# Effects of estradiol supplementation during the luteal phase of in vitro fertilization cycles: a meta-analysis

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**Objective:** To clarify whether adding $E_2$ to standard luteal P supplementation is beneficial both in GnRH agonist and antagonist IVF cycles.
**Design:** Meta-analysis of nine randomized controlled trials.
**Setting:** University hospital center for reproductive medicine and IVF.
**Intervention(s):** None.
**Main Outcome Measure(s):** Clinical pregnancy rate (PR) per patient, clinical PR per embryo transfer (ET), implantation rate, ongoing PR per patient, clinical abortion rate, and ectopic PR.
**Result(s):** There were no statistically significant differences between $E_2$+P versus P-only group regarding overall IVF outcomes. From seven studies including GnRH agonist cycles, no statistical significant differences were found between the two groups in clinical PR per patient (relative risk [RR] 1.32, 95% confidence interval [CI] 0.79–2.19), clinical PR per ET (RR 1.83, 95% CI 0.96–3.49), implantation rate (RR 1.20, 95% CI 0.34–4.21), ongoing PR per patient (RR 1.34, 95% CI 0.37–4.82), clinical abortion rate (RR 1.05, 95% CI 0.48–2.28), and ectopic PR (RR 0.53, 95% CI 0.07–4.10). Clinical PR per patient (RR 0.94, 95% CI 0.62–1.42) and ongoing PR per patient (RR 1.09, 95% CI 0.79–1.50) from three studies including GnRH antagonist cycles only were all similar between the two groups.
**Conclusion(s):** The combined data presented in this meta-analysis suggest that the addition of $E_2$ to P for luteal phase support does not improve IVF outcomes in GnRH agonist and antagonist cycles. However, the authors feel that there is an obvious need for further large-scale studies regarding GnRH antagonist cycles. (Fertil Steril® 2010;93:428–36. ©2010 by American Society for Reproductive Medicine.)

**Key Words:** Estradiol, luteal phase, in vitro fertilization, GnRH agonist, GnRH antagonist

Luteal phase support has been a routine practice in IVF-ET because stimulated IVF cycles are associated with a defective luteal phase in almost all patients (1, 2). Three recent meta-analyses demonstrated that hCG is equally effective (3, 4) or superior to P (5) for luteal phase support with respect to clinical pregnancy rate (PR). Nonetheless, P is often favored, because hCG has a potential for increasing rates of ovarian hyperstimulation syndrome (4, 6).

Various formulations of P are currently available, including oral, vaginal, rectal, and IM forms. Vaginal P gel and IM P were found to have similar clinical and ongoing PR (7). However, in a subsequent meta-analysis, clinical PR and delivery rate were significantly higher when IM P was used compared with vaginal application (3). Intramuscular P has been widely used for luteal phase support but is often associated with a number of side effects, including painful injections with a rash, inflammatory reactions, and abscess formations (8). In these circumstances, vaginal administration of P can be a viable alternative. Moreover, intravaginal route of P supplementation is regarded as a first-choice luteal support regimen in stimulated IVF cycles (9).

An earlier report indicated that serum $E_2$ concentrations severely drop at the end of the luteal phase (10); therefore, a concern has been raised about an additional supply of $E_2$ during the luteal phase in IVF cycles. In the first half of 1990, two prospective randomized studies were performed to evaluate the possible benefit of adding 6 mg (11) and 2 mg (12) $E_2$ valerate daily in women treated with a GnRH agonist long protocol and gonadotropins for IVF. In those studies, the clinical PRs were almost equal between the groups with and without $E_2$ cotreatment.

During the luteal phase, ovarian $E_2$ has experienced a sharp fall after its preovulatory peak and starts to rise again. The differences in luteal $E_2$ in conception and nonconception cycles start to appear on day 9 to 10 with respect to the LH peak (13). Based on these observations, two studies were conducted in which patients with a precipitous drop of luteal phase serum $E_2$ (14) or serum $E_2$ concentration $<100$

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pg/mL at 11 days after ET (15) were selected. In those studies, oral $E_2$ was additionally administered within 10 days after ovulation triggering (14) or 11 days after ET (15) and significantly higher clinical (14) or ongoing (15) PR per patient was observed. Farhi et al. (16) compared IVF outcomes with and without 2 mg $E_2$ valerate as a luteal phase support in patients with serum $E_2$ concentration at triggering day >2,500 pg/mL. In that study, $E_2$ was started 11 days after ET and a significantly higher clinical PR per ET and implantation rate was noted in GnRH agonist long protocol cycles but not in short protocol. Although $E_2$ was started several days later after ET and the patients were selected according to serum $E_2$ concentration at specific points, three studies consistently demonstrated the beneficial effect of adding $E_2$ as a luteal phase support.

