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Review article

# Does elevated serum progesterone on the day of human chorionic gonadotropin administration decrease live birth rates?

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ABSTRACT

The impact of elevated serum progesterone levels on pregnancy and live birth during in vitro fertilization (IVF) remains unclear. Our objective was to investigate whether elevated serum progesterone on the day of human chorionic gonadotropin (HCG) administration is associated with lower pregnancy and live birth rates. This mini review provides a synopsis of the literature in addition to some of our own data. On the whole pregnancy and live birth rates decrease with increasing progesterone on the day of HCG administration even after adjusting for confounders. The findings from the majority of manuscripts investigating this question appear to be in agreement.



## 1. Introduction

During controlled ovarian hyperstimulation (COH), elevation of serum progesterone is generally prevented by suppressing luteinizing hormone (LH) secretion with a gonadotropin releasing hormone (GnRH) agonist or antagonist. Despite these medications, increases in serum progesterone are still observed, with elevated progesterone on the day of HCG administration in as many as 35% of cycles.[1–3] This phenomenon has been referred to as premature luteinization, progesterone elevation, and premature progesterone rise.[4–7]

Whether elevated serum progesterone on the day of HCG administration influences clinical pregnancy and live birth in women undergoing COH has been debated since Schoolcraft et al.,[5] reported lower pregnancy rates following a pre-ovulatory increase in serum progesterone. Numerous studies have suggested that progesterone elevation is associated with decreased pregnancy rates,[5,6,8–12] while others have presented contradictory data.[13–18] Doldi et al.[19] even reported a positive association between elevated progesterone and pregnancy in patients with polycystic ovary syndrome. An additional issue is the definition of normal and elevated progesterone during COH, as cut-off values for elevated levels have ranged from 0.4 to 3.0 ng/mL.[7,11,20–23]

A number of authors have attributed the elevated serum progesterone to the excess number of follicles recruited during COH; while each follicle presumably produces a normal amount of progesterone, together they result in a high overall level.[8,16] In order to account for the magnitude of response to COH, as progesterone levels positively correlate with follicle number and estradiol levels, some authors have proposed that the progesterone/estradiol ratio may more accurately define premature luteinization.[9,17,24] Interestingly, other authors have reported that a high ratio on the day of HCG administration may suggest diminished ovarian reserve rather than a normal physiologic increase in late follicular progesterone, as typically seen in the presence of many follicles.[6,25,26]

In the most definitive report to date a meta-analysis of over 60,000 cycles by Venetis et al.,[7] concluded that elevated progesterone on the day of HCG administration is associated with a decreased probability of pregnancy achievement in fresh IVF cycles in women undergoing COH using GnRH analogs and gonadotrophins.

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## 2. Boston IVF study

In our own center we performed a retrospective cohort study of all patients age 18–44 years at the start of their first fresh embryo, non-donor IVF cycle who had progesterone measured on the day of HCG administration and excluded all cycles involving donor oocytes and/or gestational carriers. In brief, our results showed that there was an association between serum progesterone and clinical pregnancy rate, live birth rate per cycle start, and live birth rate per embryo transfer (Fig. 1). There was a borderline-significant reduction in live birth rate per cycle start ($P = 0.06$) and a significant reduction in live birth rate per embryo transfer ($P = 0.02$) with increasing progesterone on the day of HCG administration. Fig. 2 shows the RR and 95% CI of live birth per cycle start and live birth per embryo transfer, respectively, adjusted for maternal age, peak estradiol level, and the number of oocytes retrieved. After adjusting for these confounders, live birth per cycle start, as well as live birth per embryo transfer decreased significantly with increasing progesterone (all $P < 0.004$). In the same data set we grouped patients into poor, intermediate, and high response to COH. The decrease in live birth rate with increasing progesterone was only significant among patients with an intermediate response to COH (data not shown). This could indicate that patients with a higher estradiol level may have a simultaneously high progesterone level but may not be experiencing premature luteinization. In relation to estradiol, we know that estradiol plays a key role in the morphology and functional differentiation of syncitiotrophoblasts, as well as modulation of uteroplacental blood flow critical for optimal fetal growth in primates.[27–29] It also appears that low levels of estradiol, as seen in early pregnancies, are required to permit the normal placental invasion of uterine spiral arteries.[30] There is evidence that not only is an elevated estradiol level toxic to implantation in mice,[31–33] it also results in aberrant placentation.[30,31] We can therefore not rule out that progesterone and estradiol go hand in hand, as has been shown by numerous studies examining the role of estradiol and progesterone ratios in maintaining pregnancy.[9,17,24]

## 3. Which progesterone level is detrimental?

Various definitions of progesterone elevation have been used in the literature, with threshold values ranging from 0.4 to 3.0 ng/ml.[7,11,12,20–23,34] However, in our own data we observed a linear relationship between serum progesterone and live birth so we conclude that it is not possible to report a threshold above which we observe a significantly reduced live birth rate. Instead, we observed a steady decline in live birth rate with increasing progesterone. This suggests that providers may want to consider canceling a fresh transfer when the progesterone is at a level whereby the chance of pregnancy is lower than that of a subsequent frozen transfer.

