# 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 17$\alpha$-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 $2\times2$ or $2\times3$ 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.

# RESULTS

## Studies Included for Systematic Review

A total of 713 abstracts were identified, 14 full text articles were reviewed, and from these 5 trials met full inclusion criteria (Supplemental Fig. 1) (8, 19–23) The 5 trials comprised 872 patients undergoing 1,010 cycles, with only 1 study allowing multiple cycles per patient (20). All five studies described inclusion criteria consistent with a general IVF patient population and were in patients undergoing fresh autologous IVF (8, 20–23) (Table 1). Four of the studies used a long GnRH agonist protocol for pituitary down-regulation (8, 20, 22, 23) and one study used multiple pituitary protocols (21). All studies used either recombinant FSH or hMG. Ovulation triggering was performed with either 5,000 or 10,000 units of hCG in all studies, except for one study that did not specify the dose (20). One of the included studies used IM P (20) and the other five studies used vaginal P. All of the studies used different protocols of P type, dose, starting and stopping times (Table 1). Primary outcomes data for each study was summarized in Table 2.

## Assessment of Bias Risk

None of the trials documented allocation concealment, blinding of the physicians or patients, or blinding of outcomes data (Supplemental Table 1, available online). Reporting of the randomization process was only clearly reported in two of the studies. Only Mochtar et al. (23) adequately reported on the flow of patients through the study, used an intent-to-treat analysis, and was at low risk of incomplete data reporting. The remaining studies either partially or completely failed to adequately report patient flow and these studies analyzed their data on a per protocol basis or unclear basis. There was no pharmaceutical support disclosed in any of the trials. Funnel plots were not used due to the low number of studies assessing the same comparisons.

None of the studies demonstrated baseline differences between the two randomized groups with regard to age, fertility diagnoses, or duration of infertility. One study reported a statistical difference in the number of supernumerary embryos for freezing between the two randomized groups (day 3 P group: 1.3 embryos for freezing vs. day 6 P group: 2.7 embryos for freezing; $P=.01$) (21). Supernumerary embryos have been associated with an increased likelihood of pregnancy (24).

## Comparison of Live Birth

Only Mochtar et al. (23) reported live birth rates. They found no difference in live birth between patients randomized to receive P 36 hours before oocyte retrieval (20.0%), the evening of oocyte retrieval (21.1%), or day 3 after oocyte retrieval (20.5%). However, this study was not powered to detect a difference in live birth rates. There was insufficient reporting of live birth in other trials to use this as the primary outcome.

## Comparison of Clinical Pregnancy

All five studies reported clinical PR as a primary outcome. The definition of clinical pregnancy was heterogeneous between the studies, ranging from undefined to defined as either a gestational sac in the uterus or to a fetus in the uterus with cardiac activity. Clinical PRs ranged from 12.9% to 61.0% in the studies (Fig. 1). Only two studies reported statistically significant differences in clinical PRs between the groups. Sohn et al. (20) reported a lower clinical PR in patients starting P 12 hours before oocyte retrieval compared with those patients starting P the evening of oocyte retrieval (12 hours before retrieval: 12.9% vs. the evening of retrieval: 24.6%; $P=.01$). Williams et al. (21) reported a lower PR in patients undergoing fresh autologous and starting P on day 6 after oocyte retrieval compared with day 3 after oocyte retrieval (6 days after retrieval: 44.8% vs. 3 days after retrieval: 61.0%; $P=.05$). There were three studies that compared clinical PR in patients starting P the evening of oocyte retrieval versus 2 days after and 3 days after oocyte retrieval (8, 19, 23). None of these studies reported significant differences in PRs between the groups.

## Comparison of Miscarriage

None of the included studies reported miscarriage as an outcome.

## Subgroup Analysis

An a priori subgroup analysis was planned to compared IM and vaginal routes of P. It has been proposed that vaginal P results in more rapid uterine uptake of the hormone and may advance the endometrium more rapidly than the IM route (10). Thus the timing of P initiation may be affected by the route of P administration. However, only one study evaluated IM P and adequate comparisons could not be made.

