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Editorial

Premature Progesterone Rise During in Vitro Fertilization: When to Freeze Embryos and When to Proceed with Embryo Transfer?

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Introduction

In the natural menstrual cycle, progesterone does not begin to significantly rise until after the LH surge and is therefore precisely timed with ovulation. This leads to synchrony of embryo and endometrial development to facilitate successful embryo implantation. During the ovarian stimulation in in vitro fertilization (IVF) cycles, serum progesterone can be prematurely elevated as a result of the intermediate substrates in the estradiol steroid pathway. While in the natural menstrual cycle this effect is insignificant, during ovarian hyperstimulation the effect is multiplied by the number of follicles developing and thus becomes clinically significant. Prematurely elevated progesterone levels have been cited as a possible source of early endometrial advancement in IVF since the 1990s with recent data that confirms progesterone levels above 1.5 ng/ml are associated with decreased pregnancy rates [1] analyzed over 4000 IVF cycles and demonstrated that progesterone levels over 1.5 ng/ml on the day of hCG decreased pregnancy rates with an OR 0.53 (95% CI 0.38-0.72) [1,2]. analyzed over 10,000 IVF cycles and also demonstrated detrimental effects of progesterone over 1.5 ng/ml on the day of HCG [2]. Microarrays studies have also demonstrated that endometrium exposed to prematurely elevated progesterone have dysregulation of genes necessary for implantation. Conversely, patients who receive donor oocytes from donors who have premature progesterone rise do not have a decreased chance of pregnancy, suggesting that the negative effect is on the endometrium and not the development with the developmental stage of the embryo. While this is the logical extension of the currently published literature, there is the need for further research before being able to firmly establish this as standard of care. First, progesterone assays vary in their accuracy, especially at the lower limits of the assay. For this reason, programs should try to assess at what progesterone values they see decreased pregnancy rates in their own patients rather than relying on published data from other assays. However, progesterone thresholds themselves are not adequate in making clinical decisions because the cost of freezing and thawing embryos in addition to a program's success rates in transfering frozen embryos must be considered. For example, progesterone thresholds that see modest reductions in pregnancy of 5-10% may not be cost effective to proceed with embryo freezing, especially in programs with lower live birth rates in frozen cycles. We are currently developing cost analysis models to address these clinical scenarios based upon the reduction in live birth rate in the fresh cycle, the likelihood of live birth in the frozen cycle, and the cost of freezing and thawing the embryo. Additionally, arguments have been made that not all cycles with elevated progesterone have a detrimental effect on pregnancy rates, such as high responders, patients with blastocyst transfers, or cycles using exogenous LH as part of the ovarian stimulation. The effect of elevated progesterone remains controversial in these patient populations.

As a result of this data, many IVF programs have begun freezing all embryos in patients with elevated progesterone and then proceeding with a frozen embryo transfer a few months later when the endomtrium can be synchronized

Finally, to date, no randomized controlled trials have been performed to demonstrate that freezing embryos in cycles with elevated progesterone is superior to proceeding with the fresh embryo transfer. This final piece of level 1 evidence is an important step to establish clinical algorithms

for managing these patients. Our program and others are in the process of answering these important research questions to provide good clinical evidence for the management of premature progesterone rise during IVF.

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