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Letrozole Versus Clomiphene Citrate As Ovulation Inducing Agents For Infertility In Women With Polycystic Ovary Syndrome - A-Systematic Review Article

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Abstract

Objective: To compare the outcomes after ovulation induction with letrozole and clomiphene citrate in patient with Polycystic Ovary Syndrome.

Background: Polycystic ovarian syndrome is the most common cause of anovulatory infertility. It is estimated that 55% to 75% women with PCOS are infertile due to chronic anovulation. Letrozole and clomiphene citrate are the two important drugs for ovulation induction in PCOS, however there is marked discrepancy of ovulation rate, pregnancy rate, abortion rate and multiple pregnancy rate between these two drugs.

Search Method: PubMed, clinical trial gov, international clinical trial registry platform, Google search and Cochrane library database were scanned for studies.

Selection Criteria: We included those RCTs which compare Letrozole versus clomiphene citrate for ovulation induction in PCOS, published between 2005 to 2020.

Data Collection and Analysis: Two review authors independently selected trials quality extracted the data.The outcomes were ovulation rate and pregnancy rate, abortion rate, multiple pregnancy rate.

Key Result: Letrozole therapy is found to improve ovulation rate, pregnancy-rate, live birth rate as compared to clomiphene citrate with reduction of chances of multiple pregnancy.

Keywords: letrozole, aromatase inhibitor, clomiphene citrate, PCOS, anovulation, ovulation induction, RCTs

Introduction

PCOS is the most common gynaecological endocrinopathy[1]. The main clinical symptoms of PCOS are irregular period and infertility. It is responsible for 55% to 75% cases resulting from anovulation. PCOS is the most common cause of infertility by doing ovulatory disfunction[2].

Ovulation induction is the standard treatment for PCOS. Among various oral ovulogen, clomiphene citrate and letrozole are most used. About 80% of women with PCOS respond to clomiphene citrate, but all of them does not show good outcome[3], it may be due to some undesired side effect of clomiphene citrate like antiestrogenic effect on endometrium and cervical mucosa which may prevent pregnancy[4,5].

Alternatively, letrozole which is an aromatase inhibitor introduced in 2001 for ovulation induction, is most used now[6].Several studies show letrozole has overcome the side effects associated with clomiphene citrate.Letrozole has short half-life of 48hours as compared to clomiphene citrate which has prolong

half-life (2 weeks), so frequency of monofollicular ovulation is increased with letrozole use[7]. That is why, incidence of multiple pregnancy is less as compared to clomiphene citrate.Letrozole does not have antiestrogenic effect on endometrium like clomiphene citrate, moreover it suppresses estrogen production which may improvise pregnancy-outcomes.

Several RCTs have been conducted to assess the drug suitable for ovulation induction with better outcomes in PCOS patients[8,9], but no studies could show intended conclusion.Moreover, there are very few meta-analysis to provide evidence to say which drug is superior to other without definitive conclusion.

Hence, this systematic review is designed to observe clinical efficacy and safety of both clomiphene citrate and letrozole and to find out which has better outcome.

1. **Aim**: To compare the outcomes of ovulation induction with Letrozole and Clomiphene Citrate for infertility in women with Polycystic Ovary Syndrome .

Objectives:

1. To select the RCTs systematically
2. To analyse the effect of ovulation induction with Letrozole
3. To assess the effect of ovulation induction with Clomiphene Citrate

3. Methodology:

3.1 Search strategy

To obtain relevant studies we searched Pubmed, Clinical trial.gov, WHO database, Google scholar, Cochrane library data base etc. The following keywords were used to searcher letrozole, aromatase inhibitor, clomiphene citrate, PCOS, anovulation, ovulation induction, RCTs.

3.2 Selection of study

Inclusion criteria

1. Should be an RCT study
2. Diagnosis of PCOS by Rotterdam 2003 criteria that any 2 of the following 3 features-
    a. Oligo ovulation and or anovulation
    b. Hyperandrogenism
    c. Presence of polycystic ovaries on USG
3. There should be comparison between letrozole and clomiphene citrate group.
4. Outcomes include at least two of the following-ovulation rate, clinical pregnancy rate, live birth rate, abortion rate, multiple pregnancy rate.

Exclusion criteria

1. Non RCT study
2. WHO type 1 anovulation
3. Study which does not compare between letrozole and clomiphene citrate
4. Study in which gonadotrophin used along with letrozole or clomiphene citrate

3.3 Types of intervention

In all the studies participant divided randomly into two groups letrozole and clomiphene citrate group for ovulation induction. Once follicles become matured advised either timely intercourse or IUI.

Protocol use for ovulation induction

In all the studies except 2 studies (Rehan R et al and S Thomas et al), conventional protocol used like letrozole 2.5 mg OD or clomiphene citrate 50 mg OD in respective group from day 3 to day 7 of cycle, if no ovulation from next cycle double the doses till max dose.