Pritts and Atwood (3) performed a meta-analysis addressing this issue based on three randomized trials (11, 12, 16). Although $E_2$ doses and duration of treatment varied, they concluded that addition of oral $E_2$ to standard P treatment improved implantation rate. However, that conclusion was derived from only one study (16); moreover, clinical PRs from three studies showed no difference between study and control group (relative risk [RR] 1.15, 95% confidence interval [CI] 0.83–1.58).

Through a Cochrane review, Daya and Gunby (4) reported that there were no significant differences in clinical or ongoing PR, miscarriage, or live birth rate when P combined with $E_2$ was compared to P alone; however, this conclusion was drawn only from two randomized trials (12, 17).

The results from four subsequent studies were quite inconsistent and controversial. Almost equal clinical PR per patient was reported in two studies (18, 19), but significantly increased PR per patient and per ET by adding $E_2$ was noted from other studies (20, 21). Interestingly, Lukaszuk et al. (21) reported a significantly higher clinical PR per patient in a 6 mg $E_2$ supplement group, but not in a 2 mg $E_2$ group, compared with no $E_2$ (56.5% vs. 48.9% vs. 36.0%, respectively).

Since 2007, four reports have been available; Drakakis et al. (22) reported a significantly higher clinical PR in an $E_2$ supplement group in patients using GnRH agonist long protocol, but this same effect was not observed in subsequent studies (23, 24). In GnRH antagonist cycles, there were no differences in clinical and ongoing PR between $E_2$ supplement vs. no supplement group (23, 25).

Although two recent meta-analyses confirmed that the addition of $E_2$ to P for luteal phase support in IVF/ICSI cycles has no beneficial effect on PR (26, 27), it is unclear whether the effect of $E_2$ supplementation is different between GnRH agonist and antagonist cycles. No meta-analysis addressing this issue has been reported.

A recent review (9) indicates that the addition of $E_2$ seems to be beneficial in long GnRH agonist protocol but not in short GnRH agonist and GnRH antagonist protocol. The conclusion about long GnRH agonist protocol stemmed from four studies (11, 12, 16, 21) but they did not attempt to perform a meta-analysis. Moreover, the conclusion about GnRH antagonist protocol was based on only one study (28).

In the present meta-analysis, we attempted to clarify the effect of $E_2$ supplement in a luteal phase of stimulated IVF cycles. Furthermore, analysis of subgroups was performed to demonstrate whether the effect of $E_2$ supplementation is different between GnRH agonist and antagonist cycles.

## MATERIALS AND METHODS

A literature search of the National Library of Medicine and the National Institutes of Health (PubMed), Medline and Cochrane Controlled Trials Register (CENTRAL; Cochrane Library) was performed using the key words "estradiol," "estrogen," "luteal phase support," "luteal supplementation," and "in vitro fertilization." The last search date was October 2008. The inclusion criteria for selecting an article were defined as follows:

1. Fresh IVF-ET cycles using autologous oocyte.
2. The patients underwent ovarian hyperstimulation with pituitary suppression by GnRH agonist or antagonist; the data could be separable according to the method of pituitary suppression.
3. $E_2$ starting on at least ET day, supplemented by oral, vaginal, or transdermal route.
4. P supplemented either vaginally or IM during an entire luteal phase.
5. Only prospective, randomized, controlled studies.
6. Published in English.

We initially found 15 original articles comparing IVF-ET outcomes after administration of $E_2$+P versus P only as a luteal supplementation. Finally, nine studies met the inclusion criteria and were reviewed in this meta-analysis (12, 17, 18, 20–23, 25, 28). All of the included studies were a prospective and randomized. We used the published data only. In all except two studies (20, 21), patients could enter the study only once. Cycle characteristics and IVF-ET outcomes from nine studies are summarized in Table 1. With one study including both GnRH agonist and antagonist cycle separately (23), IVF outcomes of GnRH agonist cycles (long protocol) could be extracted from seven studies and outcomes of GnRH antagonist cycles could be obtained from three studies.

Six studies were excluded in this meta-analysis. In the study by Smitz et al. (11), 28% of the subjects underwent zygote intrafallopian transfer, which could not be separated from IVF-ET results. Estradiol valerate was administered from 4 days after retrieval. Gleicher et al. (14) recruited 330 consecutive ovarian stimulation cycles; however, most patients underwent intrauterine insemination (IUI), which could not be separated from IVF-ET results. In the study by Kaider and Coulam (15), oral $E_2$ was started when serum $E_2$ concentration was <100 pg/mL and serum hCG concentration >5 mIU/mL 11 days after ET. Farhi et al. (16) started oral $E_2$ 7 days after ET in patients with serum $E_2$