Original Article

Unilateral or Bilateral Laparoscopic Ovarian Drilling in Polycystic Ovary Syndrome: A Meta-analysis of Randomized Trials

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Abstract

Objectives: On the first line of polycystic ovary syndrome (PCOS) treatment, ovulation with clomiphene citrate (CC) is induced. However, 25% of patients need alternative therapy. Laparoscopic ovarian drilling (LOD) can result in successive ovulations and is not linked to ovarian hyperstimulation. In this systematic review and meta-analysis, we aimed to consider the efficacy of unilateral LOD (ULOD) versus bilateral LOD (BLOD) for enhancing fertility and improving fertility outcomes in women with CC-resistant.
Materials and Methods: A comprehensive literature search was conducted up to July 15, 2023, to identify relevant randomized controlled trials in PubMed, Scopus, Google Scholar, and Cochrane Library databases. Thirteen articles were included in the meta-analysis. After data extraction, we performed a meta-analysis.
Results: As the main unit of analysis for each variable, the standardized mean difference was used between the two groups. The random effects model was used for analysis and heterogeneity was assessed by I^2 statistics. Publication bias was inspected through funnel plots and Begg's and Egger's regression tests. The included studies were divided into two general categories. In the first category, surgical treatment of LOD was compared with other treatments. Whereas, in the other category, ULOD was compared with BLOD.
Conclusion: In summary, this meta-analysis did not find a significant difference in the rate of ovulation, pregnancy, miscarriage, and live birth between the two groups. However, LOD could cause damage to the ovarian reserve, but it has long-term effects on improving the menstrual cycle and reproduction. In general, LOD is a significant method for the treatment of infertility in PCOS, which needs further investigation.

Keywords: Laparoscopic ovarian diathermy, laparoscopic ovarian drilling, polycystic ovary syndrome, unilateral laparoscopic ovarian drilling

Introduction

Polycystic ovary syndrome (PCOS) is specified by multiple ovarian cysts, which is the most prevalent endocrine condition and affects 20% of females of reproductive age. PCOS, with a global prevalence of 6%–10%, is a major contributor to anovulatory infertility and metabolic illnesses affecting women of reproductive age. Ovulatory dysfunction, polycystic ovarian morphology, and diverse presentations of hyperandrogenism are

Article History:
Submitted: 18-Jul-2023
Revised: 22-Feb-2024
Accepted: 27-Feb-2024
Published: 12-Dec-2024

Supplementary material available online

Access this article online

Quick Response Code:

Website: https://journals.lww.com/gmit

DOI: 10.4103/gmit.gmit_89_23

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How to cite this article: Zakerinasab F, Behfar Q, Al Saraireh TH, Naziri M, Yaghoobpoor S, Deravi N, *et al*. Unilateral or bilateral laparoscopic ovarian drilling in polycystic ovary syndrome: A meta-analysis of randomized trials. Gynecol Minim Invasive Ther 2025;14:14-23.

the hallmarks of this condition.[1] The hormonal and metabolic disturbances caused by PCOS have an impact on reproductive health. Anovulation is the main cause of infertility in 75%–80% of cases. The hypothalamic–pituitary axis is disrupted, insulin secretion and androgen levels are amplified, and ovarian function is altered in the pathophysiology of PCOS.[2] On the first line of treatment, ovulation with clomiphene citrate (CC) is induced for PCOS patients. Unfortunately, this therapy in 25% of patients fail to ovulate and therefore need alternative therapy.[3] If patients do not respond to a dosage of 150 mg/day of CC therapy, clomiphene resistance is diagnosed.[4]

Laparoscopy is a minimally invasive surgical procedure performed by making small incisions in the abdomen, applicable for diagnosing and treatment of abdomen and pelvic organ disease.[5,6] For the first time, laparoscopic ovarian drilling (LOD) was introduced by Gjönnaess in 1984.[7] Then, in 1993, the Lee-Huang point was introduced as a location between the xiphoid and umbilical for the initial laparoscopic incision in gyneco-oncology surgeries. Nowadays, this anatomical point is used in other gynecology surgeries, such as LOD.[8] Therefore, LOD considered an effective second line of treatment for PCOS with an ovulation rate of 80% and 60%–80% rate of pregnancy.[4,9] One study recommended LOD as the first line of treatment for women who received laparoscopy therapy for other reasons. In this study, CC treatment is considered as an adjuvant therapy.[10] Moreover, in some CC-resistant women, response to CC therapy for the second time after laparoscopic electrocautery has been observed.[11] The surgical method can result in successive ovulations without the need for further therapy and is not linked to ovarian hyperstimulation. Concerning factors include tubo-ovarian adhesions and the potential for premature ovarian failure (POF) after LOD. The likelihood of periovarian adhesion development and POF increases during LOD as injury to the ovarian surface increases when employing a monopolar needle.[4] It is possible that performing LOD treatment for one ovary will help reduce its complications by reducing the number of diathermy points. Therefore, in addition to investigating the effect of LOD treatment on fertility factors, it is important to compare unilateral LOD (ULOD) versus bilateral LOD (BLOD).