Rehan R et al 2009, used Letrozole step up protocol like

Tab Letrozole 2.5 mg

1. OD on day 2
2. BD on day 3
3. TDS on day 4
4. QID on day 5 & 6

Start with Clomiphene Citrate (CC) 50 mg OD or Letrozole 2.5 mg OD from day 2 to day 6 of cycle then folliculometry after 5-7 days of last dose of cc or letrozole, if dominant follicle less than 10mm then from same day double the dose (100mg in CC cycle or 5 mg in letrozole cycle) for another 5 days, again do folliculometry. The protocol is continued in same cycle till max dose of letrozole 7.5mg or CC 250 mg or till size of the follicle reached 18mm.

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3.4 Types of outcome measures

Primary outcome

1. **Clinical pregnancy rate per women** - defined as no of woman having present of fetal cardiac activity on USG at 7weeks per total no of study patient.
2. **Ovulation rate** - calculated as no of women developed mature follicle per no of cycle of stimulation.

Secondary outcome

1. **Live birth rate** - delivery of a live foetus after 20 weeks of gestation per woman.
2. **Abortion rate** - involuntary loss of clinical pregnancy before 20weeks of gestation per woman.
3. **Multiple pregnancy rate per woman** - more than one intrauterine gestation on USG per total no of clinical pregnancy in respective group.

Measurement of the outcome variable

The primary outcome for this review was to estimate the pooled effect size of clinical pregnancy rate and ovulation rate. The secondary outcomes for this review were live birth, multiple pregnancy rate, abortion rate.

Assessment of risk of bias

The risk of bias of the included studies were assessed by using Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) [Higgins 2019].

Five domains of possible biases were evaluated:

1. bias arising from the randomisation process.
2. bias due to deviations from intended interventions.
3. bias due to missing outcome data.
4. bias in measurement of the outcome.
5. bias in selection of the reported result.

Each study was assessed for different types of biases by two review authors and rated them as low, some concerns, and high risk of bias. The result was summarised in 'Risk of bias' table and graph.

3.5 Statistical analysis

The extracted data were analysed in Review Manager (RevMan) 5.4 version software. The extracted data for the outcomes were dichotomous, the results in letrozole and clomiphene citrate group were expressed as odds ratio (OR) with 95% confidence interval (CI). We interpreted the pooled odds ratio in form of forest plots. The unit of analysis for the outcome clinical pregnancy was woman randomised. The heterogeneity of included studies was measured by the I^2 statistic (Higgins 2011). The value of I^2 statistic more than 50% was considered as moderate heterogeneity. We conducted sensitivity analysis according to the overall risk of bias of studies. The possibility of publication bias was assessed by the funnel plot.

4. Results

4.1 Characteristics of included studies

We searched 30 relevant trials out of which only 20 RCT trials identified as potentially relevant to our analysis but only 12 RCTs fulfilled the inclusion criteria of our meta-analysis. (Figure 1) A total of 2492 participants (6343 cycle) were enrolled, of which 1243 (3123 cycle) belongs to letrozole group and 1249 (3220 cycle) belongs to clomiphene citrate group. The characteristics of the included studies are listed in table 1.

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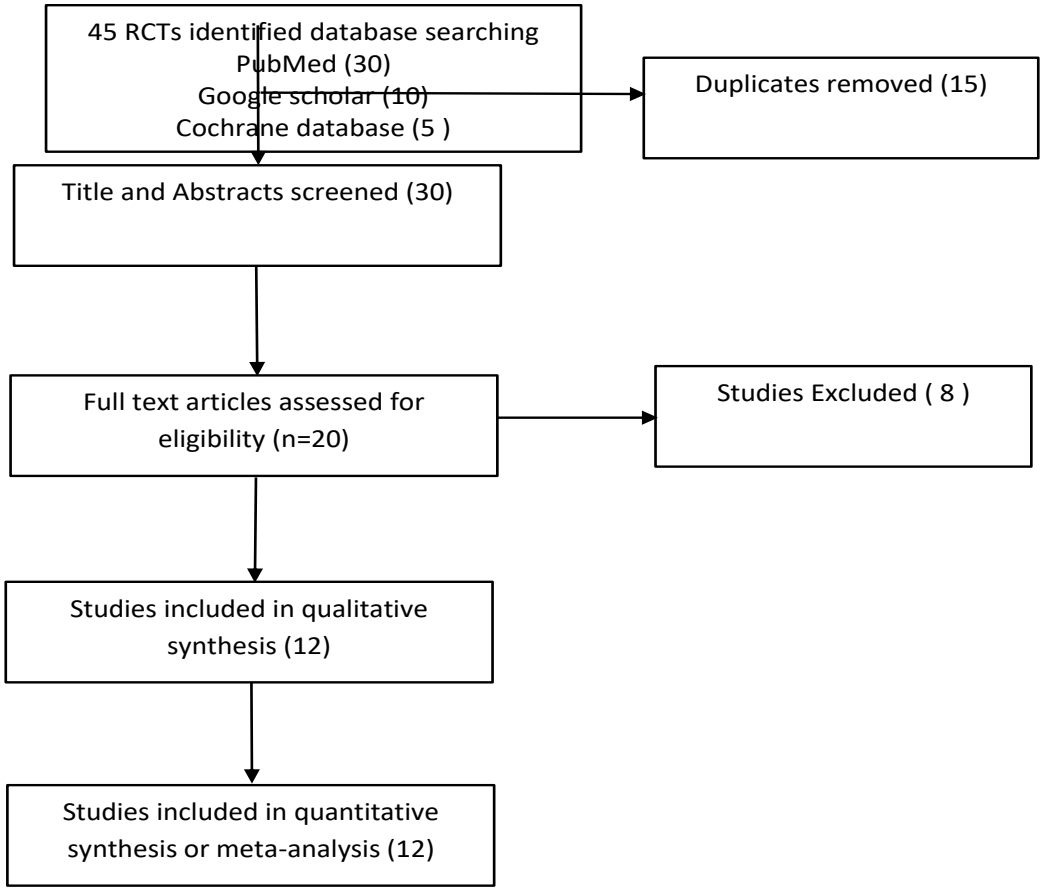

