample size justification

A sample size calculation was done to calculate the number of subjects needed in each group. Reference to Rimington et al. [16], the pregnancy rate in LOD and IVF was 36%. We assumed that our current pregnancy rate would be 50%, with a significance level of 0.05 and 80% power, at least 190 patients (95 patients per group). A total sample size of 200 was required to consider any dropouts.

All statistical tests were done using a significance level of 95%. A value for $p < 0.05$ was considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc., Chicago, IL, USA) was used for the statistical analyses. Data were presented as (mean ± SD) or median (range) for continuous variables and as frequency and percent for categorical variables. Comparisons between groups were done using Phi-Cramer test for categorical variables. The study adhered to the CONSORT guideline.

Results

All PCOS subjects resistant to CC (285) who came to the center and were willing to do ICSI were asked to participate in the study. Forty-six subjects refused to participate, and 27 subjects were excluded; 15 were not fit for surgery and 12 could not convince the husband to do ICSI. Enrolled subjects (212) were randomized to the drilling group and the control group, 106 in each group. Twelve subjects were excluded after randomization where ET was canceled in 5/106 cases in the drilling group (three cases because of no fertilization due to unexpected bad ejaculation and two cases because of no good cleavage) while 7/106 cases were canceled in the control group (three cases because of severe OHSS, two cases because of no fertilization, and two cases because of no good cleavage). The dispositions of these subjects are shown (Fig. 1).

Baseline characteristics

Only 200 (who completed the ICSI-ET cycle) subjects were included in the analysis, 101 in the LOD group, and 99 in the control group. There was no statistically significant difference ($p > 0.05$) between the two groups regarding the age, duration of infertility, and BMI, as shown in Table 1.

The two groups were comparable ($p > 0.05$) regarding the AFC, AMH level, FSH level, LH level, the estradiol (E2) level, the prolactin (PRL) level, and the thyroid-stimulating hormone (TSH), as shown in Table 1.

Ovarian induction and ICSI parameters

Ovarian stimulation days were significantly ($p < 0.001$) higher in the drilling group 12.91 (1.91) days than in the control group 11.24 (2.03) days. Also, the dose of gonadotropin was insignificantly (p value 0.117) higher in the drilling group 36.42 (11.23) ampoules than in the control group 34.09 (9.67) ampoules. Also, there