In this systematic review and meta-analysis, we aimed to consider the efficacy of unilateral LOD (ULOD) or bilateral LOD (BLOD) versus other treatment and ULOD versus BLOD for enhancing fertility and improving fertility outcomes in women with CC resistant.

Materials and Methods

The researchers followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The research protocol has been registered on the Open Science Framework (https://osf.io/63bhj), and a checklist was used for the search strategy, screening, and data selection.

Data extraction

Two reviewers (FA and MN) extracted data containing general study details (authors, year, and country), study design, primary goals, sample information (inclusion and exclusion criteria, sample size, and age distribution), and results. If the number of participants were not clear, we used the lowest possible number.

Literature search methodology

This systematic review was performed based on randomized controlled trial studies and PRISMA guidelines.[12] We tried to answer the following question: How is the efficacy of both ULOD and BLOD treatments for women with CC-resistant PCOS to improve fertility outcomes such as ovulation, pregnancy, miscarriage, and live birth rate?

This research was performed on the following databases which were published in English: PubMed, Scopus, Google Scholar, and Cochrane Library of Controlled Trials. We produced a subset of citations related to our research question, using the following Medical Subject Headings and text words: “unilateral Ovarian drilling” OR “unilateral Ovarian diathermy” AND “polycystic ovary syndrome” OR “PCOS” AND “ovulation” AND “pregnancy.” The reference lists of retrieved publications were manually searched to identify any missing relevant publications.

Study quality assessment

The quality of the included literature was evaluated by two independent authors (MN and FA), according to the Cochrane risk-of-bias assessment tool for randomized controlled trial studies [Supplementary Figure 1].

Statistical analysis

The current meta-analysis was accomplished to investigate the impact of unilateral and BLOD in PCOS using Stata V. 15 (Stata Corp, College Station, TX, USA). After data extraction by the authors, we performed a meta-analysis on sufficient data and gathered all the information in Tables 1 and 2 to use them in the result section. As the main unit of analysis for each variable, the standardized mean difference (SMD) was used between two groups (the control and the patient groups). The cutoff values were set by Cohen for the review of medium, small, and large effect sizes (0.5, 0.2, and 0.8, respectively). The random effects model was used for analysis and heterogeneity was assessed by I^2 statistics. Values larger than 50% were declared as moderate to high heterogeneity. When there were enough studies to examine the relationship between pregnancy rate and live birth rate, meta-regression was performed as potential effect modifiers. Publication bias

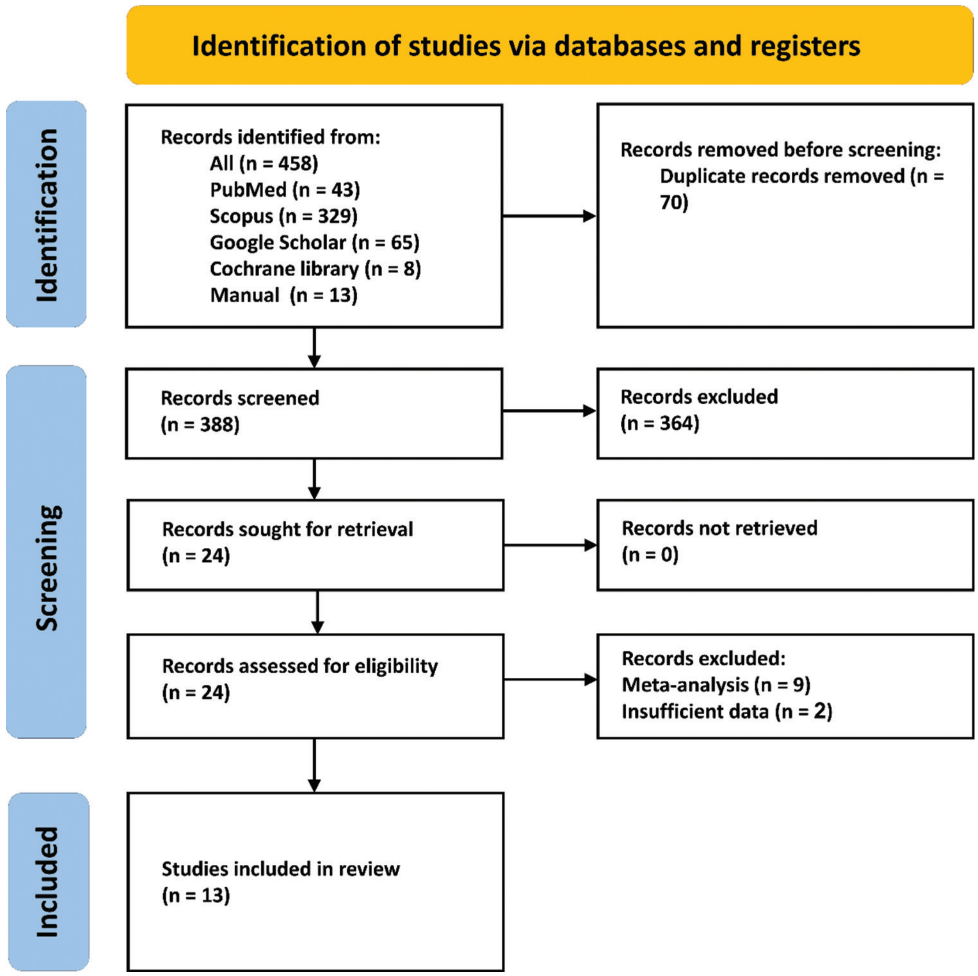

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for current systematic review which included searches of databases and registers only

was visually inspected through funnel plots. Also, Begg's and Egger's tests were performed to ensure more rigor.