# DISCUSSION

The results of this systematic review suggest that the timing of luteal P support initiation can affect the likelihood of pregnancy. Studies performed on luteal support initiation before oocyte retrieval versus day of oocyte retrieval suggest a potential decreased likelihood of pregnancy if P was initiated before oocyte retrieval (Fig. 1). When P was initiated on the evening of oocyte retrieval versus days 1–3 after oocyte retrieval, studies found no difference in clinical PR. One study investigated P initiation on day 3 or 6 after oocyte retrieval and reported a decreased likelihood of pregnancy on day 6 initiation. These results suggest a window between the evening of oocyte retrieval and day 3 after retrieval as the ideal time for initiation of P.

Multiple factors affecting P timing and serum levels during the luteal phase in ART cycles have been proposed. These include endometrial advancement from premature P release, disruption of granulosa cells (GCs) during oocyte retrieval, pituitary down-regulation or blockade of GnRH receptors, hypothalamic suppression of GnRH, method of oocyte maturation induction, and differing routes of P administration.

During the past 5 years, data from several large retrospective studies have demonstrated that even subtle early increases in P effect PRs. Bosch et al. (9) and Xu et al. (25)

## TABLE 1

**Study characteristics of trials meeting inclusion in the systematic review.**

| Authors | Country of study | Patients | Cycle type | Ovarian stimulation | Progesterone type | Randomization groups (by initiation of P) | P Regimen | Ovulation triggering |
|---|---|---|---|---|---|---|---|---|
| Sohn et al., 1999 | USA | General IVF—no exclusion reported | Fresh autologous IVF | Long GnRH agonist with hMG and/or FSH | Progesterone 12.5 mg IM then 25 mg IM<br>Progesterone 25 mg IM | Group A: 12.5-mg dose 12 h before OR and the evening of OR then 25-mg dose<br>Group B: evening of OR | Daily through first trimester | hCG (amount not stated) |
| Williams et al., 2001 | USA | General IVF—no exclusion reported | Fresh autologous IVF | Long GnRH agonist, luteal GnRH agonist stop, or GnRH agonist microdose flare.<br>Recombinant FSH 150–450 IU daily | Prometrium, 200 mg vaginally TID | Group A: morning of day 3 after OR<br>Group B: morning of day 6 after OR | Daily until 10 wk gestation | 10,000 units hCG |
| Fanchin et al., 2001 | France | General IVF— excluded patients with abnormal uterus | Fresh autologous IVF | Long GnRH agonist.<br>Recombinant FSH 225 IU FSH for 5 d, then flexible dosing | Crinone 8% vaginally | Group A: immediately after OR<br>Group B: evening of ET | Daily until pregnancy ruled out | 10,000 units hCG |
| Baruffi et al., 2003 | Brazil | General IVF— no exclusion reported | Fresh autologous IVF | Long GnRH agonist.<br>Recombinant FSH 150–300 IU daily | Utrogestan, 400 mg vaginally | Group A: evening of OR<br>Group B: evening of ET | Not stated | 5,000–10,000 units hCG |
| Mochtar et al., 2006 | Netherlands | General IVF— no exclusion reported | Fresh autologous IVF | Long GnRH agonist.<br>Recombinant FSH, hMG, or hpFSH | Micronized P 400 mg vaginally BID | Group A: evening of hCG administration<br>Group B: evening after OR<br>Group C: evening 3 d after OR | Daily until 18 d after OR | 10,000 units hCG |

*Note:* BID = twice daily; hpFSH = highly purified FSH; OR = oocyte retrieval; TID = three times daily.

