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Progesterone luteal support after ovulation induction and intrauterine insemination: an updated systematic review and meta-analysis

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Objective: To evaluate the effect of progesterone (P) for luteal phase support after ovulation induction (OI) and intrauterine insemination (IUI).
Design: An updated systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Patients undergoing OI-IUI for infertility.
Intervention(s): Exogenous P luteal support after OI-IUI.
Main Outcome Measure(s): Live birth.
Result(s): Eleven trials were identified that met inclusion criteria and constituted 2,842 patients undergoing 4,065 cycles, more than doubling the sample size from the previous meta-analysis. In patients receiving gonadotropins for OI, clinical pregnancy (relative risk [RR] 1.56, 95% confidence interval [CI] 1.21–2.02) and live birth (RR 1.77, 95% CI 1.30–2.42) were more likely in P supplemented patients. These findings persisted in analysis of live birth per IUI cycle (RR 1.59, 95% CI 1.24–2.04). There were no data on live birth in clomiphene citrate or clomiphene plus gonadotropin cycles. There was no benefit on clinical pregnancy with P support for patients who underwent OI with clomiphene (RR 0.85, 95% CI 0.52–1.41) or clomiphene plus gonadotropins (RR 1.26, 95% CI 0.90–1.76).
Conclusion(s): Progesterone luteal phase support is beneficial to patients undergoing ovulation induction with gonadotropins in IUI cycles. The number needed to treat is 11 patients to have one additional live birth. Progesterone support did not benefit patients undergoing ovulation induction with clomiphene citrate or clomiphene plus gonadotropins. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Intrauterine insemination, live birth, luteal support, ovulation induction, progesterone

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Successful implantation requires synchrony between a competent blastocyst and a receptive secretory phase endometrium (1). As estrogen rises during the follicular phase and a dominant follicle emerges, the mid-cycle LH (2) peaks and ovulation occurs (2). The pulsatile LH secretion stimulates the corpus luteum to produce P, which induces endometrial secretory transformation and promotes receptivity (3).

Fertility treatments may interfere with the luteal phase via several mechanisms. Ovulation induction (OI) may

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result in a premature rise of P and alterations in endometrial receptivity (4, 5). Furthermore, supraphysiologic E_2 elevation from ovarian stimulation may cause pituitary down-regulation and alterations in luteal phase LH secretion (6, 7). Supraphysiologic E_2 levels are often associated with multifollicular development during assisted reproductive technology (ART) (8), whereas only one to two dominant follicles may be achieved during OI and IUI. The use of GnRH analogs for pituitary down-regulation and mechanical disruption of follicles during oocyte aspiration may further affect luteal function (9, 10). Luteal support with exogenous P after ART is routine because it is associated with higher pregnancy and live birth rates (11, 12); however, there is no consensus on the use of P after OI-IUI.

In 2013 our group published a systematic review and meta-analysis of randomized, controlled trials (RCTs) to evaluate the effect of luteal phase P support after OI-IUI (13). This analysis concluded that luteal phase support was beneficial in gonadotropin IUI cycles but not in clomiphene citrate (CC) IUI cycles. The endogenous rise of LH as a result of CC may provide further stimulation for the developing corpus luteum, which in turn will favorably impact the luteal phase (14). In contrast, stimulation with gonadotropins directly may result in negative feedback of E_2 at the hypothalamus and decreased LH release, similar to ART cycles (15).

In the past 3 years there have been several new RCTs published on this topic. The total number of subjects and papers has doubled since the prior review, necessitating new statistical analysis of the published data. The goal of this study was to review these recent publications and perform an updated meta-analysis to determine the impact of P supplementation after OI-IUI.

MATERIALS AND METHODS

Study Design

This is an updated systematic review and meta-analysis of RCTs evaluating exogenous P luteal support during the luteal phase after OI-IUI (13). The objective of this study was to identify eligible RCTs that have been published since our previous meta-analysis in 2013 and update the systematic review and meta-analysis.

Literature Search

PubMed and Embase literature searches were performed for published RCTs evaluating P luteal supplementation vs. no luteal support after OI-IUI. Our previous meta-analysis conducted a literature search through January 8, 2013 and identified five studies meeting inclusion criteria (13). An updated literature search was performed, limited to publications from January 1, 2013 to the date of search execution, which occurred on September 12, 2016. The search used specific key words and database indexing terminology (available online as Supplemental Addendum).

Study Selection

Study selection was performed according to the same criteria as in the previous meta-analysis (13). Only published RCTs that compared exogenous P during the luteal phase after OI-IUI vs. no P were included. Any type of ovulation induction was allowed, including CC, exogenous gonadotropins, hCG, aromatase inhibitors, or a combination of these medications. All types of exogenous P were permitted, including oral, IM, or vaginal formulations. Publication in any language was allowed. Exclusion criteria included nonrandomization, timed intercourse cycles, natural cycles, publication as abstract only, book chapters, or review articles.

The literature search identified 31 new publications, which were independently reviewed by three investigators (K.A.G., J.R.Z., and M.J.H.) to identify eligible studies. Of the 31 abstracts reviewed, 25 studies were excluded on the basis of abstract data indicating failure to meet inclusion criteria. Six full-text articles were reviewed for inclusion and exclusion criteria, all of which met inclusion criteria. There were no disagreements among the three reviewing investigators regarding the studies eligible for inclusion. Study quality and the potential for bias within each study was evaluated, considering randomization method, concealment of allocation, blinding of providers and patients, and flow of patients through the randomization, treatment, and outcome stages.

Data Collection

Data from studies that met inclusion criteria were extracted independently by two investigators (K.A.G. and J.R.Z.). Clinical pregnancy and live birth data were extracted from intent-to-treat results. When intent-to-treat results were not reported, data were calculated as intent-to-treat by making the denominator the number of patients enrolled, instead of the reported per-protocol results. Continuous data were extracted in the form of mean and SD. 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 conflicts of interest. The primary outcome was live birth per patient. Secondary outcomes included clinical pregnancy per patient, clinical pregnancy per cycle, and live birth per cycle. Sensitivity analyses were performed excluding trials that allowed individual subjects to cross over into both treatment and control arms over multiple cycles.

Data Synthesis

Data for synthesis were obtained from intent-to-treat results when reported. Primary analyses were performed using per-patient data, and additional analyses were performed using per-cycle data. Heterogeneity was evaluated using the Q test and I^2 index values and reported for each outcome as P value and percentage, respectively. Random-effects models were used when studies had clinical heterogeneity in the ovulation induction method (i.e., medication type) used or when the I^2 index was $>50\%$ (16). A fixed-effect model was used when the same type of ovulation induction method was used in all studies and the I^2 index was $<50\%$. Sensitivity analyses