Results

Study selection

Through an extensive search in databases, 458 studies were found. These studies were obtained as follows: 43 from PubMed, 329 from Scopus, 65 from Google Scholar, 8 from Cochrane Library, and finally 13 from searching the sources of the past meta-analyses. Seventy studies were automatically excluded due to duplicates. The remaining 388 studies were subjected to title and abstract evaluation, and 364 were manually excluded. Among the remaining studies, 11 studies were excluded due to ineligibility, of which nine studies were meta-analyses and two studies did not provide sufficient data. Finally, 13 studies, which were published from August 2002 to April 2020, were selected to be included in the meta-analysis [Table 1 and Figure 1].

Demographics

The included studies were divided into two general categories. In the first category, surgical treatment of LOD was compared with other treatments. Whereas, in the other category, ULOD was compared with BLOD. In the LOD/control groups, 9, 8, 8, and 5 studies reported age,[13-21] body mass index (BMI),[13-19,21] infertility duration,[14-21] and preovarian volume,[13-17] respectively. In addition, in hormonal profile, 8, 7, and 3 studies reported preluteinizing hormone (LH),[13-19,21] preflinders sensitive line,[14-19,21] and pre-T,[13,16,20] respectively. According to the analysis, only age and pre-LH had a significant difference between the two groups, and their heterogeneity ranged from zero to moderate (age: $I^2 = 63.5$, BMI: $I^2 = 0$, infertility duration: $I^2 = 41.2$, preovarian volume: $I^2 = 53.9$, pre-LH: $I^2 = 0$, prefollicle stimulating hormone [FSH]: $I^2 = 13.6$, pre-T: $I^2 = 0$). Besides, in ULOD/BLOD groups, four studies[22-25] reported age and infertility duration, and three studies[23-25] reported hormonal profiles, including pre-LH and pre-FSH. None of the variables had significant differences and only the infertility duration had substantial heterogeneity (age: $I^2 = 0.8$, infertility duration: $I^2 = 80.9$, pre-LH: $I^2 = 0$, and pre-FSH: $I^2 = 0$) [Table 2 and Figures 2, 3].

Table 1: Baseline characteristic features of included randomized controlled trials

First author	Country	Case	Control (*n*/intervention)	Inclusion criteria	Exclusion criteria	Follow-up	Recorded outcome
Farquhar[13]	New Zealand	29/LOD	21/3 cycles of urinary or recombinant Gonadotropin therapy	Age: 20–38 CC-resistance PCOS Infertility >12 months BMI <33 kg/m^2 and <35 for European and Pacific Island women Normal semen analysis	Other known causes of infertility	6 months	Ovulation, pregnancy, ovarian volumes, pre- and post-gonadotropin and androgen levels, menstruations
Zakhera[14]	Egypt	75/LOD	75/CC + tamoxifen	Age: 18–38 Infertility ≥2 years No hormonal treatment in the last 3 months Normal semen values	-	6 months	Live birth rate, pregnancy, miscarriage, restored ovulation, endometrial thickness, lead follicles
Abu Hashim[15]	Egypt	132/LOD	128/letrozole	CC-resistant PCOS Patent fallopian tubes proved by hysterosalpingography Normal semen analysis	Other causes of infertility Age >40 BMI >35 Contraindication to GA History of LOD History of metformin and hormonal drugs intake in last 6 months Specific diet or physical activity	6 months	Live birth rate, miscarriage, pregnancy, endometrial thickness, ovulation, menstruation
Roy[16]	India	21/LOD	22/rosiglitazone	Age: 20–40 CC-resistant PCOS Documented patent tubes on hysterosalpingography No other infertility factor	Other PCOS like syndromes	6 months	Ovulation, pregnancy, miscarriage, post-LH, post-FSH, post-T
Liu[17]	China	70/LOD	71/letrozole	CC-resistant PCOS Patent fallopian tubes confirmed by hysterosalpingography or hysteroscopy Normal semen analysis Normal serum prolactin, TSH and 17-OH progesterone No systemic disease No gonadotropin or other hormonal drug treatment during in last 3 months Normal blood count and blood chemistry	Other reasons of infertility Uterine cavity lesions or ovarian cyst Age >40 years old BMI >26 kg/m^2 Contraindications to GA History of pelvic surgery, other endocrine diseases, liver or kidney disease	6 months	Ovulation, endometrial thickness, pregnancy, abortion, live birth rate
Kandil[18]	Egypt	122/LOD	124/TND	Normal semen analysis Normal uterine cavity Bilateral tubal patency as shown by hysterosalpingography	Basal FSH >15 Endocrine disorders Comorbidities Contraindications for laparoscopy Organic pelvic disease Abnormal semen	3 and 6 months	Ovulation, pregnancy, AMH, AFC
Gibreel[19]	Egypt	105/LOD	105/LOD + endometrial scratching	Age: 20–39 PCOS Fertile semen analysis, and Bilateral tubal patency as demonstrated by hysterosalpingogram	Endometriosis Uterine cavity Anomaly or mass Male factor infertility Endocrinopathy Endometrial curettage in last 6 months	3 months	ovulation, pregnancy, live birth rate, miscarriage

