

Impact of Estradiol Supplementation during Luteal Phase Support on the *In vitro* Fertilization Clinical Outcome: Systematic Review and Meta-Analysis

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Abstract

Background: At present, progesterone administration is widely used. There is no agreement on whether estradiol (E_2) addition should be supplement to progesterone (P) as luteal phase support (LPS). The present meta-analysis was conducted to clarify whether E_2 supplementation as LPS has beneficial effect on the clinical outcome after *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI).

Methods: MEDLINE, Google Scholar and the Cochrane Library were searched from the incipency until May 2019. The primary outcome was clinical pregnancy rate (CPR), ongoing pregnancy rate (ongoing PR), embryo implantation rate (IR), spontaneous abortion rate (AR). Thirteen, seven, four, and ten studies were included while evaluating the effect of E_2 supplementation on CPR, ongoing PR, IR, and AR, respectively.

Results: The results showed that E_2+P group had significant higher CPR (OR=1.39, $P=0.0001$) and ongoing PR (OR=1.36, $P=0.01$) than that of P-only group. No significant differences were found between IR ($P=0.47$) and AR ($P=0.43$) between E_2+P and P- only groups. Subgroup analysis of the GnRH-a/ant showed that GnRH-a protocol group had a significant higher CPR (OR=1.37, $P=0.02$) and ongoing PR (OR=1.76, $P=0.002$) with E_2+P , whereas GnRH-ant protocol group had no difference in CPR ($P=0.6$), ongoing PR ($P=0.44$), IR ($P=0.18$), and AR ($P=0.87$) among E_2+P and P- only groups.

Conclusions: The results suggest that E_2 supplementation as LPS has beneficial effect on the clinical outcomes only during cycles with GnRH-a protocol.

Keywords: Luteal phase support; Estradiol; IVF; ICSI; Ovarian stimulation

Abbreviations: ART: Assisted Reproductive Technology; IVF-ET: *In vitro* Fertilization - Embryo Transfer; ICSI: Intracytoplasmic Sperm Injection; LPS: Luteal Phase Support; GnRH-ant: Gonadotrophin-Releasing Hormone antagonist; GnRH-a: Gonadotrophin-Releasing Hormone agonist; E_2 : Estrogen; P: Progesterone

Summary

This study aimed to clarify whether estradiol (E_2) supplementation as luteal phase support (LPS) has benefit effect on the clinical outcomes after IVF/ICSI. A meta-analysis was conducted. E_2+P group had significant higher CPR and ongoing PR than that of P-only group. GnRH-a protocol group had a significant higher CPR and ongoing PR with E_2+P , whereas GnRH-ant protocol group had no difference in CPR, ongoing PR, IR, and AR among E_2+P and P- only groups. So, E_2 supplementation as LPS has beneficial effect on the clinical outcomes only during cycles with GnRH-a protocol.

Background

Controlled ovarian hyper-stimulation during *in vitro* fertilization/ intracytoplasmic sperm injection (IVF/ ICSI) always results in a defective luteal phase because of the pituitary down-regulation with Gonadotropin-releasing hormone agonist (GnRH-a) and the loss of granular cell after ovarian retrieval [1]. So, it is necessary to provide luteal phase support (LPS) in IVF/ICSI cycles, especially in cycles with long GnRH-a protocol.

In a physiological condition, the corpus luteum secretes not only progesterone (P) but also estradiol (E_2). At

present, P administration is widely used. There is no agreement on whether E₂ addition should be supplement to P as LPS. The level of E₂ falls sharply after ovulation and slowly rises again during the luteal phase. The role of E₂ in the process of embryo implantation is unclear.