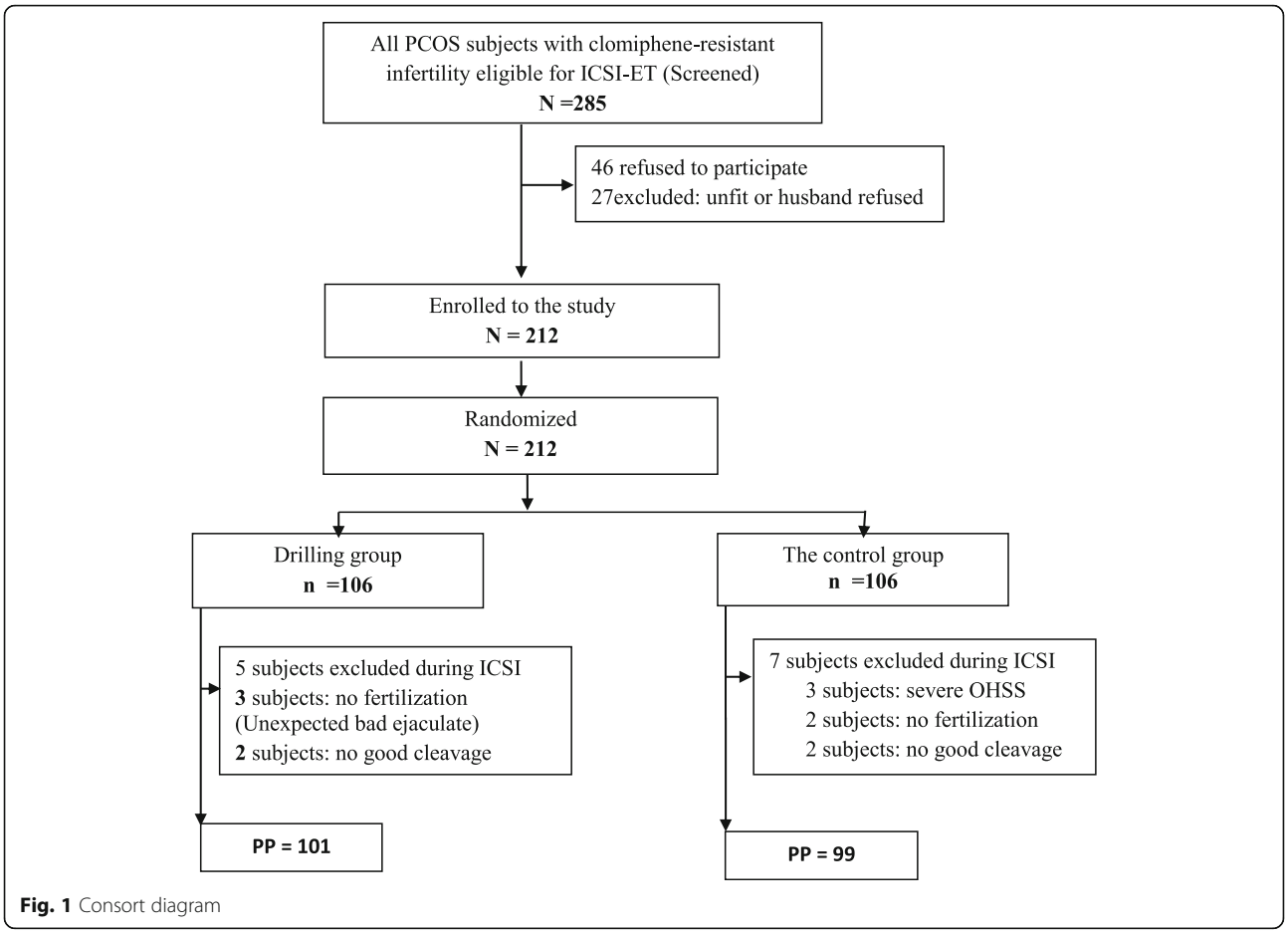

Fig. 1 Consort diagram

was a significant ($p < 0.001$) difference in the triggering day between the two groups which was slightly later in the drilling group. In addition, there was a significant ($p < 0.001$) difference in the dosage protocol between both groups, with lower fixed dosage protocol (24%) of patients in the drilling group compared to (67%) the control group.

Endometrium thickness, E2 level at triggering day, and the number of oocytes retrieved were significantly ($p < 0.001$) lower in the drilling group than in the control group, as shown in Table 2.

In spite of the number of embryos cleaved, the numbers of grade 1 and grade 2 embryos were significantly ($p < 0.01$) different between both groups; the number of

Table 1 Baseline characteristics

	Drilling group $N = 101$	Control group $N = 99$	p
Age in years	30.4 (4.4)	29.1 (5.9)	*0.067*
Duration of infertility in years	6.6 (2.8)	6.5 (3.6)	*0.8*
BMI	28.5 (3.8)	28.2 (4.2)	*0.5*
Antral follicle count (AFC) before drilling	16.5 (4.9)	16.5 (5.2)	*0.9*
Anti-Mullerian hormone (AMH) in ng/ml before drilling	2.7 (0.6)	2.8 (0.8)	*0.4*
Follicle stimulating hormone (FSH) in mIU/ml	6.0 (1.5)	5.9 (1.6)	*0.5*
Luteinizing hormone (LH) in mIU/ml	9.0 (1.6)	9.1 (2.5)	*0.8*
Estradiol (E2) in pg/ml	54.1 (20.2)	54.0 (21.1)	*0.9*
Prolactin (PRL) in ng/ml	12.5 (7.6)	12.43 (5.1)	*0.9*
Thyroid stimulating hormone (TSH)	1.9 (0.8)	1.88 (0.8)	*0.9*

Data are presented as mean (SD)