Contd...

Table 1: Contd...

First author	Country	Case	Control (*n*/intervention)	Inclusion criteria	Exclusion criteria	Follow-up	Recorded outcome
Hafizi[20]	Iran	30/LOD	30/dose adjust LOD	Age 18–35 years Infertility >2 years PCOS No other reasons of infertility except for ovulation disorder	Withdrawal of follow-up lost Finding any other etiologies for infertility	6 months	Ovulation, pregnancy, post-LH, AFC, AMH, T, DHEAS
Nada[21]	Egypt	101/ LOD + ICSI-ET	99/ICSI-ET	Age: 20–35 Infertility ≥1 year CC-resistant PCOS	Any other cause of infertility History of ICSI-ET and chronic diseases Hormonal or major medical diseases drugs Ovarian tumors LOD outside in another center Severe endometriosis, uterine anomalies, or hydrosalpinx Severe male factor infertility	-	Pregnancy, implantation, abortion, live birth rate, miscarriage
Youssef[22]	Egypt	43/ ULOD	44/BLOD	Infertility secondary to anovulation	-	8 weeks/1 year after ovulation	Pre-/post- FSH, LH, and T post-operative nausea, vomiting and pain, Ovulation, pregnancy, miscarriage
Zahiri Sorouri[23]	Iran	45/ ULOD	45/BLOD	Oligomenorrhea and/or anovulation, hyper-androgenism PCOS	Evidence of tubo-peritoneal diseases and endometriosis	6 months	Menstrual, ovulation, pregnancy
Rezk[24]	Egypt	52/ ULOD	53/BLOD	PCOS	FSH <15 Comorbidities Contraindications for laparoscopy, Endocrine disorders Organic pelvic disease Abnormal semen	3 and 6 months	Ovulation, pregnancy. AMH, AFC
El-Sayed[25]	Egypt	48/ ULOD	47/BLOD	CC-resistant PCOS Age: 25–35 Infertility ≤3 years BMI <30 kg/m^2 LH ≥10 IU/mL - LH/FSH ratio ≥2 - free androgen index ≥4 Normal semen analysis Normal OGTT	Hyper-androgenic disorders	6	Menstrual, ovulation, pregnancy

LOD: Laparoscopic ovarian drilling, CC: Clomiphene citrate, PCOS: Polycystic ovary syndrome, BMI: Body mass index, TSH: Thyroid-stimulating hormone, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AFC: Antral follicle count, DHEAS: Dehydroepiandrosterone sulfate, OGTT: Oral glucose tolerance tests, GA: General anaesthesia, AMH: Anti-müllerian hormone, ICSI-ET: Intracytoplasmic sperm injection / embryo transfe, TND: Transvaginal ovarian needle drilling

Ovulation

Six studies in the LOD/control category with a total of 759 participants and four studies in the ULOD/BLOD category with a total of 377 participants reported adequate data related to ovulation. The correlation of ovulation between the two groups in each category was statistically analyzed. In the LOD/control groups, the relative risk (RR) was 1.11 (95% confidence interval [CI] =0.91, 1.35), which indicates a slight increase in the ovulation rate in the LOD group compared to the control, although this difference was not statistically significant. On the other hand, in the ULOD/BLOD group, the RR was 0.76 (95% CI = 0.54, 1.07), which shows a slight decrease in ovulation in the ULOD group compared to BLOD; however, this difference was still not statistically significant. Both studies showed substantial heterogeneity (I^2 = 74.3%