Some studies have indicated that the decrease of E₂ levels in mid-luteal or late luteal might have negative effect on the clinical pregnancy [2]. The difference of E₂ level between pregnant and non-pregnant women starts to appear on the 9th day to 10th day after the luteinizing hormone (LH) peak [3]. Therefore, endometrial maturation with good receptivity also needs adequate concentrations of E₂ level during the window of implantation (WOI) [4]. Additionally, some studies showed that E₂ supplementation for LPS would improve the clinical pregnancy outcome [5]. However, some studies did not find beneficial effect of E₂ supplementation on reproductive outcomes in women undergoing IVF/ICSI [6].

So far, there were five systematic reviews with different results. Four meta-analyses confirmed that the E₂ supplement for LPS in IVF/ICSI cycles has no beneficial effect on pregnancy rate (PR) [8-10,12]. One meta-analysis study [11] addressed this issue, and showed improved clinical pregnancy rate (IR) with E₂ supplementation to standard P LPS.

Therefore, it was necessary to evaluate whether supplementation of E₂ have beneficial effect on outcome of IVF/ICSI cycles. The present systematic review and meta-analysis aimed to clarify the effect of luteal E₂ supplementation.

Methods

Literature retrieval

MEDLINE, Google Scholar and the Cochrane Library were searched from the inception until May 2018. The keywords used to search relative studies were as follows: one including terms on luteal phase support/ luteal support, one including terms on estrogen/oestrogen/oestradiol/estradiol supplementation, one including clinical outcome of IVF/ICSI (clinical pregnancy rate, ongoing pregnancy rate, embryo implantation rate, and abortion rate), and the last one about assisted reproductive technologies (ART, IVF, ICSI, assisted reproduction, *in vitro* fertilization, intracytoplasmic sperm injection). A number of literatures were generated via combining the subsets with "AND". Papers published in non-English were excluded. The eligibility of included papers was reviewed by two reviewers independently and the third reviewer was asked to review the paper when the discrepancy was happened.

Study selection and data extraction

Studies which evaluated estrogen supplementation for LPS in women undergoing IVF/ICSI were included and analyzed. The main outcome index was the clinical

pregnancy rate (CPR), ongoing pregnancy rate (ongoing PR), embryos implantation rate (IR) and/or abortion rate (AR).

For studies to be eligible, outcome data (with CPR, ongoing PR, IR, and/or AR with/ without estradiol supplementation) were extracted in 2×2 tables. We also recorded the first author, publication year, and study design, sample size, ovarian stimulation protocol, the dose and route of P and E₂, and all the reproductive outcomes. Newcastle - Ottawa Quality Assessment Scales was used to evaluate the observational researches' quality. Two reviewers completed the quality assessment, and any discrepancy was settled by a third reviewer.

Data analysis

The Odds Ratio (OR) with the 2x2 tables was used to conduct a standard meta-analysis. Forest plots were used to evaluate the heterogeneity of the included studies graphically and the I² value was used to evaluate the heterogeneity quantitatively among studies. An overall OR and its 95% CI were calculated via fixed or random effect model. Because of the low power of X² test for heterogeneity of a meta-analysis, the statistical significant was considered when the P value <0.1 rather than <0.05, especially in the studies with small sample size. RevMan 5.0 (Cochrane Collaboration, Oxford, UK) was implied to perform the statistical analyses.

Results

Studies selection and characteristics

The search strategy yielded 381 citations. 305 irrelevant studies were excluded after reviewing the title and/or abstract. Of the 76 remaining publications, 49 were excluded as clinical outcome of IVF/ICSI were not reported or defined. Four studies were system review and meta-analysis. An additional eight papers were excluded because we could not get a 2x2 table from the result. (Supplementary table 1).

The characteristics of included studies are described in table 1. Fifteen prospective studies were included in our meta-analysis, and implied long protocol with GnRH-a, GnRH-ant, or both undergoing IVF/ICSI. In these studies, there were thirteen studies for clinical pregnancy, seven studies for ongoing pregnancy, four studies for embryo implantation, and ten studies for abortion. A total of 2971 cycles were included in the analyses, comprising 1572 couples received E₂ supplementation and 1399 couples received P₄ only as LPS in IVF/ICSI cycles. The sample size varied from 44 to 402 cycles. The dose of E₂ and P, together with the route of administration and the duration of treatment, is presented. E₂ was administered orally in nine studies, transdermally in three studies; vaginally, transdermal/orally, and vaginal/orally in only one study, respectively. P was given vaginally in most studies, while it was administrated by IM injection in four trials, by

vaginal/oral, transdermal/oral in only one study, and IM routes in four studies. The duration and doses of E₂ and/or P₄ varied between studies.