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## TABLE 2

**Primary pregnancy outcomes in the five included randomized controlled trials reported on a per patient basis.**

| Study | Initiation of P in relation to OR (day 0) | Patients (n) | Implantation rate | *P* value | Biochemical pregnancy | *P* value | Clinical pregnancy | *P* value | Live birth | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Sohn et al., 1999 | 12 h before | 158 (cycles) | NR | NR | NR | NR | 12.9% | .011 | NR | NR |
| | Day 0 | 156 (cycles) | NR | | NR | | 24.6% | | NR | |
| Williams et al., 2001 | Day 3 | 59 | 27% | NS | NR | NR | 61.0% | .05 | NR | NR |
| | Day 6 | 67 | 20% | | NR | | 44.8% | | NR | |
| Fanchin et al., 2001 | Day 0 | 43 | 18% | NR | NR | NR | 42.0% | .26 | NR | NR |
| | Day 2 | 41 | 12% | | NR | | 29.0% | | NR | |
| Baruffi et al., 2003 | Day 0 | 51 | 12.6% | .98 | NR | NR | 27.4% | 1.00 | NR | NR |
| | Day 2 | 52 | 13.4% | | NR | | 28.8% | | NR | |
| Mochtar et al., 2006 | 36 h before | 130 | NR | NR | 25.4% | NR | 23.1% | .56 | 20.0% | NR |
| | Day 0 | 128 | NR | | 30.5% | | 28.1% | | 21.1% | |
| | Day 3 | 127 | NR | | 32.3% | | 29.1% | | 20.5% | |

*Note:* OR = oocyte retrieval; NR = not reported.

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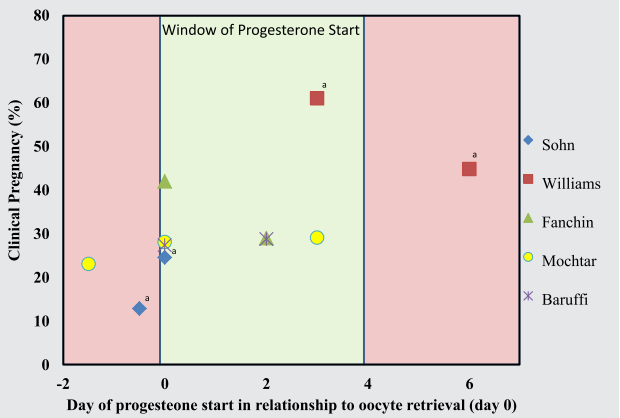
combined to examine more than 14,000 cycles; both investigative groups were able to show that P levels at more than 1.5 ng/mL on the day of hCG trigger decreased PRs. Numerous additional studies have also supported this work (26–30). Microarray studies evaluating expression of genes and RNA involved in endometrial receptivity and implantation have demonstrated dysregulation of genes and proteins when exposed to premature elevation in P (31–33). Although it is clear that subtle premature increases in P affect PRs by advancing the endometrium, it is unclear whether modulating P initiation can mitigate this risk.

Disruption of the GC mass during oocyte retrieval has been posited as an explanation for the shortened luteal phase in ART cycles. However, data have shown that endogenous P levels are much higher after oocyte aspiration in ART cycles when compared with natural cycles. Natural midluteal P levels are typically about 15 ng/mL (34, 35). Midluteal P levels after hCG trigger and follicle aspiration are much higher, ranging from 30–80 ng/mL (36, 37). Furthermore, data from Haas et al. (38) have demonstrated good luteal P levels with hCG support alone. This would suggest that the CL functions well in response to LH receptor activation. These data strongly suggest that oocyte retrieval does not affect endogenous P or timing of supplementation.

Long GnRH agonist protocols to suppress premature ovulation are commonly used in ART cycles. Constant GnRH agonist exposure results in down-regulating the pituitary GnRH receptor and decoupling after receptor signaling mechanisms (39–41). Long GnRH agonist protocols still have suppressed LH levels 9 days after the agonist was discontinued (42, 43). This decreased LH pulsatility does not allow for adequate P to be produced by the CL. However, hCG for final oocyte maturation continues to stimulate the CL after retrieval. This stimulation ends at about day 5 or 6 and this may explain the outcomes in the study by Williams et al. (21). Patients who started luteal support on day 6 had lower PRs. These individual factors play a role in the endogenous levels of P and suggest a window for when luteal support is needed (Fig. 1).