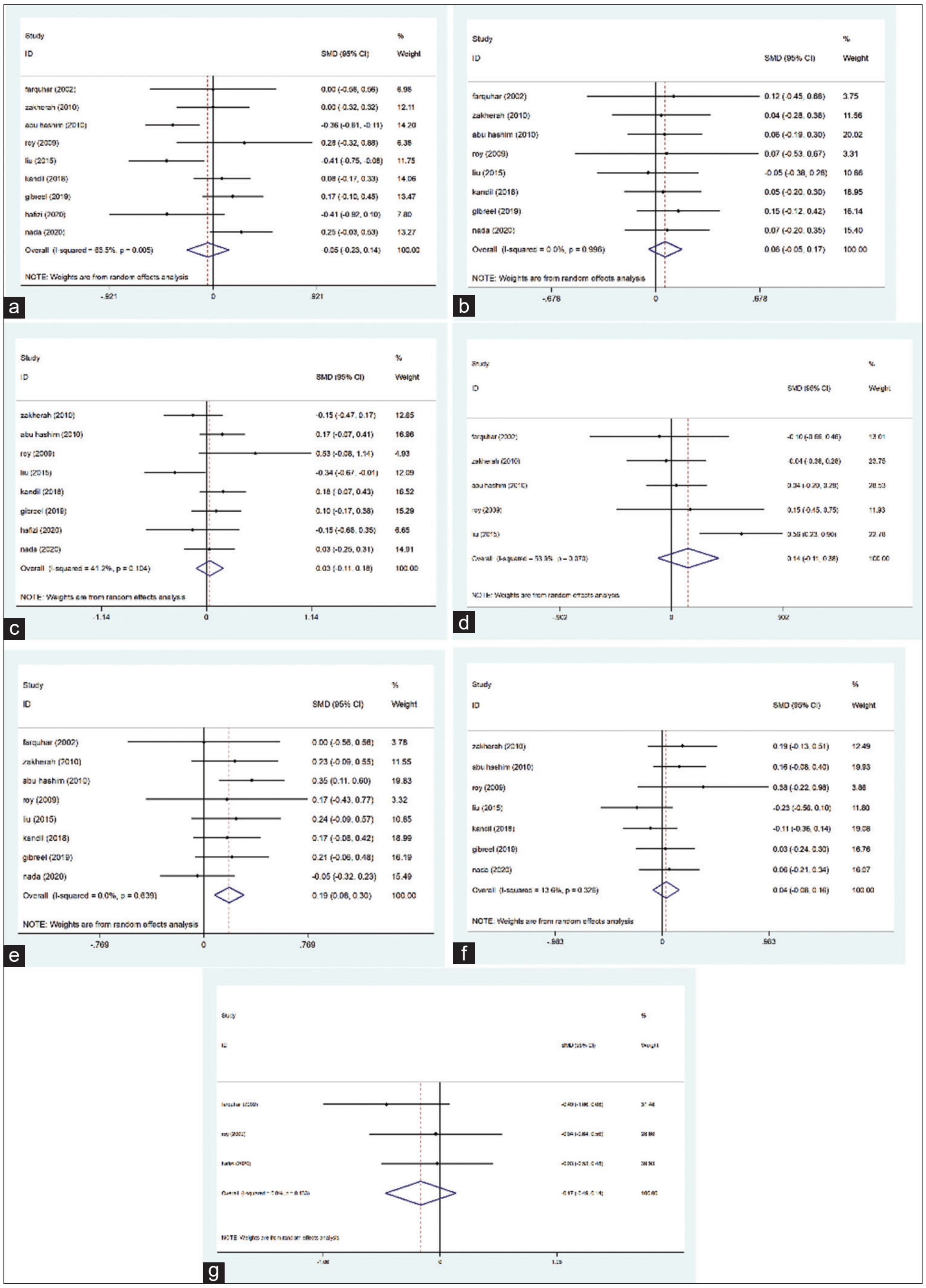

Figure 2: Forest plot for demographics of laparoscopic ovarian drilling/control; (a) Age, (b) Body mass index, (c) Infertility duration, (d) Preovarian volume, (e) Preluteinizing hormone, (f) Prefollicle stimulating hormone, (g) Pre-T. SMD: Standardized mean difference, CI: Confidence interval

and I^2 = 75.4%, respectively). In summary, this meta-analysis did not find a significant difference in the ovulation rate between the two groups [Figure 4].

Pregnancy

Nine studies in the LOD/control category with a total of 1360 participants and 4 studies in the ULOD/BLOD category with a total of 377 participants reported adequate data related to pregnancy. The correlation of pregnancy between the two groups in each category was statistically analyzed. In the LOD/control groups, there was a slight increase in the pregnancy rate in the LOD group compared to the control, but it was not statistically significant (RR = 1.09, 95% CI = 0.87, 1.38, P = 0,033). On the other hand, in the ULOD/BLOD group, the RR was 0.63 (95% CI = 0.36, 1.10), which shows a slight decrease in ovulation in the ULOD group compared to BLOD. However, this difference was still not statistically significant. Studies showed moderate

