Timing luteal support in assisted reproductive technology: a systematic review

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Objective: To summarize the available published randomized controlled trial data regarding timing of P supplementation during the luteal phase of patients undergoing assisted reproductive technology (ART).
Design: A systematic review.
Setting: Not applicable.
Patient(s): Undergoing IVF.
Intervention(s): Different starting times of P for luteal support.
Main Outcome Measure(s): Clinical pregnancy (PR) and live birth rates.
Result(s): Five randomized controlled trials were identified that met inclusion criteria with a total of 872 patients. A planned meta-analysis was not performed because of a high degree of clinical heterogeneity with regard to the timing, dose, and route of P. Two studies compared P initiated before oocyte retrieval versus the day of oocyte retrieval and PRs were 5%–12% higher when starting P on the day of oocyte retrieval. One study compared starting P on day 6 after retrieval versus day 3, reporting a 16% decrease in pregnancy in the day 6 group. Trials comparing P start times on the day of oocyte retrieval versus 2 or 3 days after retrieval showed no significant differences in pregnancy.
Conclusion(s): There appears to be a window for P start time between the evening of oocyte retrieval and day 3 after oocyte retrieval. Although some studies have suggested a potential benefit in delaying vaginal P start time to 2 days after oocyte retrieval, this review could not find randomized controlled trials to adequately assess this. Further randomized clinical trials are needed to better define P start time for luteal support after ART. (Fertil Steril® 2015;103:939–46. ©2015 by American Society for Reproductive Medicine.)
Key Words: Progesterone, luteal support, in vitro fertilization

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The increase of P in the luteal phase during natural human reproduction is exquisitely timed to embryo development. The LH surge induces oocyte maturation, ovulation, and P production from the corpus luteum (CL). The P hormone action produces endometrial changes in gene expression, histologic appearance, and structural arrangements that lead to an endometrium receptive for implantation 5–6 days after ovulation (1). Pulsatile pituitary LH and eventually hCG from the implanted pregnancy stimulate CL P (1, 2), which is necessary for maintenance of the pregnancy until placental P production is adequate. Pituitary down-regulation by GnRH analogues in assisted reproductive technology (ART) results in a dysfunctional luteal phase for some patients. Exogenous P administration has been used successfully in IVF to overcome this deficiency. Failure to use luteal phase P results in low pregnancy rates (PRs) between 0 and 18% (3).

Although it is clear that exogenous luteal support improves the rates of

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successful implantation and early pregnancy in ART, there has been significant debate and research regarding timing, dose, and routes of P administration (4–6). With regard to the timing of P initiation, there is endogenous P production from the corpus luteum (CL) after hCG triggering that persists until 5–6 days after oocyte retrieval (3, 7). Therefore it is likely that P supplementation should be initiated before day 5–6, but it is not clear how early should P be initiated before the decrease of endogenous P. It has also been proposed that early P administration may be of benefit for ET by the smooth muscle relaxing effect of P on the uterus (8). Conversely, ART cycles may be associated with advancement of the endometrium leading to embryo-to-endometrial asynchrony and implantation failure (9) and too early administration of P may further expand this asynchrony (10). These data suggest a window of P initiation in ART cycles in which embryo-to-endometrial synchrony and exogenous luteal phase support can be optimized.

This systematic review was performed to summarize the available published randomized controlled trial data regarding timing of starting P supplementation during the luteal phase of patients undergoing ART.

MATERIALS AND METHODS

Study Design

This study was a systematic review of the effect of day of P initiation for luteal support in ART cycles. This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All aspects of the systematic review were decided before the literature search and no post hoc changes were made.

Literature Search

Literature searches were conducted to retrieve randomized controlled trials comparing different starting times for luteal phase exogenous P support in ART cycles. Databases searched included PubMed and Embase. Additional literature searches were performed on the references from identified studies. The searches were performed in English, were executed in January 2014, and searched the databases from January 1, 1990 through December 31, 2013. Searches used key words and specific database indexing terminology when available (search strategy is in detail in Supplemental Addendum, available online).

Study Selection

Criteria for inclusion in the study were established before the literature search. Inclusion was limited to studies that were published of randomized controlled trials, compared different starting time of P, and study participants who were infertile or subfertile. Any type of exogenous P was allowed, including IM and vaginal administration. Any type of autologous fresh ART cycle was included. Exclusion criteria included frozen ETs, nonrandomization, studies in which all arms of the trial initiated P at the same time point, and data published as abstract only, meeting proceeding, book chapter, or review article. The studies were screened independently in parallel by two investigators (M.T.C. and M.J.H.) and there were no disagreements in the studies identified for inclusion. The search strategy yielded 709 publications after to duplication removal. Studies identified from the references of other articles added an additional 4 studies for a total of 713 studies after duplication removal (Supplemental Fig. 1, available online). The 713 abstracts were reviewed and 699 records were excluded during this review for failure to meet inclusion criteria based on data presented in the abstract, leaving 14 full text articles that were evaluated for inclusion and exclusion criteria. Of these, five articles met full inclusion criteria. One study was excluded as it evaluated 17α-hydroxyprogesterone (17-OHP) for suppression of uterine contractions, but otherwise had the same luteal support for both arms (11). Other studies were excluded when full text evaluation demonstrated that the studies compared different P regimens with the same P initiation times in all arms (12–18). One study (19) was excluded in fresh donor recipients where the recipient endometrium was timed with the donor. Study quality and the potential for bias within each study was also ascertained, specifically evaluating for randomization method, concealment of allocation, blinding of providers and patients, and flow of patients through the randomization, treatment, and outcome stages.

Data Collection

Data were extracted in sequence by three authors (M.T.C., J.M.S., and M.J.H.). Outcomes data (clinical pregnancy, live birth, and miscarriage) were extracted from the source articles in the form of 2×2 or 2×3 tables based on intent-to-treat results. When intent-to-treat results were not reported, data were extracted from the provided per-protocol results. Continuous data were extracted in the form of mean, SD, and population size. Additional extracted data included author, year of publication, journal, country of origin, randomization method, sample size, number of patients randomized, number of cycles performed, method of ovulation induction, type of P support, duration of P support, method of ovulation triggering, trial registry, and the reporting of conflicts of interest. A priori primary outcome was live birth and secondary outcomes were clinical pregnancy and miscarriage. Data were collected for per patient outcomes. No post hoc analyses were performed after data collection.

Meta-analysis

A meta-analysis of the data was planned to compare starting points of P in fresh ART cycles. However, the studies had a high degree of clinical heterogeneity with regard to the timing, dose, and route of P. One study was in donor oocytes with fresh time recipients, but the recipients did not receive ovarian stimulation or hCG trigger, making their luteal phase significantly different that the other five studies. Finally, Sohn et al. (20) allowed multiple cycles per patients and had variation in P doses between the groups. Based on these factors it was determined that the data were of insufficient quality to justify meta-analysis.