## FIGURE 1




Window of P initiation. Graphic representation of clinical pregnancy rates (PRs) on the y axis and day of P initiation on the x axis. Markers represent the six different randomized controlled trials results. The *red shaded* area represents time points with potential lowered PRs if P is started. The *green shaded area* represents the window of P start times based on the available randomized controlled data. [a]Results reported as statistically significant in the primary studies.

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Several routes of P initiation have been studied for luteal support including oral, vaginal, and IM. The oral route provides significantly less bioavailability because of the liver's first pass effect and have been shown to be inferior to IM P (44, 45). This has left significant debate over the comparison between vaginal and IM routes. Cicinelli et al. (46) demonstrated higher serum P levels with IM administration versus vaginal administration (29.4 vs. 4.8 ng/mL); however, IM P had lower levels of endometrial P (0.43 vs. 1.05 ng/mL). The debate on the route of P administration has led to a related discussion of P timing.

Propst and coworkers (47) randomized women undergoing IVF to IM or vaginal P on the day after oocyte retrieval. The vaginal arm had a decreased likelihood of clinical pregnancy and live birth. The same group, in a subsequent

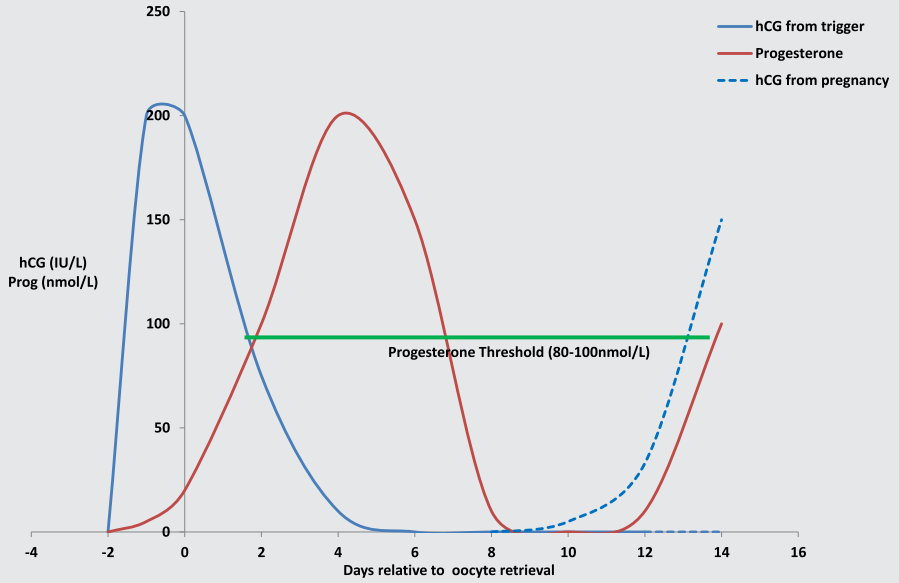
randomized controlled trial, delayed the initiation of vaginal P until 48 hours after oocyte retrieval but kept IM P at 24 hours after retrieval. Live births were similar in each group (10). Taking all these data together would suggest a first-pass effect with the uterus, resulting in quicker peak levels in the endometrium and more rapidly advancing the implantation window. This is further supported by a prospective nonrandomized trial. When vaginal P was initiated 2 days after oocyte retrieval, higher PRs were obtained with vaginal compared with IM P (48).

Summarizing the data on these various factors that affect endogenous and exogenous P levels reveal numerous variables modulating P during the window of implantation in an ART cycle, the most important of which are the method of oocyte maturation triggering and the timing of P supplementation. In the natural menstrual cycle, P levels increase slightly before ovulation, continue to increase during the next several days, and peak at 7 days after ovulation (49). In the unsupplemented ART cycle with hCG triggering, P levels initially increase from the luteal effects of hCG, then decrease to very low levels, only to once again increase if hCG from the pregnancy rescues the CL (3) (Fig. 2). In recombinant LH or GnRH agonist trigger protocols, the initial decrease of P from the CL occurs even more rapidly (3). This creates a window during which exogenous P must be administered to keep the level at more than 80–100 nmol/L (50), bridging P production of the CL between the triggering stimulation and the hCG stimulation of the pregnancy (Fig. 2).

