Premature progesterone elevation in controlled ovarian stimulation: to make a long story short

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Over the past decades many of us have contributed to the controversy surrounding the origins and consequences of premature progesterone elevation during controlled ovarian stimulation. In this article, we attempt to retrace the progression of information on this complex subject which required reviewing a number of publications that often contradicted one another. The definition of premature progesterone elevation, the pathophysiological mechanisms underlying the high peripheral progesterone levels, and the debated consequences of this event on in vitro fertilixation-embryo transfer outcome will be addressed from a historical perspective. (Fertil Steril® 2018;109:563–70. ©2018 by American Society for Reproductive Medicine.)

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During the follicular phase of the menstrual cycle, the bulk of progesterone present in the circulation is modest, relatively constant, and nearly all derived from ovarian and adrenal secretions (1). Yet antral concentrations of this hormone increase progressively with the preovulatory follicular growth and granulosa cells secrete sizable amounts of progesterone in response to luteinizing hormone (LH) stimulation in vitro (2). The increasing production of progesterone by the leading follicle is often insufficient to significantly alter peripheral blood progesterone levels, although, slight increases in plasma progesterone have been documented during the 2-3 days before the onset of the mid-cycle LH surge (3). From a physiological standpoint, a facilitating role of plasma progesterone elevation in the initiation of the LH and follicle-stimulating hormone (FSH) preovulatory surges has been considered (4, 5). Indeed, while an acute rise in estradiol is a necessary condition for the mid-cycle LH and FSH surges, progesterone is likely to partake in the positive feedback response of gonadotropin release in a time-dependent manner (4, 5).

Moreover, controlled ovarian stimulation (COS) induces conspicuous changes in ovarian hormones during the follicular phase that drastically contrast with those observed in the menstrual cycle. In COS, hyperstimulated ovaries secrete remarkable, growing amounts of progesterone throughout the follicular phase irrespective of the absence (6, 7) or the presence (7, 8) of pituitary desensitization by gonadotropin-releasing hormone (GnRH) analogues.

Over the past decades numerous investigators focused on both the genesis of this non-physiological process and its possible consequences on the results of assisted reproductive technologies. The outstanding interest on this specific topic was motivated not merely by pathophysiological doubts or by the need of identifying predictive factors of cycle fecundity, but by the unusual inconsistency of reported conclusions.

Therefore, we decided the time had come to provide the readers with a historical perspective of early and contemporary publications, underlining those that were original or confirmatory and focusing on the mechanisms and consequences of premature progesterone elevation that may possibly be helpful in improving practical COS management.

GENESIS OF PREMATURE PROGESTERONE ELEVATION

In contrast to the modest progesterone levels that characterize the first part of the menstrual cycle, a progressive and significant increase in the serum concentrations of this steroid takes place throughout the follicular phase in COS

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(6–8). In pituitary-functioning COS cycles, an acceleration of this phenomenon is observed toward the last days of the follicular phase while plasma LH levels start to increase (7, 9). The substantial circulating progesterone levels present during the late follicular phase of COS may be attributed to an amplified response of the granulosa cells of multiple follicles to endogenous LH (9). This process, designed as premature luteinization, specifically comprises the elevation of plasma progesterone levels that occurs as a result of a spontaneous LH surge (10–12), blunted LH surge (12, 13), or before the leading follicular diameter has reached 20 mm (14). In this latter case, however, the occurrence of LH surge prior to progesterone elevation was extensively confirmed (14). Yet, sporadic cases of progesterone elevation without overt LH surge have been reported during pituitary-functioning COS (15).

On account of its endogenous LH-dependence, the occurrence of premature luteinization was supposed to be prevented by the extended down-regulation of pituitary GnRH receptors induced, at first, by GnRH agonists (16–18), then by GnRH antagonists, during COS. Indeed, the follicular production of progesterone resulting from endogenous LH surges, or premature luteinization, has been shown to be virtually eliminated by GnRH agonist administration (13), as these drugs safely prevent the preovulatory LH surge. However, the progressive increase in plasma progesterone during the follicular phase of COS was surprisingly not precluded by GnRH analogues (7,8,16–19). Because of the presumably different nature of these two phenomena, we have proposed to denominate the persistent increase in circulating progesterone levels observed during COS, a fortiori with pituitary control by with GnRH analogues, as premature progesterone elevation rather than premature luteinization.