Figure 1: Study flow diagram

Table 1: Summary of characteristics of included studies (LE-letrozole, CC-clomiphene citrate, OR-ovulation rate, PR-clinical pregnancy rate,LBR-live birth rate,AR-abortion rate, MPR-multiple pregnancy rate.)

Publication	Country	Study design	Intervention	No of patient	Cycle	Outcome measure
Legro et al. 2014	USA	Double-blind, prospective multicenter trial	LE CC	374 346	1352 1425	OR,PR,LBR,AR,MPR

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Elkhateeb et al. 2016	Egypt	Prospective randomized controlled trial (RCT)	LE CC	100 100	242 249	OR,PR,MPR
Amer et al. 2017	UK	Single centre, two-arm double-blind RCT	LE CC	80 79	261 278	OR,PR,LBR,AR,MPR
Badway et al (Sept) 2009	Egypt	Prospective randomized trial	LE CC	218 220	540 523	OR,PR,AR,MPR
Atay et al 2006	Turkey	Prospective, randomized study	LE CC	51 55	51 55	OR,PR,AR
Bayar et al 2006	Turkey	Double blind, prospective randomized study	LE CC	38 36	99 95	OR.PR,AR
Roy et al 2012	India	Prospective randomized clinical trial, randomized	LE CC	98 106	294 318	OR,PR,LBR,AR,MPR
Dehbashi et al. 2009	Iran	Prospective double-blind study, randomized	LE CC	50 50	50 50	OR,PR,LBR,MPR
Begum et al 2009	Banglades h	Prospective, randomized, not	LE CC	32 32	32 32	OR,PR,LBR

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		blinded, controlled trial				
S.Thomas et al. 2019	USA		LE CC	49 43	49 43	OR,PR,MPR
Kar et al. 2012	India	Prospective randomized trial	LE CC	52 51	52 51	OR,PR,AR,MPR
Sharief et al. 2015	Iraq	Prospective clinical trial	LE CC	35 40	35 40	OR,PR,MPR
Chakravorty et al. 2016	India	Prospective, randomized, not blinded, controlled trial	LE CC	66 61	66 61	OR,PR,

4.2 Effect of the interventions

Table 2 showed the pooled effect of outcomes in the letrozole and clomiphene citrate group for the included studies.

Table 2: Effect of letrozole versus clomiphene citrate for the outcomes

Outcome	**No of studies**	**Participants**	**Statistical method**	**Effect Estimate, I^2 statistic (p value)**
Clinical pregnancy	12	2400	Odds Ratio (M-H, Random, 95% CI)	1.71 (1.30, 1.77), 40% (0.08)
Ovulation	12	6251	Odds Ratio (M-H, Random, 95% CI)	1.40 (1.07, 1.84), 76% (<0.00001)
Live birth	5	1285	Odds Ratio (M-H, Fixed, 95% CI)	1.81 (1.40, 2.34), 0% (0.76)
Abortion	6	1754	Odds Ratio (M-H, Fixed, 95% CI)	1.47 (1.00, 2.15), 0% (0.56)

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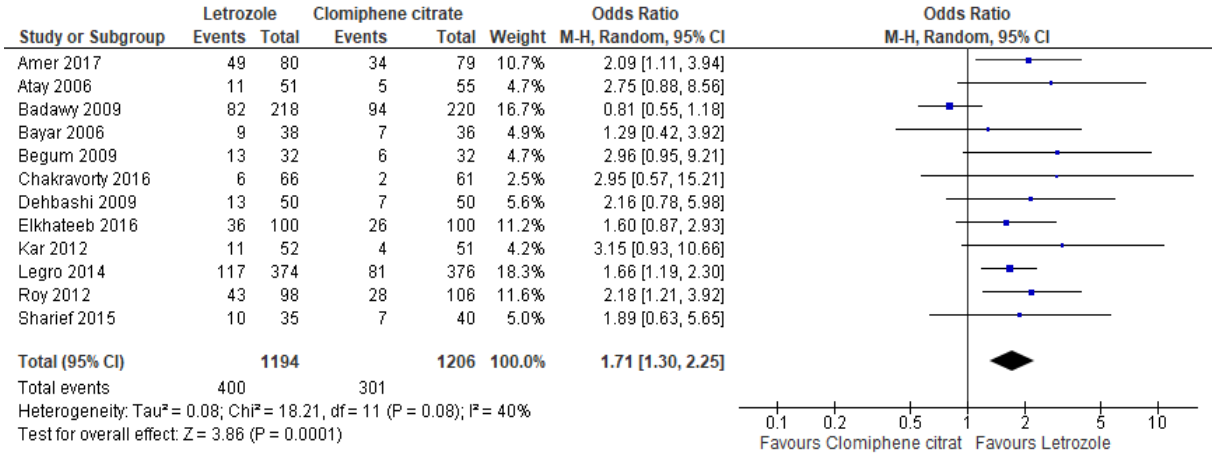
Multiple pregnancy	8	643	Odds Ratio (M-H, Fixed, 95% CI)	0.55 (0.28, 1.10), 0% (0.53)