It is important to point out that most of these studies in this present review involved long GnRH agonist protocols with hCG triggering in fresh autologous ART cycles. This impacts the luteal phase in several distinct ways that were reviewed. The hCG trigger results in higher levels and a longer duration of endogenous P release compared with a GnRH agonist or recombinant LH trigger (3, 51). Patients undergowing fresh autologous cycles will have initial endogenous P production after hCG trigger, whereas patients with donor recipient using an artificial cycle will not have this endogenous production. For these reasons, the results of this meta-analysis should be interpreted primarily in autologous fresh IVF with long GnRH agonist protocols and hCG triggering.

There are limitations on the data reviewed in this article. First, there were only five studies that met inclusion criteria, limiting the volume of evidence available for analysis. Second, there was significant clinical heterogeneity throughout all five studies with differences in P preparation, dose, and timing between the studies, making meta-analysis not possible. Thus, the results of the studies should be interpreted with caution. Although meta-analysis data synthesis can use random effects models to account for some heterogeneity between studies, the studies in this review varied so greatly in their clinical protocols that it was believed inappropriate to attempt to synthesize the outcomes statistically. For example, the five trials studied six different initiation times of P supplementation, making it inappropriate to attempt to statistically combine the effects of P initiation into meaningful data. Most

## FIGURE 2




Summary of hCG and P levels from the time of hCG trigger until early pregnancy during assisted reproductive technology (ART). After hCG trigger (day -2), hCG levels rapidly increase to approximately 200 IU/L at the time of oocyte retrieval (day 0) and are then cleared by approximately day 5 after retrieval (Beckers et al., 2003). Progesterone levels follow more slowly, as granulosa cells (GCs) become luteinized, and peak approximately at day 5 after retrieval and rapidly decrease thereafter (Beckers et al., 2000). This creates several days during which endogenous P levels lack hCG stimulation and require supplementation to remain at more than the threshold of 80–100 nmol/L to maintain pregnancy (Andersen and Andersen, 2014).

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of the randomized trials did not adequately report on allocation, concealment, and blinding, which could introduce potential bias. Open-label trials may be subject to potential bias as a result of physician and patient awareness of treatment allocation (52) and there is meta-epidemiologic evidence to suggest that unclear allocation concealment or lack or blinding may cause overoptimistic estimates of treatment effects (53). For these reasons, the heterogeneity and limited data indicate that the results of this systematic review should be interpreted with caution.

In conclusion, these data from this systematic review suggest that starting P on the day before oocyte retrieval or waiting until day 6 after retrieval may result in lower PRs. There appears to be a window for P start time between the evening after 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 adequate randomized controlled trials to adequately assess this. It remains unclear whether PRs can be improved by delaying the P initiation until the end of this P window to avoid endometrial advancement (54). Additional randomized clinical trials are needed to better define P start time for luteal support, particularly for vaginal P, which may more rapidly advance the endometrium.