Table 2 Ovarian induction and ICSI parameters

	Drilling group N = 101	Control N = 99	p
Dose of gonadotropin (number of ampoules)	36.4 (11.2)	34.1 (9.7)	*0.1*
Days of gonadotropin injection (stimulation days)	12.9 (1.9)	11.2 (2.0)	< 0.001
Triggering day (day of HCG injection)	14.4 (2.0)	13.2 (2.0)	< 0.001
Dosage protocol, number (%)			
Fixed	24 (24)	66 (67)	< 0.001
Step up	77 (76)	25 (25)	
Step down	0 (0)	8 (8)	
Endometrium thickness in mm	9.5 (1.77)	11.8 (1.9)	< 0.001
Estradiol (E2) level at triggering day	2371.9 (898.51)	3168.1 (1541.9)	< 0.001
Number of oocytes retrieved	10.7 (6.05)	13.6 (5.5)	< 0.001
Mature oocytes (M2)	7.4 (3.69)	8.4 (3.3)	*0.0499*
Less mature oocytes (M1)	1.7 (1.54)	2.6 (1.6)	< 0.001
Germinal vesicles (GV) or immature oocytes	1.4 (1.96)	2.1 (2.2)	*0.014*
Empty zona (EZ)	0.3 (0.85)	0.1 (0.7)	*0.1*
Number of fertilized oocytes	6.2 (3.09)	6.3 (2.5)	*0.6*
AFC after LOD	12.4 (3.4)	16.5 (5.2)	< 0.001
AMH after LOD	2.1 (1.3)	2.8 (0.8)	< 0.001
Number of embryos cleaved	5.4 (2.8)	4.3 (2.0)	*0.002*
Grade 1 embryos	4.3 (2.3)	3.0 (1.3)	< 0.001
Grade 2 embryos	0.7 (0.9)	1.2 (1.0)	*0.001*
Grade 3 embryos	0.3 (0.6)	0.3 (0.5)	*0.8*
Number of embryos transferred	3.3 (1.0)	3.1 (1.5)	*0.3*
Day of embryo transfer (usually day 3)	3.0 (0.4)	2.7 (1.0)	*0.049*
Number of embryos ready for freezing	1.2 (1.9)	0.8 (1.6)	*0.1*

All data are presented as mean (SD) except dose protocol

embryos transferred and the number of frozen transferred were not significantly different (p value 0.324), as shown in Table 2.

Implantation rate and pregnancy outcomes

The implantation rate was non-significantly (p value = 0.3) higher in the drilling group than in the control group. It was 17.8% in the drilling group and 14.5% in the control group.

The clinical pregnancy rate per ET cycle, as confirmed by US, was significantly (p = 0.046) higher in the drilling group than in the control group. It was 51% in the drilling group and 36% in the control group.

The number needed to harm (NNH) equals 6.61; only one out of seven cases using drilling will not get pregnant.

In addition, multiple pregnancies were not significantly (p = 0.265) different between both groups, as shown in Table 3.

Abortion rate till 20 weeks was 5 cases (9.6%) of pregnant women in the drilling group and 4 cases (10.8%) of pregnant women in the control group (p value = 0.6).

The live birth rate was 42 (41%) and 29 (29%) in the drilling group and the control group, respectively (p value = 0.075).

Safety outcomes

There was a significant (p = 0.046) difference as regards the rate of OHSS between the two groups. OHSS was more in the control group (23%) than in the drilling group (11%). Severe OHSS was occurred only in the control group (7%), as shown in Table 3.

In addition, coasting was significantly needed (p < 0.001) to stop the stimulation for fear of OHSS in the control group (18%) as compared to the drilling group (only 2%).

Moreover, no major complications were encountered following LOD. Minor complications encountered were pain, minimal vaginal bleeding, and postoperative cough in some cases.

Discussion

In our study, we tested the question: Does LOD, when used in PCOS patients with clomiphene-resistant infertility, have

Table 3 Pregnancy outcomes and OHSS

	Drilling group	Control group	*p*
Pregnancy rate: confirmed by HCG then US			
Yes	52 (51%)	35 (36%)	0.044
No	49 (49%)	64 (64%)	
EER (experimental event rate)	*0.51*		
CER (control event rate)	*0.36*		
ARR (absolute risk reduction)	*− 0.15 (− 0.28 to − 0.02)*		
NNT (number needed to treat)	*− 6.61 (− 3.65 to − 65.46)*		
NNH (number needed to harm)	*6.61 (3.65 to 65.46)*		
Pregnancy outcome			
Single	46 (45.5%)	32 (32.3%)	0.3
Twins	5 (5.0%)	2 (2.0%)	
Triplets	1 (1.0%)	1 (1.0%)	
Implantation rate	17.8%	14.5%	*0.3*
Abortion rate till 20 weeks	5 (9.6%)	4 (10.8%)	*0.6*
Live birth rate	42 (41%)	29 (29%)	0.075
OHSS			
No	90 (89%)	76 (77%)	0.046
Mild	8 (8%)	3 (3%)	
Moderate	3 (3%)	13 (13%)	
Severe	0 (0%)	7 (7%)	
Coasting: to stop stimulation for fear of OHSS			
No coasting	99 (98%)	81 (82%)	< 0.001
Coasting	2 (2%)	18 (18%)	

Data are presented as number (%)

a positive impact on outcomes of ICSI-ET in terms of increased pregnancy rate? The results of this study showed that LOD may be effective in increasing the pregnancy rate in those patients. The live birth rate was insignificantly higher in the drilling group than in the control group.