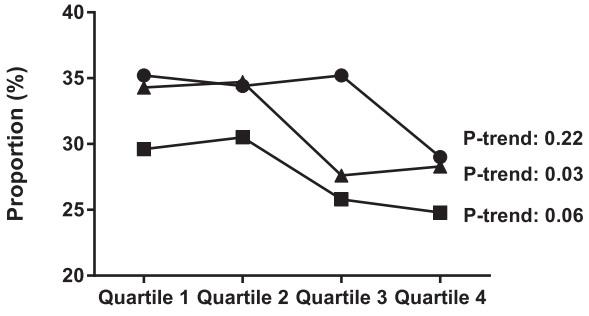


**Fig. 1.** The proportion of patients achieving clinical pregnancy (circles), live birth per cycle start (squares) and live birth per embryo transfer (triangle) in relation to the Progesterone levels on the day of HCG administration. Cycles are separated into quartiles (see Figure 2) from a total of 1578 cycles.

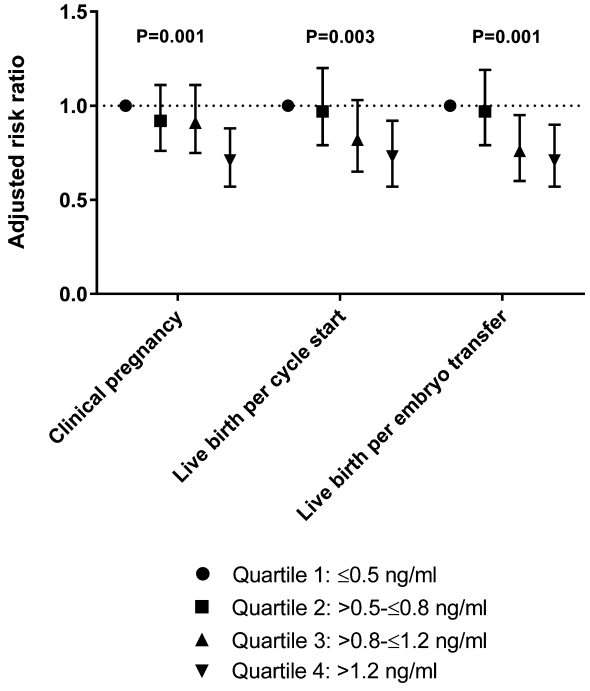


**Fig. 2.** Adjusted risk ratio and 95% confidence interval for pregnancy outcomes according to the Progesterone levels on the day of HCG administration. Cycles are separated into quartiles of progesterone levels from a total of 1578 cycles.

Our own finding of decreased live birth rates with progesterone >0.8 ng/ml is consistent with the pooled meta-analysis data from over 60,000 patients.[7]

## 4. Mechanisms of action

It has been proposed that high follicular progesterone concentration advances the endometrium and alters the synchrony between embryo and endometrium.[35] This has been thought to impact cleavage and blastocyst stage embryo transfers differently. Two authors have reported a negative impact on pregnancy outcomes following cleavage-stage transfer but not blastocyst transfer, which could suggest that performing blastocyst stage transfer allows the endometrium to recover from the supraphysiologic steroid concentrations.[24,36] On the contrary, we have found that elevated progesterone led to a decrease in the likelihood of live birth regardless of the developmental stage of the embryo at the time of transfer, therefore suggesting that a blastocyst transfer is not able to overcome the effects of elevated progesterone on the day of HCG administration. Our findings are further supported by similar conclusions from the large meta-analysis, in which the authors did not detect a significant moderating effect of the developmental stage of the embryo at transfer on the association between progesterone elevation and pregnancy.[7] It has also been proposed to account for ovarian response by factoring in the number of oocytes retrieved. Xu et al.[11] has suggested three progesterone thresholds above which ongoing pregnancy rates declined in women with ≤4 oocytes retrieved, 5–19 oocytes retrieved, and ≥20 oocytes retrieved. Bosch et al.[8] reported a lower ongoing pregnancy rate in women with progesterone >1.5 ng/ml regardless of the number of oocytes retrieved.

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