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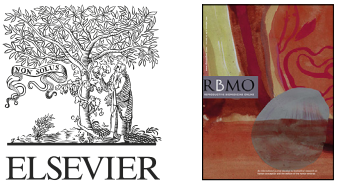

LETTER

# Strong variation in progesterone production of the placenta in early pregnancy – what are the clinical implications?

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We thank Dr Tesarik (*Tesarik, 2020*) for his interest in our study on the onset of placental progesterone production in patients receiving dydrogesterone for scheduling endometrial receptivity and for supporting early pregnancy in anovulatory ('artificial') frozen-thawed embryo transfer cycles (FET) (*Neumann et al., 2020*). In his letter, Dr Tesarik suggests that the luteo-placental shift can be delayed and that this delay could be a cause for miscarriage. Indeed, in our study a strong variation in placental progesterone production between individual singleton pregnancies can be observed (Figure 4A, *Neumann et al., 2020*). *Csapo et al. (1973)* performed lutectomy in 11 spontaneously pregnant patients approximately 50 days post menstruation and observed a drastic decline in serum progesterone levels to approximately 5–6 ng/ml shortly after lutectomy, followed by complete abortion in seven and incipient abortion in four out of eleven patients. Csapo et al. also found that progesterone administration could prevent abortion after lutectomy at this time point. Furthermore, lutectomy at approximately 58 days post menstruation or beyond did not lead to abortion (*Csapo et al., 1974*). In our study, we observed mean serum placental progesterone levels of 4.4±2.4 ng/ml (95% confidence interval 3.4 to 5.4 ng/ml) on day 30–36 post embryo transfer, e.g. at the same approximate time that Csapo et al. performed lutectomy leading to abortion in the 1973 study, and 9.3±3.4 ng/ml (95% confidence interval 7.9 to 10.8 ng/ml) on day 37–43 post embryo transfer, e.g. the gestational age at which the placenta has taken over control according to the Csapo experiments (*Csapo et al., 1974*). To illustrate the inter-pregnancy variation in the time-point at which this approximate progesterone production can be observed, we have plotted the cumulative number of singleton pregnancies in our cohort for which we estimate a placental progesterone production resulting in a serum concentration of at least 10 ng/ml against the estimated post menstruation gestational week (FIGURE 1). A variation of approximately four gestational weeks amongst ongoing, viable singleton pregnancies in reaching this selected threshold can be seen, and some pregnancies reach this threshold as late as the eleventh gestational week.

It is important to note that it is yet to be determined if 30mg dydrogesterone is indeed the optimal progestogenic daily dose in an artificial FET cycle. We therefore intend, as a next step, to investigate the incidence of miscarriage in FET cycles according to blood concentration of dydrogesterone and 20α-dihydrodydrogesterone in a large cohort of patients (clinicaltrials.gov: NCT03507673). It is also important to note that it is as yet unknown if placental progesterone production interacts with progestogenic activity originating from the corpus luteum or exogenous source. In our study, all patients received 10mg dydrogesterone three times daily and treatment was not modified systematically in patients with low progesterone, although physicians were allowed to increase dydrogesterone dosage up to 50mg at their discretion after a positive pregnancy test. This FET model with dydrogesterone usage would allow the study of the interaction of progestonic drug dose administered and placental response. Furthermore, this model would also allow a test of Dr Tesarik's hypothesis that delayed luteo-placental shift would cause miscarriage, by identifying pregnancies with low placental progesterone production and by increasing and/or prolonging the dydrogesterone administration within the context of a randomized trial. In our cohort, we observed a relatively high miscarriage rate (39%). However, we think that low progesterone levels in miscarrying pregnancies are a consequence of the demise of the conceptus, rather than its cause, since miscarriages can be predicted in our

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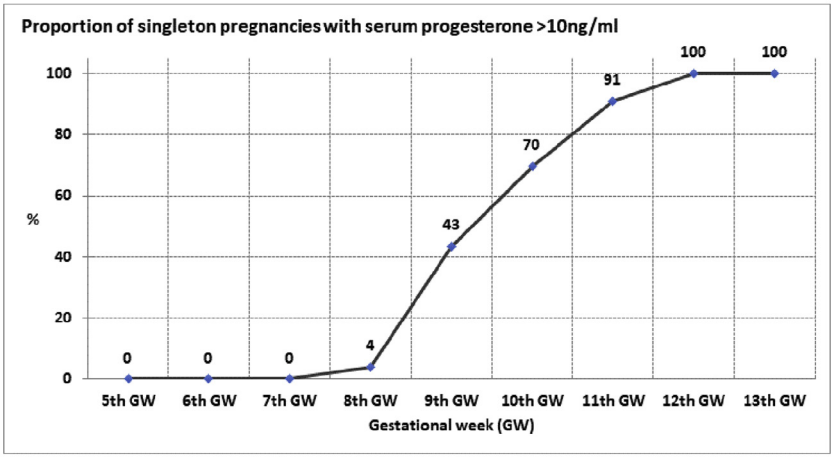


**FIGURE 1** Proportion of ongoing, singleton pregnancies having reached serum progesterone levels of >10ng/ml after a frozen-thawed single blastocyt embryo transfer in an artificial cycle by gestational age post menstruationem (n = 28).

cohort by abnormally low hCG levels earlier in pregnancy, rather than by the onset of placental progesterone production. Of note, a recent large trial on vaginal progesterone for prevention of threatened abortion has failed to identify a causal link between early pregnancy progesterone treatment and abortion prevention, albeit in a different setting than artificial FET (*Coomarasamy et al., 2019*).

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