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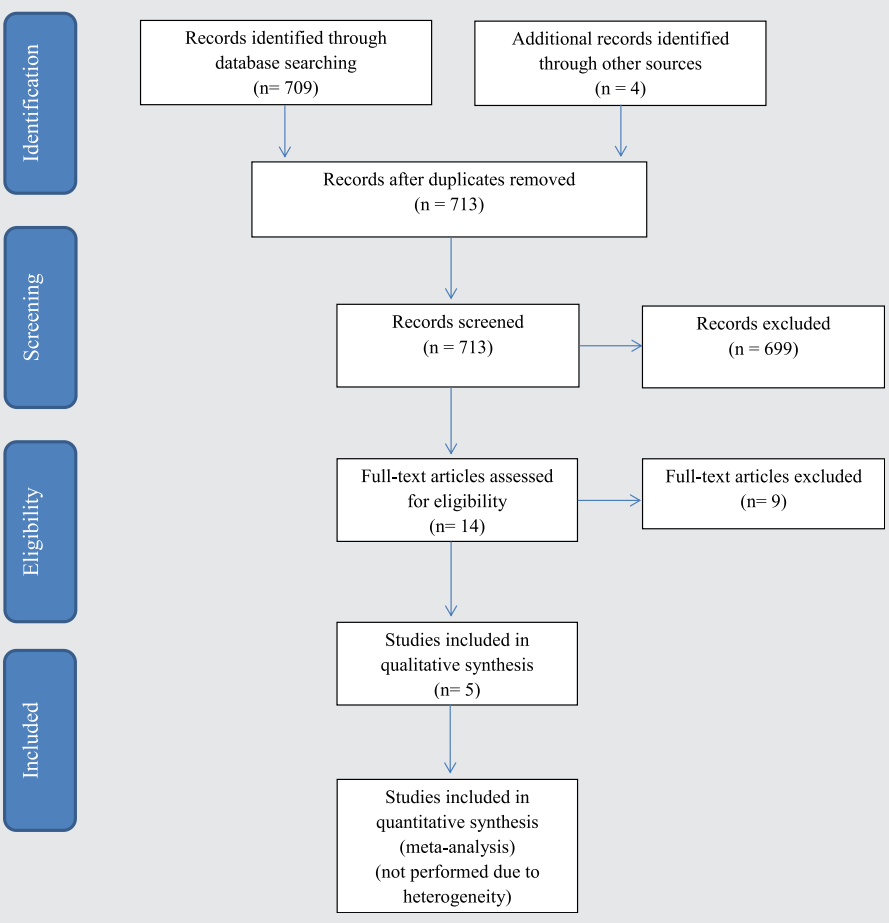
## SUPPLEMENTAL ADDENDUM. DETAILED MEDLINE SEARCH STRATEGY.

((((fertilization in vitro[majr] OR IVF[tiab] OR "in-vitro fertilization"[tiab] OR "in-vitro fertilization"[tiab] OR "assisted reproduction"[tiab] OR "oocyte retrieval"[tiab] OR oocytes/drug effects[majr]) AND ("progesterone luteal support"[tiab] OR "luteal phase support"[tiab] OR progesterone[majr] OR progesterone[tiab] OR "intravaginal progesterone"[tiab] OR "vaginal progesterone"[tiab] OR "progesterone vaginal"[tiab] OR "intramuscular* progesterone"[tiab])) OR ((((fertilization in vitro[majr] OR IVF[tiab] OR "in-vitro fertilization"[tiab] OR "in-vitro fertilization"[tiab] OR "assisted reproduction"[tiab] OR "oocyte retrieval"[tiab] OR oocytes/drug effects[majr] OR "assisted reproduction") AND (luteal phase[mh] OR luteal cells[mh]) AND (progesterone[majr] OR progesterone[tiab] OR "intravaginal progesterone"[tiab] OR "vaginal progesterone"[tiab] OR "progesterone vaginal"[tiab] OR "intramuscular* progesterone"[tiab]))) AND ("1990/01/01"[PDat]: "2014/12/31"[PDat]) AND Humans[Mesh] AND English[lang])).

## SUPPLEMENTAL FIGURE 1




Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

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## SUPPLEMENTAL TABLE 1

**Assessment of bias in the included randomized controlled trials including assessments of randomization, allocation concealment, blinding, data reporting, and declaration of conflicts of interest.**

| Authors | Randomization | Allocation concealment | Blinding of participants | Blinding of outcomes | Complete data reporting | Analysis type | Conflicts of interest or pharma sponsorship | Trial registry |
|---|---|---|---|---|---|---|---|---|
| Sohn et al., 1999 | Permuted block design | None | None | None | No | Per protocol | Not stated | Not stated |
| Williams et al., 2001 | Sealed envelope technique | None | None | None | No | Per protocol | Not stated | Not stated |
| Fanchin et al., 2001 | Not stated | None | None | None | No | Per protocol | Not stated | Not stated |
| Baruffi et al., 2003 | Drawing lots, using randomization table | None | None | None | No | Per protocol | Not stated | Not stated |
| Mochtar et al., 2006 | Sealed envelope | None | None | None | Yes | Intent to treat | Not stated | Not stated |

*Connell. Timing ART P support. Fertil Steril 2015.*