4.3 Clinical pregnancy

All the 12 RCTs including 2400 women reported clinical pregnancy rate. Analysis showed use of letrozole resulted in higher clinical pregnancy rate compared to clomiphene citrate [OR 1.71 (95%CI -1.30 to 1.77), I2 = 40%]. (Figure 2) Moreover, in sensitivity analysis according to the risk of bias of the individual study showed similar estimate of clinical pregnancy. (Figure 7).

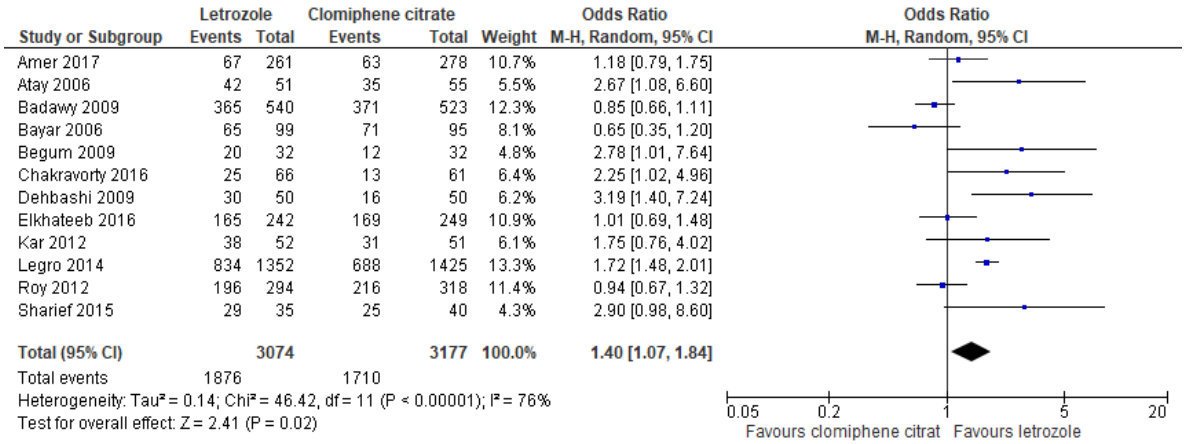
Figure 2: Forest plot showing effect of letrozole vs. clomiphene citrate for clinical pregnancy rate



4.4 Ovulation per cycle

12 RCTs consisting of 6251 cycles were used to report the ovulation rate. The analysis showed use of letrozole having increased ovulation rate compared to clomiphene citrate group [1.40 (1.07, 1.84), 76%]. (Figure 3) Further in sensitivity analysis by risk of bias showed similar effect of letrozole compared to clomiphene citrate for ovulation rate per cycle. (Figure 8).

Figure 3: Forest plot showing effect of letrozole vs. clomiphene citrate for ovulation rate



4.5 Live birth

Five studies including 1285 women, reported live birth rate. Pooled analysis of five studies (Amer 2017, Begam 2009, Dehbashi 2009, Legro 2014, Roy 2012) showed letrozole use resulted in increased live birth rate compared to clomiphene citrate for ovulation induction in PCOS women [1.81 (1.40, 2.34), I^2 = 0%]. (Figure 4)

4.6 Multiple pregnancy rate

11 RCTs including 693 women with clinical pregnancy reported multiple pregnancy rate per

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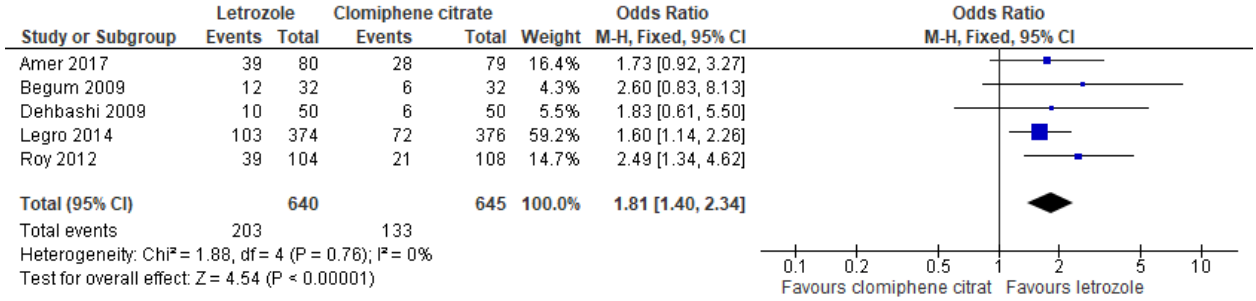
woman. However, 3 studies (Kar et al., Bayer e al., Begum et al.) reported zero multiple pregnancy. Pooled analysis of 643 clinical pregnant participants showed use of letrozole for ovulation induction result in reduced number of multiple pregnancies compared to clomiphene citrate group [0.55 (0.28, 1.10), 0%] (Figure 4)