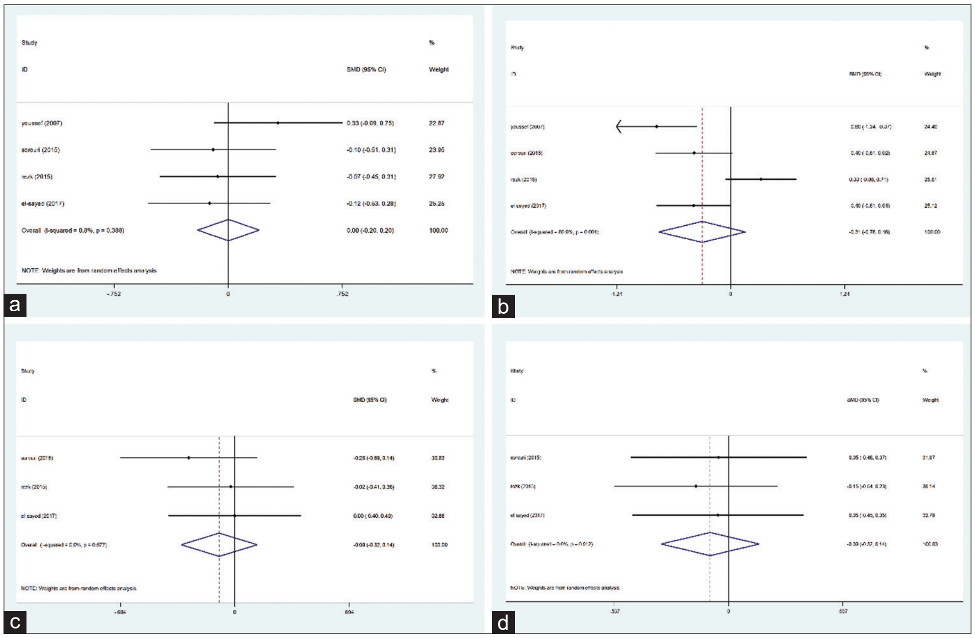

Figure 3: Forest plot for demographics of unilateral laparoscopic ovarian drilling/bilateral laparoscopic ovarian drilling; (a) Age, (b) Infertility duration, (c) Preluteinizing hormone, (d) Prefollicle stimulating hormone. SMD: Standardized mean difference, CI: Confidence interval

Table 2: Meta-analysis of demographic features

	Number of studies	SMD	95% CI	I^2 (%)
LOD/control				
Age	9	−0.05	0.23–0.14	63.5
Duration fertility	8	0.03	−0.11–0.18	41.2
BMI	8	0.06	−0.05–0.17	0
Preovarian volume	5	0.14	−0.11–0.38	53.9
Pre-LH	8	0.19	0.08–0.30	0
Pre-FSH	7	0.04	−0.08–0.16	13.6
Pre-T	3	−0.17	−0.49–0.14	0
ULOD/BLOD				
Age	4	0	−0.2–0.20	0.8
Fertility duration	4	−0.31	−0.78–0.16	80.9
Pre-LH	3	−0.09	−0.32–0.14	0
Pre-FSH	3	−0.09	−0.32–0.14	0

SMD: Standardized mean difference, CI: Confidence interval, LH: Luteinizing hormone, LOD: Laparoscopic ovarian drilling, BLOD: Bilateral LOD, ULOD: Unilateral LOD, FSH: Follicle-stimulating hormone, BMI: Body mass index

to substantial heterogeneity (I^2 = 52.1% and I^2 = 78.5%, respectively). In summary, this meta-analysis did not find a significant difference in the pregnancy rate between the two groups [Figure 4].

Miscarriage

Seven studies in the LOD/control category with a total of 1054 participants reported adequate data related to miscarriage. The correlation of miscarriage between the two groups was statistically analyzed. The RR was 1.13 (95% CI = 0.64, 1.99), which indicates a slight increase in the ovulation rate in the LOD group compared to the control, although this difference was not statistically significant. Studies showed no heterogeneity (I^2 = 0%). In summary, this meta-analysis did not find a significant difference in the miscarriage rate between the two groups. Only one study in the ULOD/BLOD category reported required data related to miscarriage. Therefore, statistical analysis was not possible [Figure 4].

Live birth rate

Six studies in the LOD/control category with a total of 1011 participants reported adequate data related to miscarriage. Whereas, in the category of ULOD, no study reported enough data about the live birth rate. The correlation of the live birth rate between the two groups was statistically analyzed. The RR was 0.99 (95% CI = 0.79, 1.24), which indicates a slight decrease in the ovulation rate in the LOD group compared to the control, although this difference was not statistically significant. Studies showed low heterogeneity (I^2 = 36.3%). In summary, this meta-analysis did not find a significant difference in the live birth rate between the two groups [Figure 4].

Sensitivity and bias analysis

The results of the sensitivity analysis revealed that any single study or cluster of studies with shared characteristics had minimal influence on the SMD and its corresponding CI, indicating robustness in the overall findings. Furthermore, Egger's regression test, Begg's test, and funnel plot analysis were performed to detect publication bias. Both Egger's regression test and Begg's test did not reveal any evidence of publication bias ($P > 0.1$), and funnel plot analysis yielded

