Elevated early follicular progesterone levels and in vitro fertilization outcomes: a prospective intervention study and meta-analysis

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Objective: To assess the impact of elevated early follicular progesterone (P) levels in gonadotropin-releasing hormone (GnRH) antagonist cycles on clinical outcome using prospective data in combination with a systematic review and meta-analysis.
Design: Nested study within a multicenter randomized controlled trial and a systematic review and meta-analysis.
Setting: Reproductive medicine center in an university hospital.
Patient(s): 158 in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI) patients.
Intervention(s): Recombinant follicle-stimulating hormone (FSH) (150–225 IU) administered daily from cycle day 2 onward; GnRH antagonist treatment randomly started on cycle day 2 or 6; assignment into two groups according to P level on cycle day 2: normal or elevated (>4.77 nmol/L or >1.5 ng/mL, respectively).
Main Outcome Measure(s): Ongoing pregnancy rate (OPR) per started cycle.
Result(s): The incidence of elevated P was 13.3%. A non-statistically-significant difference in OPR was present between the normal and elevated P groups (27.0% vs. 19.0%). No differential impact of early or late GnRH antagonist initiation on the effect of elevated or normal P on OPR was observed. A systematic search of Medline and EMBASE from 1972–2013 was performed to identify studies

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analyzing elevated early P levels in GnRH antagonists. The meta-analysis (n = 1,052) demonstrated that elevated P levels statistically significantly decreased the OPR with 15% (95% CI −23, −7 %). Heterogeneity across the studies, presumably based on varying protocols, may have modulated the effect of elevated P.

Conclusion(s): From the present meta-analysis it appears that early elevated P levels are associated with a lower OPR in GnRH antagonists. The incidence of such a condition, however, is low.

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Key Words: Clinical outcome, GnRH antagonist, IVF, progesterone levels

The end of the menstrual cycle is characterized by regression of the corpus luteum and reduced progesterone (P) production, which reaches its nadir at menstruation. This process is known as functional luteolysis (1) and is followed by structural regression of the corpus luteum, which occurs after a decrease in P synthesis (2). The reduced production of P is associated with a decline in steroidogenic acute regulatory (StAR) gene and protein expression. Additionally, several molecules such as tumor necrosis factor-α and interleukin-1β, a reduced luteal perfusion, and apoptosis are thought to contribute to functional and structural luteolysis (2).

In in vitro fertilization (IVF) cycles cotreated with gonadotropin-releasing hormone (GnRH) antagonist to prevent premature luteinization, the timing of commencing ovarian stimulation is related to the onset of menses. However, what is reported as the onset of menses may in fact sometimes be breakthrough bleeding, possibly as a result of inefficient luteolysis.

The causes for disturbed luteolysis remain unclear. Perhaps the mechanisms underlying functional luteal regression play a certain role. It is also possible that ovarian aging plays a role in creating a disturbed luteal endocrine milieu. Significantly higher P levels in the early follicular phase of a spontaneous cycle have been demonstrated in women who had a poor response during a previous IVF treatment; these levels are possibly caused by continued production by the corpus luteum. These women tended to have a higher median age (3). The investigators suggested that the follicular phase characteristics of these poor responders indicated ovarian aging.

The presence of elevated serum P levels on day 2 of the cycle has been associated with a decreased chance of pregnancy, which might be elicited by advanced or disrupted endometrial receptivity (4). Furthermore, the presence of a still functioning corpus luteum may provide a suboptimal endocrine milieu for new follicular growth and subsequently affect pregnancy rates (5, 6). Little information is available concerning the association of elevated P levels at initiation of ovarian stimulation with IVF outcome. In long GnRH agonist cycles, suppression of gonadotropins results in basal levels of steroid hormones at initiation of stimulation and thus consistently normal P levels (7). However, elevated baseline P levels have been reported in short GnRH agonist cycles (8, 9) and GnRH antagonist cycles (4, 10, 11). The incidence of high P levels on cycle day 2 (CD 2) in GnRH antagonist cycles has been shown to be between 4.9% and 13.3% (4, 10, 11). Delaying the administration of gonadotropins in GnRH antagonist cycles could result in normalization of P values (4). Recently, it has been suggested in an uncontrolled study that pretreatment with a GnRH antagonist during 3 consecutive days before ovarian stimulation leads to normalization of P levels, resulting in adequate ovarian stimulation and acceptable pregnancy rates (10).

Thus, it can be postulated that starting GnRH antagonist cotreatment on day 2 of the cycle may suppress elevated early follicular P levels, thereby improving the chance of achieving in-phase endometrial maturation at the time of embryo transfer. We assessed the impact of elevated early follicular P levels (>4.77 nmol/L or >1.5 ng/mL) on ongoing pregnancy rates in GnRH antagonist cycles. For this, we used previously unused prospective data derived from patients who had participated in a recently published randomized study comparing an early (CD 2) or late (CD 6) starting GnRH antagonist protocol. These data were then analyzed as part of a systematic literature review and meta-analysis.

MATERIALS AND METHODS

Patient Population

Our present study was derived from a nested study (11) as part of a large open-label multicenter randomized controlled trial (RCT) on the timing of GnRH antagonist initiation, conducted between March 2009 and July 2011 in the Netherlands (12). The study was approved by our institutional review board and registered on the Clinical Trial Web site (www.clinicaltrials.gov, NCT00866034). We recruited 200 women undergoing IVF or intracytoplasmic sperm injection (ICSI) from the IVF outpatient clinic of the Department of Reproductive Medicine and Gynecology of the University Medical Center Utrecht. A Web-based computer-generated randomization schedule was used for randomization. The participants and clinicians were not blinded to group allocation. Informed consent was obtained from all patients, and each patient was enrolled into the study only once. The inclusion criteria were: age $\leq$ 39 years, body mass index (BMI) $\leq$ 32 kg/m^2, regular cycle, and no more than two previous unsuccessful IVF-ICSI cycles. Patients diagnosed with World Health Organization (WHO) class 1 and 2 were excluded.