4.7 Abortion rate

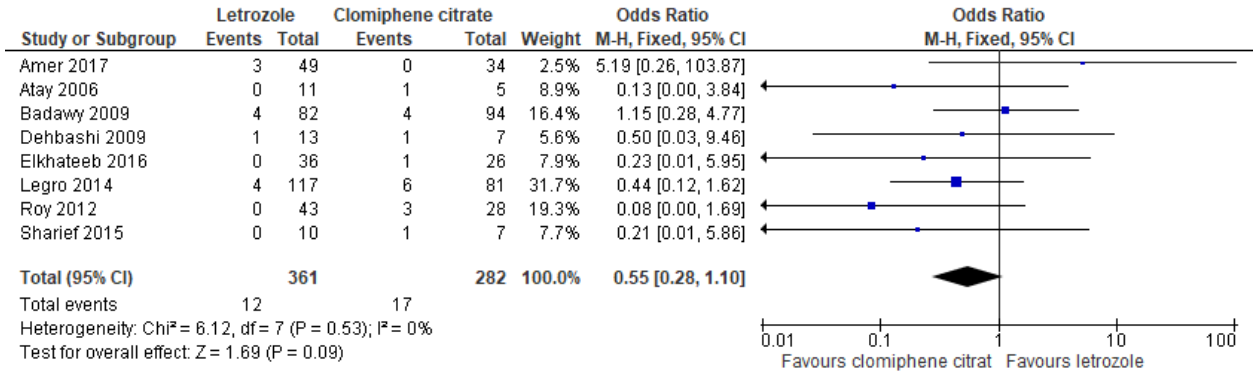
Six RCTs including 1754 women reported abortion rate per woman. Pooled analysis of six studies showed use of letrozole resulted in slightly higher rate of abortion as compare to clomiphene citrate group [1.47 (1.00, 2.15), 0%]. (Figure 4).

Figure 4: Forest plot showing effect of letrozole vs. clomiphene citrate for live birth rate, multiple pregnancy rate and abortion rate.

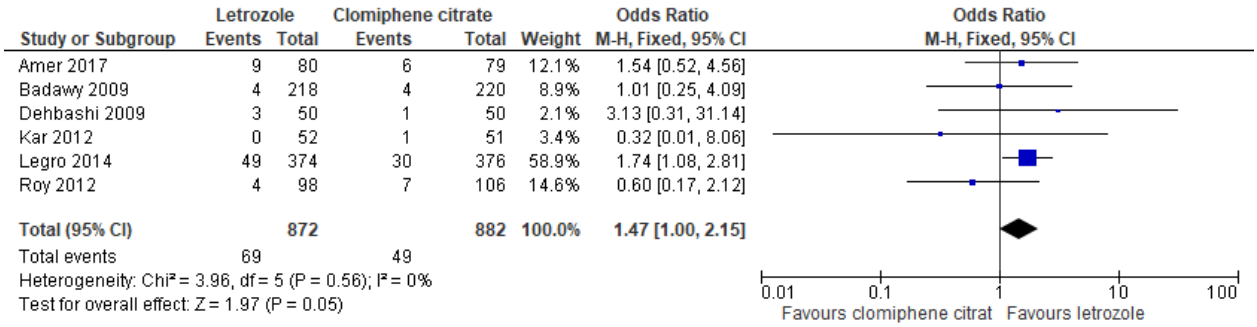
Live birth



Multiple pregnancy rate



Abortion rate



4.8 Risk of bias

Overall, three studies had low, four had some concerns, and five studies had high risk of bias as assessed by the reviewers. Majority of the studies had not mentioned the randomizationrandomisation process explicitly in the

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studies, hence judged as some concerns and only three studies had low risk of bias related to randomizationrandomisation process. All the studies except one reported low risk of bias in terms of missing outcome data, whereas one study had some concerns about selection of reported result. Three studies had some concerns, one had high risk of bias about deviations from the intended result, ten studies had low risk of bias in terms of outcome measurement as assessed by the reviewers. (Figure 5; figure 6).

Study ID	**D1**	**D2**	**D3**	**D4**	**D5**	**Overall**
Amer 2017						
Atay 2006						
Badawy 2009						
Bayar 2006						
Begam 2009						
Chakravorty 2016						
Dehbashi 2009						
Elkhateeb 2016						
Kar 2012						
Legro 2014						

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Sharief 2015						
Roy 2012						

Note: D1 - RandomizationRandomisation process

D2 - Deviations from the intended interventions

D3 - Missing outcome data

D4 - Measurement of the outcome

D5 - Selection of the reported result

Figure 5: Risk of Bias summary of each individual study

Figure 6: Risk of bias graph about each risk of bias domain presented as percentages across all included studies.