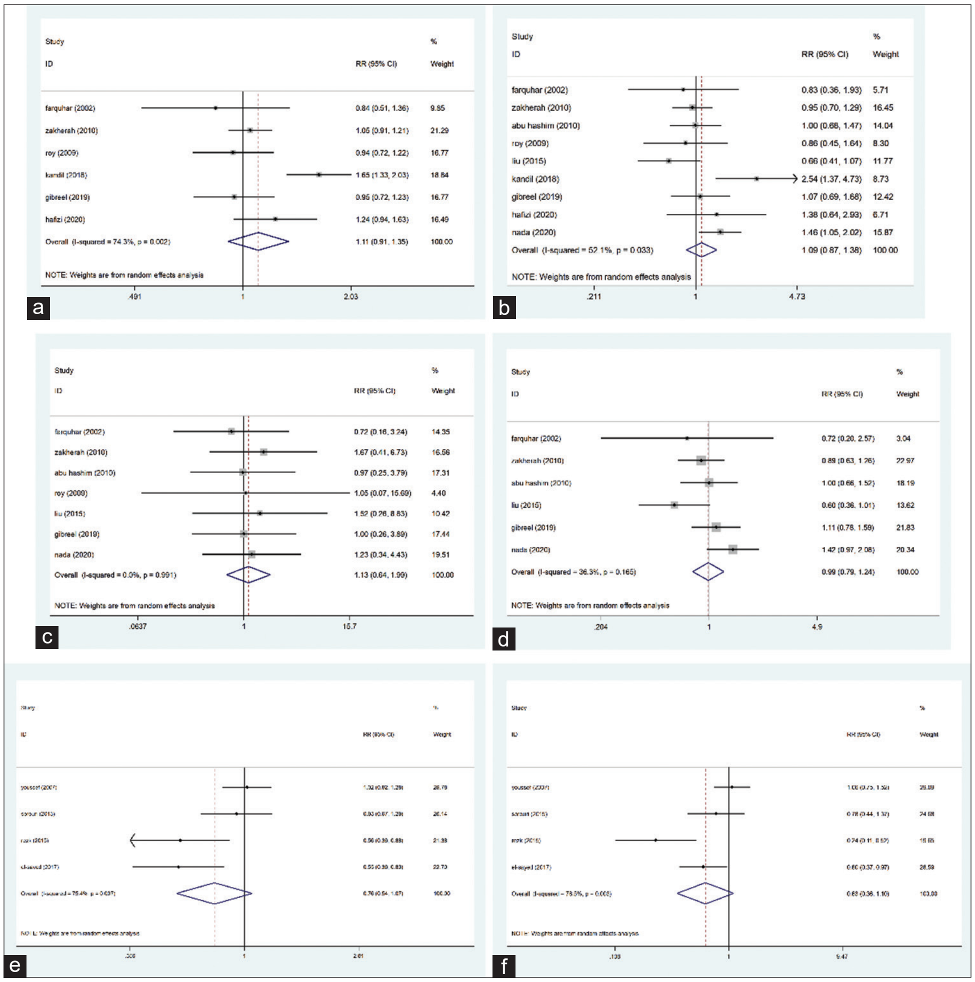

Figure 4: Forest plot for outcomes of laparoscopic ovarian drilling (LOD)/control; (a) Ovulation, (b) Pregnancy, (c) Miscarriage, (d) Live birth rate and outcomes of unilateral LOD/bilateral LOD, (e) Ovulation, (f) Pregnancy. RR: Relative risk, CI: Confidence interval

a symmetric plot for the number of retrieved oocytes. Therefore, we did not detect any publication bias.

Discussion

PCOS is a condition characterized by prolonged anovulation and infertility. One of the common treatments for this condition is the administration of CC. Losing weight and consumption of increasing insulin sensitivity drugs can also help in treatment. About 25% of cases fail with CC therapy, requiring alternative treatment. One of the alternative treatments is the administration of gonadotropins, which is associated with some risks, such as hyperstimulation of the ovary and multiple pregnancies, and is also expensive.[22,23] Aromatase inhibitors can also be used for treatment.[14] LOD surgery is also a suitable method for treating these patients.[22]

This systematic and meta-analysis study includes 13 articles with a total of 1737 participants. It aimed to investigate the effect of LOD surgery on improving reproduction in PCOS patients resistant to CC treatment. Our study did not find any significant difference between the two groups about ovulation rate, pregnancy rate, miscarriage rate, and live birth rate.

By burning and puncturing the follicles, LOD improves the flow of follicular fluid and reduces the abnormal effect of hormones on ovarian function. In addition, LOD normalizes the synthesis of hormones and regulates the effect of the growth factor on the ovary. By improving the internal environment of the ovary, the function of the hypothalamus–pituitary–ovarian axis returns to its original state, which results in the normal functioning of the ovary in PCOS patients.[17]

In this meta-analysis, two categories of studies were analyzed. The first category compares LOD with other available treatments. In the following, we discuss the advantages and disadvantages of these methods and their comparison with LOD.

LOD treatment had a similar effect on reproduction compared to administration of gonadotropins. The administration of gonadotropins is an expensive treatment that causes hyperstimulation of the ovary and multiple pregnancies. Whereas, the surgical treatment of LOD is preferred due to the lack of these effects. This method leads to spontaneous ovulation after surgery. In some patients, additional medical therapy is needed for ovulation after LOD, which is more effective than before surgery. Another benefit of LOD is increasing the sensitivity of the ovary to oral ovulation stimulation drugs, which improves the outcomes of medical therapy.[13]

One of the problems of individuals with PCOS is an increase in BMI, which contributes to poorer fertility results by creating insulin resistance.[13] Therefore, insulin sensitizer consumption, such as biguanides and thiazolidinediones, improves patient outcomes. The effect of these medications with LOD was compared in the study of Roy *et al*.[16] Administering rosiglitazone simultaneously with CC improves insulin resistance, while this difference was nonsignificant in the LOD group. However, both methods increased the rate of ovulation and fertility, but it was not statistically significant, which could be due to the low sample size.