Meta-analysis

Thirteen, seven, four, and ten studies were obtained in our meta-analysis to assess the effect of E₂ supplementation on CPR, ongoing PR, IR, and AR after IVF/ICSI treatment, respectively.

When evaluated the effects of E₂ addition on the CPR, thirteen studies were analyzed including 1401 cycles with E₂ supplementation and 1228 cycles with P only as LPS. The CPR was significantly increased in women with E₂

supplementation as LPS compared with those with P only as LPS. The statistical heterogeneity was moderate with P<0.1 (I²=74%). The random effects model was applied with a combined OR 1.39 (95% CI, 1.18, 1.64; P=0.0001) (Figure 1).

Seven studies were included to evaluate the effects of E₂ addition on the ongoing PR, including 690 cycles with E₂ supplementation and 669 cycles with P only as LPS. The PR was significantly increased with E₂ supplementation as LPS compared with those with P only as LPS. The statistical heterogeneity was moderate with P<0.1 (I²=58%). The combined OR was 1.36 (95% CI, 1.07, 1.72; P=0.01) (Figure 2).

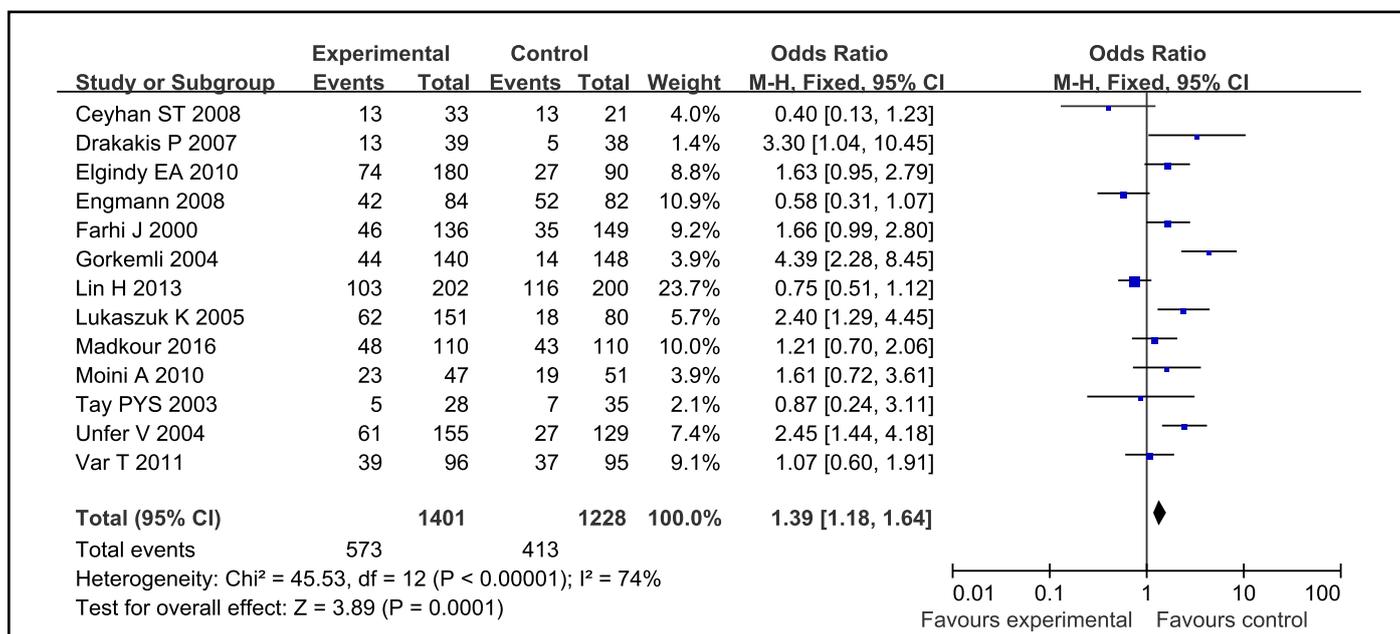


Figure 1: Forest plot showing the results of meta-analysis of studies comparing the effect of E₂+P and P only as LPS on clinical pregnancy after IVF/ICIS.

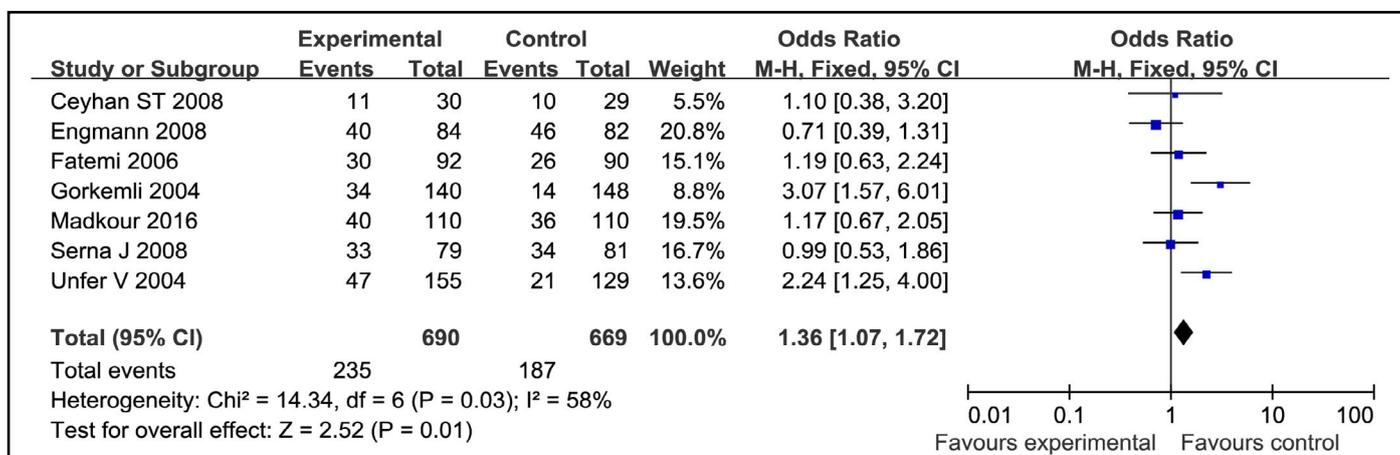


Figure 2: Forest plot showing the results of meta-analysis of studies comparing the effect of E₂+P and P only as LPS on ongoing pregnancy after IVF/ICSI.

Of fifteen studies, ten studies evaluated the effect of E₂ supplementation on IR and AR, respectively. These results of the meta-analysis indicated that there was no beneficial effect in patients with E₂ supplementation as LPS. The Q statistic P-value for ongoing PR and AR were all below 0.1, indicating heterogeneity of the studies ($I^2=54\%$, $P=0.09$; $I^2=40\%$, $P=0.09$). The random effects model was implied and these combined ORs for IR, AR were 1.08 (95% CI, 0.88, 1.31; $P=0.47$) and 0.86 (95% CI, 0.58, 1.26; $P=0.43$), respectively. (Supplementary Figures 1 and 2).