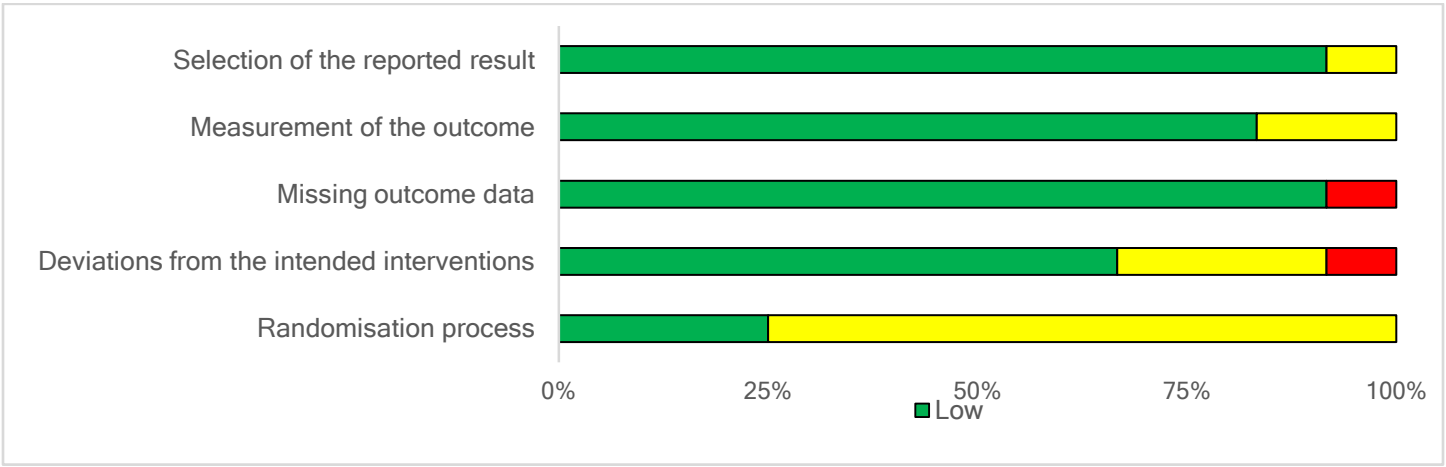

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Figure 7: Sensitivity analysis by risk of bias of individual studies for clinical pregnancy