Letrozole is a drug that increments the endometrial thickness as a result of improving the angiogenesis of the uterus. In addition, it causes the synchronization of ovulation and the development of the uterus. Altogether, these factors contribute to less miscarriage. Therefore, the combination of letrozole with LOD can lead to further improvement in patient outcomes.[17]

Another method is transvaginal ovarian needle drilling (TND) surgery, which is a simple and inexpensive procedure, with less invasiveness and complications than LOD. It can improve ovulation, pregnancy, and hirsutism, but these effects are temporary. In contrast, LOD could cause damage to the ovarian reserve, but it has long-term effects on improving the menstrual cycle and reproduction. As a result, LOD can be considered a better method than TND.[18]

In the study by Zakhera,[14] the LOD method was compared with the simultaneous use of CC and tamoxifen, which showed similar outcomes in ovulation and pregnancy rates. However, abortion was less in the medical treatment group, which could be due to the greater thickness of the endometrium. Considering the cost and fewer side effects, medical therapy is preferred to LOD.

Another category that was investigated in this meta-analysis is the comparison of ULOD and BLOD. In addition to the advantages mentioned, LOD also has disadvantages. The adverse effects of this procedure include adnexal adhesion, reduction of ovarian function, and premature menopause in the long-term.[13,16,22,23] Considering the similar effects of ULOD and BLOD on the reproductive outcomes of patients, the ULOD procedure can reduce the complications. Moreover, more damage to the ovaries leads to the enhancement of complications; therefore, minimizing the number of cavities in each ovary can also contribute to reducing complications.[16,22,23,25] Another reason for the preference of ULOD over BLOD is the shorter surgery time despite the similar efficiency.[22] However, there is some evidence that BLOD is better. In El-Sayed *et al*.'s[25] study, BLOD showed a higher rate of menstrual cycle resumption, ovulation, and cumulative pregnancy.

The disagreement between different study results can be due to the diversity in the technique used, the dominant ovary, and the amount of energy applied to the ovary.[24,25]

Conclusion

This systematic review and meta-analysis have investigated the effect of LOD surgical procedures on the reproductive outcomes of PCOS patients. No statistically significant difference was observed in the rate of ovulation, pregnancy, abortion, and live birth compared to other treatments in control group. More specific studies that investigate the effects of unilateral and BLOD are needed. In general, LOD is a significant method for the treatment of infertility in PCOS, which should be further investigated.

Acknowledgments

We extend our sincere appreciation to the authors of the source articles included in this review. Their meticulous research and valuable contributions have laid the foundation for our study. We are also grateful to the participants of these studies whose involvement has contributed to the advancement of knowledge in the field.

Author contributions

Study conception and design: F.Z; Search and study selection: T.HAS, Q.B, Data extraction: S.Y, N.D; Quality assessment: R.K, F.Z; Data analysis: M.N; Drafting manuscript: T.HAS, F.Z, Q.B, M.N, S.Y, N.D, R.K, F.AM; Critical revision: F.AM. All authors were cooperated in final correction of manuscript. All authors approved the submitted version of the manuscript.

Data availability statement

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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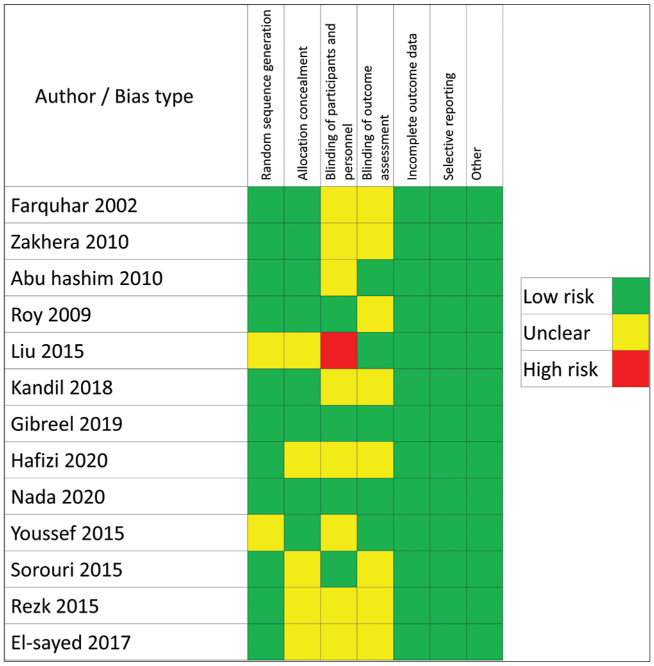
Supplementary Material



Supplementary Figure 1: The quality assessment of included randomized controlled trials using the Cochrane risk-of-bias tool