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Editorial

Luteal Phase Progesterone and Four Decades Of In Vitro Fertilization: Many Questions Still Unanswered

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The rise of progesterone in natural human reproduction is exquisitely timed to embryo development. The luteinizing hormone surge induces oocyte maturation, ovulation, and progesterone production from the corpus luteum. Progesterone hormone action produces endometrial changes in gene expression, protein production, histologic appearance, and structural arrangements which all lead to an endometrium receptive for implantation five to six days after ovulation. After implantation, corpus luteal progesterone is necessary for maintenance of the pregnancy until placental progesterone production begins. It has long been recognized that in vitro fertilization (IVF) results in a dysfunctional luteal phase. Corpus luteal progesterone production is dependent on pulsatile pituitary release of LH, which is suppressed in IVF by the supraphysiologic serum levels of estradiol and the use of exogenous GnRH analogues. Exogenous progesterone administration with vaginal and intramuscular administration has been used successfully for several decades in IVF to overcome this deficiency.

While it is clear that progesterone supplementation is necessary in IVF, the exact starting and stopping points of supplementation is unclear. Oocyte maturation is most commonly induced with human chorionic gonadotropin (HCG) and the LH action of HCG provides for corpus luteal progesterone production for up to five days. Starting progesterone prior to oocyte retrieval has demonstrated negative effect on pregnancy, likely due to advancement of the endometrium. Conversely, delaying progesterone initiation until day 6 after oocyte retrieval also has a demonstrated negative effect on pregnancy, likely due to a lack of adequate progesterone. This results in a window of progesterone initiation that is rather wide, from day of oocyte retrieval to three days later. Some studies have suggested that delaying the initiation of vaginal progesterone until two days after oocyte retrieval results in higher pregnancy rates and many IVF centers have adopted this protocol. However, there are no randomized controlled trials to confirm that delaying progesterone initiation is beneficial.

IVF protocols stop progesterone supplementation from times ranging as early 4 weeks gestation to as long as 12 weeks gestation. Two factors are important in deciding when to stop progesterone supplementation: when does hCG from the pregnancy stimulate adequate amounts of corpus luteum progesterone and when does the placenta take over progesterone production. These changes occur around 4-5 weeks and 7 weeks gestation respectively. One recent RCT demonstrated that progesterone could be stopped at the 5th week of gestation; however the study was underpowered to detect clinically meaningful changes in pregnancy rates.

Taken together, these facts suggest a window of progesterone initiation in IVF. Give progesterone too early and implantation may fail due to embryo-endometrium asynchrony. Give progesterone too late and the pregnancy may fail due to inadequate progesterone support. This progesterone initiation window appears to be between the day of oocyte retrieval and the 3rd day after retrieval. Can we improve pregnancy rates by delaying the progesterone initiation until the end of this window to avoid endometrial advancement? Can we reduce medication cost and exposure by stopping progesterone as soon as pregnancy is documented by HCG levels which are adequate to drive corpus luteum progesterone? While we have learned a great deal about exogenous luteal phase support over the past decades of IVF, there is still a need for research to better address the basic questions of the timing of progesterone support.