The mechanisms responsible for the unexpected lack of influence of pituitary suppression by GnRH analogues on the progesteronic profile during the follicular phase of COS have been long debated. One of the proposed hypotheses implicated the sensitivity of hyperstimulated ovaries to residual endogenous LH levels. Indeed, in the menstrual cycle, during the first part of the follicular phase, LH receptors are confined to thecal and other interstitial cell types outside the lamina basalis of the follicle complex, whereas FSH receptors are present in the granulosa cells inside the lamina basalis. During the second part of the follicular phase, the dominant follicle acquires LH receptors on the granulosa cells. The induction of these receptors demands exposure to both estrogens and FSH (20, 21). Extrapolating this physiological mechanism to pituitary-suppressed COS cycles, it seemed conceivable that the supraphysiologic exposure of ovaries to FSH (22) might engender a hypersensitization of the granulosa cells to the residual endogenous LH levels (23), thereby leading to an increase in the production of progesterone. This attractive hypothesis was, however, defied by at least three clinical situations. First, the bioavailability of endogenous LH levels remaining after GnRH analogue administration is markedly reduced (24). Second, the fact of doubling the GnRH agonist dose was ineffective to prevent plasma progesterone elevation during the follicular phase (25). Finally, the observation that this phenomenon persisted even in the presence of curtailed endogenous LH levels by the use of a potent GnRH antagonists during COS (26).

Another possibility that could account for the occurrence of premature progesterone elevation was that granulosa cells are stimulated, not by low residual LH levels, but rather by the considerable amount of exogenous LH activity administered to foster the maturation of multiple follicles. This hypothesis was in keeping with the observation that patients displaying higher progesterone levels during the follicular phase of COS often received larger amounts of exogenous gonadotropins. Indeed, the bulk of exogenous gonadotropins has been shown to be positively related to plasma progesterone levels, with dose (8,23,27–30) and time (8,31–33) dependence.

To test the hypothesis of a possible link between exogenous gonadotropins and premature progesterone elevation, we studied the short-term effects of human menopausal gonadotropin (hMG) administration on plasma progesterone levels at the end of COS. In that investigation conducted in 1995, an extensive analysis of the progesteronic profile during the 24 hours following the last hMG injection in pituitary-desensitized COS cycles was undertaken (34). Nine women undergoing COS with time-release GnRH agonist and hMG for in vitro fertilization (IVF)-embryo transfer (ET) had serial blood samplings starting just before the last hMG administration (225 IU). Blood samples were drawn before the injection (baseline), every 30 minutes for 1 hour, hourly for 4 hours, and every 3 hours for the remaining part of the 24-hour period. Plasma progesterone levels (mean ± standard deviation [SD]) increased consistently from baseline, 0.29 ± 0.06 ng/mL, to peak at 0.62 ± 0.10 ng/mL ($P<.004$) approximately 12 hours after hMG administration. Thereafter, progesterone levels decreased progressively to reach values not different from baseline 24 hours after hMG administration (0.34 ± 0.06 ng/mL). These data indicated a time relationship between hMG administration and a slight, yet significant, increase in plasma progesterone culminating 12 hours after hMG injection. Hence, from these results it can be hypothesized that premature progesterone elevation is a consequence of the action of hMG on the hyperstimulated ovaries.

Originally, the prevailing views suggested that LH component of hMG was the most likely factor responsible for the observed effects of exogenous gonadotropins on plasma progesterone levels (34). Hence, at that time, we verified whether preparations containing very low LH concentrations (purified FSH) could exert milder or no effects on the progesteronic profile during the last day of COS. Following a similar design as the preceding study (34), seven women received purified FSH instead of hMG.

Much to our surprise, the 225-IU injection of purified FSH containing less than 1% of LH was associated with similar, or even exacerbated, changes in the progesteronic profile than those observed after hMG administration (35). Plasma progesterone levels, that were at 0.37 ± 0.12 ng/mL just before the injection, increased to 0.86 ± 0.21 ng/mL approximately 15 hours after ($P<.01$). These results, confirmed later (36–39), supported the hypothesis of a stimulatory effect of exogenous FSH administration on plasma progesterone