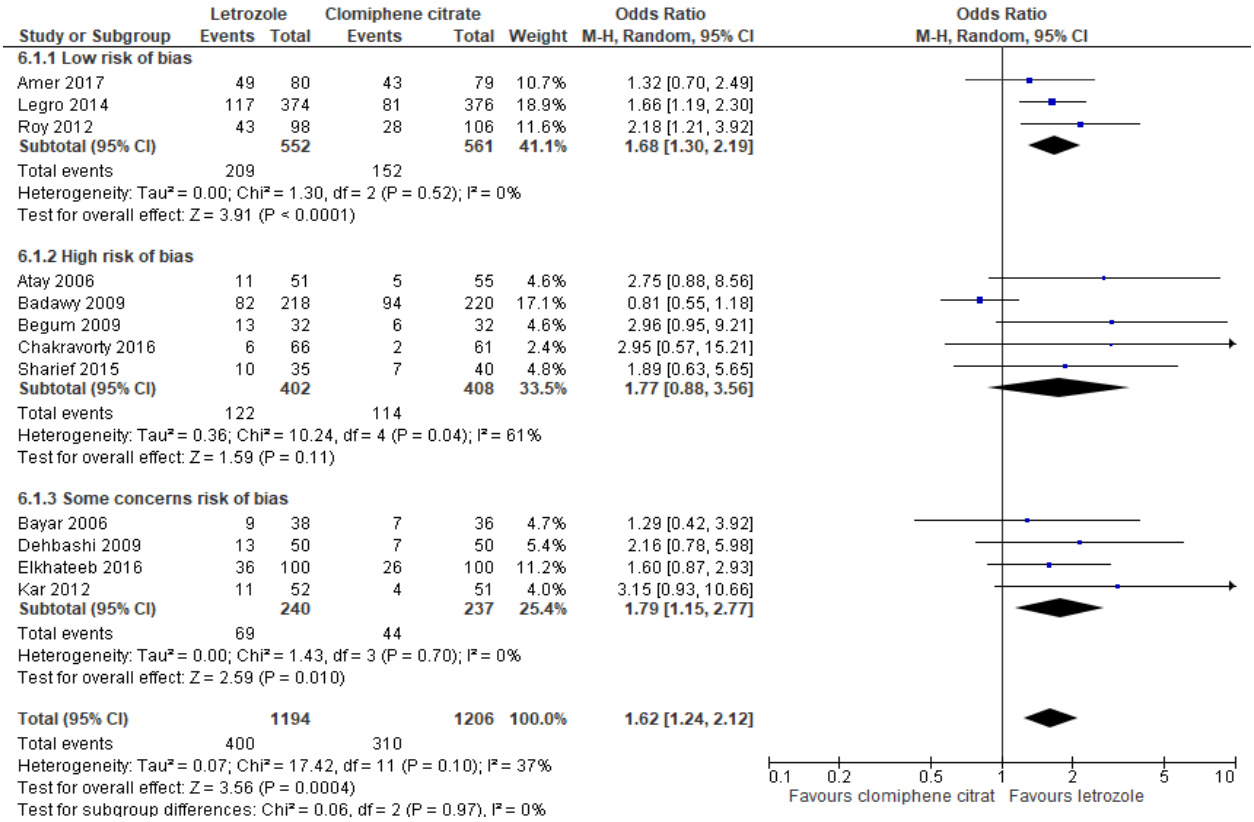
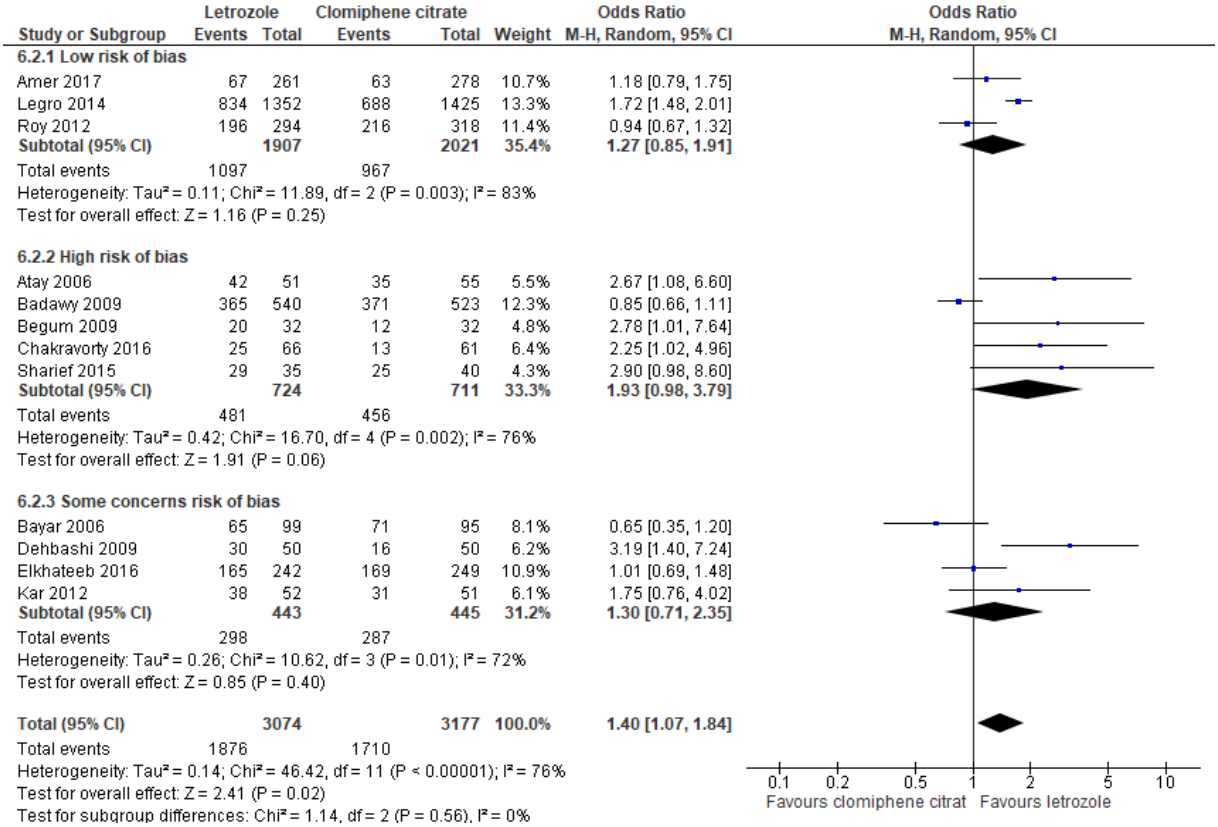


Figure 8: Sensitivity analysis of included studies by risk of bias for ovulation rate



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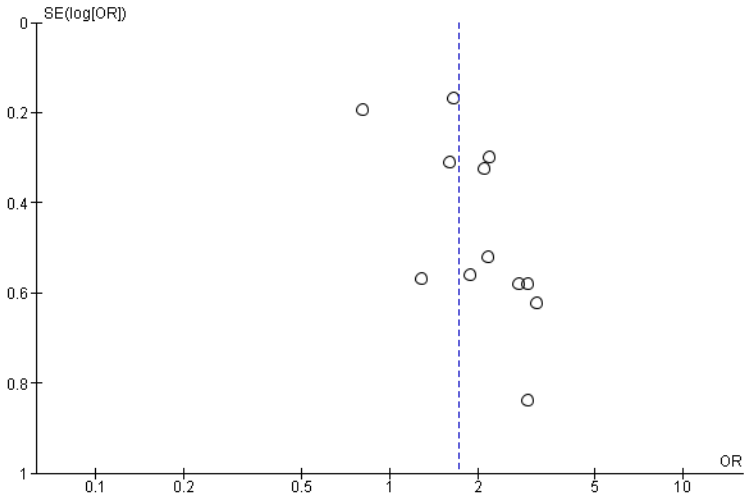
4.9 Publication bias

Funnel plot was plotted for the primary outcomes. A funnel plot for the outcome of clinical pregnancy showed in Figure 9 indicates that the findings of this review may possibly not influenced by publication bias.