The results of our study showed that the ovarian stimulation days were significantly higher in the drilling group. Also, the dose of gonadotropin was insignificantly higher in the drilling group. Also, the triggering day was significantly later in the drilling group. The fixed dosage protocol was used in a less number of patients in the drilling group than in the control group. Endometrium thickness, E2 level at triggering day, and the number of oocytes retrieved were significantly lower in the drilling group. In spite of the number of embryos cleaved, the numbers of grade 1 and grade 2 embryos were significantly different between both groups; the number of embryos transferred and the number of frozen transferred were not significantly different. Drilling significantly improved the pregnancy rate decreased the rate of OHSS and reduced the need for coasting. LOD did not improve the oocyte number; however, the quality of the oocytes might be improved. One of the disadvantages of LOD in our study is the reduction of the ovarian reserve that expressed in decreasing the number of oocytes retrieved and increasing the stimulation days and the dose; however, LOD seems to normalize hyper-responder patients with improvement in the oocytes' quality, not the number. Also, we have an increased rate of multiple pregnancies, but this is simply due to the increase of the number of embryos transferred, and it is accepted for our patients as they accept the risk of multiple pregnancies more than the failure of ICSI cycles.

Improved oocyte quality in the LOD group may be due to drilling itself or secondarily to decrease the need to coasting and step down gonadotropin therapy.

To our knowledge, during the last two decades, there were only three studies addressed in the same topic; two of them were retrospective studies [14, 15] and only one small sample size randomized controlled trial [16] which is also mentioned in the Cochrane review [17].

Contrary to the results of our study, all of the three studies showed that there were no significant increases in pregnancy rates due to LOD. However, all mentioned increased trend but it was not statistically significant. In addition, as mentioned before, two of these studies were observational retrospective studies and only one RCT, but with a small sample size of 50 women.

The results of Rimington et al. [16] showed no evidence of a significant difference in pregnancy rate with the addition of LOD to IVF when compared to IVF alone. Also, it showed no evidence of a significant difference neither in multiple pregnancy rates nor in the OHSS rate.

The retrospective study of Tozer et al. [15] showed no statistically significant differences ($p > 0.05$) were observed between both groups as regards the number of retrieved oocytes, ongoing pregnancy rates, and the incidence of OHSS. However, the number of embryos available for transfer was significantly higher in the control group (without drilling).

The results of the retrospective study of Eftekhar et al. [14] showed that ovarian cauterization before ICSI-ET in patients with PCOS reduced the risk of OHSS. Despite the same pregnancy rate in both groups, more obtained oocytes and embryos were seen on women without ovarian drilling than women with LOD.

The advantages of this study are being assessor-blinded multicenter randomized controlled trial with enough sample size. Moreover, it does offer the benefit of being the first head-to-head comparison using a randomized controlled trial design. However, one limitation of this study is that the drilling group needs more gonadotropins dose and more stimulation days. Another limitation of the study is that a higher percentage (30%) of the original population declined/excluded from the

study (85/285) which may jeopardize the generalizability of the study. Moreover, we did not test for glucose metabolism in such population with insulin resistance. Another limitation was missing reporting the details of coasting; however, we did it in a range of 1–2 days. Also, the exact cause of the cancellation was not reported in every case, which is another limitation in the current study.

Conclusions

Finally, we conclude that the laparoscopic ovarian drilling for PCOS patients with clomiphene-resistant infertility before ICSI-ET improves the clinical pregnancy outcome with an OHSS rate reduction.

Abbreviations

AFC: Antral follicle count; AMH: Anti-Mullerian hormone; ARR: Absolute risk reduction; ASRM: American Society for Reproductive Medicine; BMI: Body mass index; CC: Clomiphene citrate; CI: Confidence interval; COCs: Cumulus-oocyte complexes; ESHRE: European Society of Human Reproduction and Embryology; ICSI-ET: Intra-Cytoplasmic Sperm Injection/Embryo Transfer; IVF: In vitro fertilization; LOD: Laparoscopic ovarian drilling; NNH: Number needed to harm; OHSS: Ovarian hyper-stimulation syndrome; PCOS: Polycystic ovarian syndrome; RCT: Randomized controlled trial; SD: Standard deviation; SERMs: Selective estrogen receptor modulators

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Authors' contributions

AMN is the principal investigator of the study, study design, management, supervision, and final revision. HA, HN, and RAM contributed to the study design, patients' recruitment, and manuscript revision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the medical ethical review committee of Cairo University on December 14, 2014, with registration number no: OG-5-14-12-2014. The purpose of this study was clearly explained in the Arabic language to all subjects before their enrollment to the study, and an informed consent form was signed by and obtained from all of those enrolled.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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