We also evaluated the effect of E₂ supplementation on the clinical outcome (CPR, ongoing PR, IR, AR) after GnRH-a protocol or GnRH-ant protocol treatment. Interestingly, the results showed that GnRH-a protocol subgroup got an increased CPR (OR 1.37; 95% CI, 1.05, 1.78; $P=0.02$) and ongoing PR (OR 1.76; 95% CI, 1.22, 2.53; $P=0.0002$) when E₂ supplementation as LPS, whereas GnRH-ant protocol subgroup did not find such effect. Additionally, there were no differences in IR and AR between E₂+P and P- only groups when GnRH-a protocol and GnRH-ant protocol subgroups were analyzed separately. (Supplementary Figures 3-6).

These studies included were all have high score via the Newcastle-Ottawa Quality Assessment Scale (not shown). There was no publication bias as a symmetrical shape was seen in the funnel plot in the evaluation the effect of E₂ supplementation on CPR, ongoing PR (Supplementary Figures 7 and 8). However, the studies showed modest publication bias when assessing the effect of E₂ supplementation on IR and AR (Supplementary Figures 9 and 10).

Discussion

So far, five systematic reviews [8-12] have evaluated whether there was positive effect of E₂ supplementation as LPS on the IVF/ICSI cycles and came into different conclusions. As far as we know, this study has the largest sample size of 2971 IVF/ICSI cycles. Besides, subgroup analysis was conducted to assess whether the effect of E₂ supplementation between the GnRH-a and GnRH-ant protocol is different.

In the present systematic review, 13, 7, 4, and 10 studies were included assessing the effect of E₂ supplementation as LPS on the clinical pregnancy, ongoing pregnancy, embryo implantation and abortion after IVF/ICSI, respectively. Our results indicated that E₂ supplementation could improve the clinical pregnancy significantly (combined OR 1.39; 95% CI 1.18, 1.64; $P=0.0001$) and ongoing pregnancy (combined OR 1.36; 95% CI 1.07, 1.72; $P=0.01$); however, we did not find significant differences in IR, and AR between E₂ + P group

and P only group. The conclusion was not completely in agreement with the systematic reviews by Jee et al. [10], Kolibianakis et al. [9] and Gelbaya et al. [8], Huang et al.[12], which suggested that the addition of E₂ for LPS have no beneficial effect on outcome of IVF/ICSI. In addition, we found that E₂ supplementation for LPS has no beneficial effect on the clinical outcomes in cycles with GnRH-ant protocol.

As we all know, the luteal function is impaired during IVF/ICSI cycles. Additionally, very low level of LH can be seen [13], which is necessary to maintain the function of the corpus luteum in humans [14]. It is well established that corpus luteum secretes both progesterone and E₂. Therefore, not only P but also E₂ as LPS would be necessary for the development of endometrium before embryo implantation. Whether imply E₂ supplementation as LPS during IVF/ICSI cycles is still controversial [15,16].

Stewart et al. [17] identified that there was a significantly different E₂ concentration between pregnant and non-pregnant women using donor insemination for the first time. Similarly, there was a rise of luteal E₂ level on day 6 in pregnant women compared with non-pregnant women trying to conceive spontaneously. Sharara and McClamrock [18] found that when the ratio of peak E₂ to mid-luteal E₂ is greater than 5, the embryo implantation rate is reduced. One study found that women received 6 mg E₂ have a better clinical pregnancy outcome in comparison to women without E₂ supplementation. The positive effect of E₂ supplementation for LPS in ICSI cycles with GnRH-a long protocol was confirmed in recent two studies [19]. A researcher reported that E₂ addition to progesterone can reduce abortion rates, but this finding was not significant [20]. Anyway, the decline of late luteal E₂ level may have negative affect on the development of endometrial before embryo implantation [21]. Increased level of L-selectin ligands-adhesion molecule can be seen in endometrium of the women with the E₂ supplementation as LPS during the phase of luteal [22].