Figure 9: Funnel plot of comparison between letrozole vs. clomiphene citrate for the outcome clinical pregnancy



5. Discussion

Anovulation in terms of oligomenorrhoea or amenorrhea is the most common symptom of PCOS. PCOS affects 4-8% women in the world in their reproductive age. Ovulation induction is most preferred treatment of choice in PCOS patients. Oral ovulogen is safe & affordable for the patient. Two oral ovulogen, clomiphene citrate and letrozole are commonly used.

Clomiphene citrate is a selective estrogen receptor modulator which is used traditionally to treat anovulation. But clomiphene citrate has an antiestrogenic side effect on cervical mucosa and endometrium. Moreover, it has long half life elimination time being 2 weeks which may hamper the implantation process. To overcome the adverse effects with clomiphene citrate, letrozole is being used now a days for better ovulation and pregnancy rates. Letrozole is an aromatase inhibitor, having short half life. Because of the less elimination time of 48 hours, it clears out of the system before implantation starts and has less side effect on cervical mucosa & endometrium as compared to clomiphene citrate.The present meta-analysis was done for 13 randomised control trials. The primary outcomes as clinical pregnancy rate, ovulation rate, live birth rate, multiple pregnancy rate and abortion rate were compared after ovulation induction with letrozole & clomiphene citrate. The analysis shows increased clinical pregnancy rate, ovulation rate, live birth rate with letrozole therapy as compared to clomiphene citrate[25].

Ovulation rate: The present analysis shows significantly higher ovulation rate (odds ratio 1.40 as in figure 3) with letrozole as compared to clomiphene citrate. Abdul Qadir Akinson et al[23]also reported similar result of higher ovulation rate with letrozole (53.06% with letrozole & 46.96% with clomiphene citrate). Similar result was also seen in the meta-analysis by Donghong He et.al[24]. This could be due to antiestrogenic effect of clomiphene citrate which depletes the oestrogen receptors of endometrium& cervical mucosa. Moreover, letrozole increases intra-ovarian androgen levels leading to higher follicular sensitivity to FSH which results into higher ovulation rate with Letrozole.

Clinical pregnancy rate: In our analysis, the clinical pregnancy rate is found to be higher with letrozole (odd ratio 1.71 as in figure 2) induced group than the CC induced group. Similar findings were reported by Abdul Qadir Akinson et al.[23], Donghong He et.al.[24], Franicet.al.[25]The half-life of clomiphene citrate is

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longer (elimination time of 2 weeks) than letrozole (elimination time of 48 hours). So, clomiphene citrate depletes the estrogen receptors of endometrium and cervical mucosa for prolonged time causing endometrial thinning that may impair the implantation process, whereas the letrozole washes out of the system before the implantation starts. Letrozole also increases integrin expression which helps in implantation. This could the reason of higher clinical pregnancy rate after letrozole therapy.

Live birth rate: Our analysis shows higher live birth rate with letrozole than clomiphene citrate. Similar was shown by Franicet.al.[25] Letrozole increases mid luteal progesterone level which is needed for maintenance of pregnancy by strengthening the decidua and implanted embryo.

Multiple pregnancy rate: Our analysis shows lower multiple pregnancy rate with letrozole therapy as compared with CC therapy. Franicet.al.[25]reported the same. As the clomiphene citrate depletes the central estrogen receptors, the normal estrogen receptor mediated feedback mechanism to suppress FSH gets blocked. As a result of which there will be growth of multiple follicle which increases the chance of multiple pregnancy.[26]

Abortion rate: Only 6RCTs shows abortion rate in our analysis which suggests slightly higher abortion rate with letrozole as compared to clomiphene citrate. Majority of the studies reported no significant difference in abortion rate with both the groups.[27]

Only 5RCTs have reported live birth rate and 6RCTs have reported abortion rate in our meta-analysis. So to mention advantages of letrozole over clomiphene citrate in relation to live birth rate and abortion rate will not be significant in our analysis.

6.Limitations:

1. Letrozole dose of various studies are not uniform
2. All trials have not reported live birth and abortion rates
3. Number
4. of study sample is not uniform in every trial
5. Socio- demographic profiles (BMI, Age) of the study population are not mentioned

7. Conclusion

Pooled analysis from this review suggests that letrozole might be a good alternative than clomiphene citrate for ovulation induction in patient with PCOS, as maximum studies are showing better outcome in view of clinical pregnancy rate and ovulation rate as compared to clomiphene citrate.

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