ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Is the effect of premature elevated progesterone augmented by human chorionic gonadotropin versus gonadotropin-releasing hormone agonist trigger?

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Objective: To compare the effect of P on live birth rate between hCG and GnRH agonist (GnRH-a) trigger cycles.
Design: Retrospective cohort study.
Setting: Large private assisted reproductive technology (ART) practice.
Patient(s): A total of 3,326 fresh autologous ART cycles.
Intervention(s): None.
Main Outcome Measure(s): Live birth.
Result(s): A total of 647 GnRH-a trigger cycles were compared with 2,679 hCG trigger cycles. Live birth was negatively associated with P in both the hCG trigger (odds ratio [OR] 0.62, 95% confidence interval [CI] 0.52–0.76) and the agonist trigger cohorts (OR 0.56, 95% CI 0.45–0.69). Interaction testing evaluating P and trigger medication was not significant, indicating that P had a similar negative effect on live birth rates in both cohorts. Progesterone ≥ 2 ng/mL occurred more commonly in GnRH-a trigger cycles compared with hCG trigger cycles (5.5% vs. 3.1%) and was negatively associated with live birth in both the hCG trigger (OR 0.28, 95% CI 0.11–0.73) and agonist trigger cohorts (OR 0.35, 95% CI 0.14–0.90). When P ≥ 2 ng/mL, the live birth rates were poor and similar in the hCG and GnRH-a cohorts (5.9% vs. 14.2%), indicating that P ≥ 2 ng/mL had a similar negative effect on live birth in both cohorts.
Conclusion(s): Elevated serum P on the day of hCG was negatively associated with live birth rates in both hCG and GnRH-a trigger cycles. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Elevated progesterone, IVF, ART, hCG trigger, GnRH agonist trigger

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Late follicular phase elevations of P during IVF occur as a consequence of premature LH elevation, and were common before the advent of GnRH analogues. This resulted from inadequate pituitary suppression and led to premature luteinization (1, 2). After the introduction of GnRH analogues for pituitary suppression, premature LH surges have become far less common and it has been shown that LH is effectively suppressed with

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GnRH antagonists and agonists (1–4). Despite the use of GnRH analogues, early increases in P levels continue to occur in down-regulated IVF cycles (1, 2, 5). Elevated P is associated with higher doses of FSH, low circulating levels of LH, high E_2 levels, and large follicular cohorts (1, 2, 6, 7). Two large retrospective cohort studies have demonstrated a negative effect of P >1.5–2 ng/mL on pregnancy outcomes in women undergoing assisted reproductive technology (ART) (8, 9).

Historically, the effect of elevated P on cycle outcome has been debated (2, 10). Several early studies demonstrated mixed effects of P elevation on cycle outcomes and a 2007 meta-analysis failed to show an effect of elevated P on day of hCG trigger and pregnancy outcome (11–15). More recently, however, studies using newer P assays and more stringent P thresholds have demonstrated the negative effects of elevated P on pregnancy (7–9, 16). A recent meta-analysis of GnRH-antagonist cycles concluded that elevated P significantly lowers pregnancy rates (PRs) (17). Although the evidence is convincing that elevated P has detrimental effects on PRs, all of these studies used cycles with an hCG trigger for final oocyte maturation. Little is known about elevated P and its effect on pregnancy in cycles using a GnRH agonist (GnRH-a) trigger for final oocyte maturation.

The GnRH-a trigger cycles are commonly used to reduce the risk of ovarian hyperstimulation syndrome (OHSS) (18). The use of GnRH-a to induce an endogenous LH surge results in a significantly different luteal phase hormone profile compared with hCG triggering (18). GnRH-a triggers are associated with lower serum levels of E_2 and P (19). Furthermore, it has been shown in oocyte donors that GnRH-a cycles have significantly shorter luteal phases than hCG cycles (20). It is biologically plausible that late follicular P elevations might have different effects on pregnancy outcomes in hCG and GnRH-a trigger cycles, given their different luteal phase characteristics. GnRH-a trigger has even been listed as an exclusion criterion in studies evaluating the effect of elevated P on IVF outcomes (21). The objective of our study was to determine whether P levels on the day of trigger had similar effects on pregnancy outcomes in hCG and GnRH-a trigger IVF cycles.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort analysis of fresh IVF cycles from 2011 to 2013. Cycles were included if serum P was obtained on the day of trigger and a fresh ET occurred. The study was performed at Shady Grove Fertility Reproductive Science Center in Rockville, Maryland, with Institutional Review Board approval.

Patients

All patients who underwent a fresh autologous ET during the periods in which serum P levels were measured on the day of trigger were included in the analysis. Exclusion criteria included cycles where no embryo was transferred, donor oocyte recipients, and cycles without P measured on day of trigger. Patients with a dual GnRH-a + hCG trigger were excluded.

Stimulation Protocol

Ovarian stimulation protocols included mixed FSH/hMG protocols with either GnRH-a or GnRH antagonist for pituitary suppression (22). Oral contraceptive (OC) treatment was generally initiated 2–3 weeks before stimulation. For GnRH antagonist cycles, the antagonist was started when the lead follicle was 14 mm in size. For GnRH-a cycles, 20 units of leuprolide acetate (LA; Lupron) was administered SC during the last 3 days of OC use. This was followed by decreasing to 5 U when ovarian suppression was confirmed with ultrasound and serum E_2 <5 pg/mL. Ovarian stimulation was achieved with both FSH and hMG preparations. When the lead follicle was ≥18 mm, 10,000 IU of hCG or 4 mg of GnRH-a was used for final oocyte maturation. In general, patients predicted to be higher responders were placed on an antagonist cycle and were more likely to receive GnRH-a trigger. Serum P levels were obtained on the day of trigger. Oocyte retrieval was performed 36 hours after trigger shot. Fertilization was achieved with either conventional IVF or intracytoplasmic sperm injection (ICSI) as clinically indicated. After retrieval, patients received vaginal P daily for luteal support. Patients receiving GnRH-a trigger received 1,500 IU of hCG immediately after egg retrieval for luteal support, unless 30 or more oocytes were retrieved, in which case hCG was not administered and luteal support was administered with daily P-in-oil. The threshold of 30 oocytes was based on internal clinical assessment balancing the risk of OHSS with the potential for improved PRs with hCG bolus. All patients received 2 mg estrace (twice daily) starting the evening of oocyte retrieval.

Ultrasound-guided ET was performed on day 3 or on day 5 if an adequate number of high-quality embryos were available. Embryos were graded as good, fair, or poor according to the simplified SART scoring system (23). Serum hCG levels were assessed at 4 weeks gestational age followed by ultrasonography confirmation of a gestational sac in all pregnant patients.

Serum P levels were measured using a solid-phase, competitive chemiluminescent enzyme immunoassay (Immunolyte 2000 Progesterone assay, Siemens Medical Solutions Diagnostic). The lower limit of detection for the assay was 0.2 ng/mL and the analytical sensitivity of the assay was 0.1 ng/mL. Intra-assay and interassay coefficients of variances (CVs) were 6.7% and 7.2%. respectively.

Outcomes

The primary outcome was live birth, defined as a live born infant after the 23rd week of pregnancy. The secondary outcome was clinical pregnancy, defined as an intrauterine gestation with cardiac activity.

Statistics

Generalized estimating equations (GEE) were used to evaluate the association of P with live birth and clinical pregnancy. The GEE modeling accounted for patients with multiple cycles and