However, other studies indicated that there was no association between the decline of mid-luteal E₂ and the clinical pregnancy outcome [23]. Muasher and colleagues [24] have also found that E₂ levels were similar between pregnant and non-pregnant women up to 10 days after oocyte retrieval. One recent study showed that pregnancy did not associated with the serum level of E₂ in mid-luteal phase or with percent E₂ decline [25]. The extent of E₂ fall during the phase of luteal of ART cycles seem have no negative effect on the clinical pregnancy outcome [26], successful pregnancy in a few cases in which E₂ supplementation was unintentionally omitted in donor oocytes cycles raised question on the necessity of E₂

addition as LPS [27]. Subsequent studies have shown that luteal E₂ is not essential in the endometrial development for embryo imbed [3,16]. In a more recent study, using GnRH antagonist protocol, the endocrine profile (FSH, E₂, and P) was similar in group receiving P alone vs. P+ E₂ during the luteal phase [17]. During a GnRH-a long protocol, women with 2, 4 or 6 mg E₂ supplementation as LPS have similar clinical pregnancy rates, and women with 2 mg E₂ have a higher miscarriage rate compared with other groups [28]. These results indicated that E₂ supplementation as PLS have no positive effect on the clinical pregnancy outcome, and were in accordance with the findings of previous researches.

In GnRH antagonist cycles, the women were divided into 3 groups according to the LPS protocol: no luteal support, vaginal micronized P, and micronized P+ oral E₂, there was no significant differences in estrogen receptor expression on the day of oocyte retrieval, 3, 5, and 10 days after retrieval [29]. In this study, women with P alone has a significantly increased PR expression in the luminal endometrium 3 days after retrieval compared with the other groups. In earlier study, there was no difference between E₂ and P receptors as well as endometrial histology in the luteal phase of ovariectomized women with or without E₂ [30]. Similarly, in a programmed cycle, biopsies of the endometrium on the 21st day and the 25th day found that there is no adverse effect on endometrial integrity when neglecting luteal E₂ supplementation, indicating that a super physiological level of P may make up for the lack of E₂ [16,30].

GnRH-a protocol is always associated with impaired luteal function, with decreased production of E₂ and P, and shortened duration of luteal phase, impaired secretion of endogenous gonadotropin. So E₂ supplementation as LPS would bring beneficial effect on the clinical pregnancy and ongoing pregnancy. Whereas, GnRH-ant cause less pituitary suppression compared with GnRH-a protocol. P₄ may be enough for the LPS, and the E₂ supplementation seems to have no beneficial effect on the clinical outcomes.

Comparatively speaking, the meta-analysis and systematic review has the merit of the improved accuracy of the OR estimates by comparison to a single study. The present meta-analysis indicated that E₂ supplementation to P as luteal phase support has beneficial effect on clinical pregnancy and ongoing pregnancy after IVF/ICSI, especially in cycles with GnRH-a protocol. Evaluating the effect on clinical pregnancy and ongoing pregnancy, there were four and two studies in which the OR was below one, and the combined OR was 1.39 (95% CI 1.18, 1.64) and 1.36 (95% CI 1.07, 1.72). While assessing the impact on implantation and abortion, the ORs of the included

studies were greater than unity, although the sample sizes of studies were small.

But then, the main weakness of this study is the higher variable between studies: different dose and duration of E₂ administration, different treatment types (IVF/ICSI) and different ovarian stimulation protocols. The inclusion/exclusion criteria for women and the definition of pregnancy loss are not always clearly stated or varied. Besides, the present meta-analysis only included papers published in English, we would miss some relative papers published in non-English.

Conclusion

Despite the weakness, the present meta-analysis demonstrates that there is an advantage only during cycles with GnRH agonist protocol. However, there was no beneficial effect on IR and AR. The benefits of additional E₂ supplementation, the optimal E₂ dose, the start and the end times of E₂ supplementation should be further clarified.

Competing Interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Jing Zhao and Jie Hao participated in the design of the study and the acquisition of data, performed the statistical analysis, drafted the article and revised it critically. Yanping Li contributed to conception and design, acquisition of data and analysis and interpretation of data. Bin Xu and Yonggang Wang participated in the interpretation of the data and the revision of the article. All authors read and approved the final manuscript.

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