Should progesterone on the human chorionic gonadotropin day still be measured?

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Objective: To evaluate in our setting whether there is currently a level of P on the hCG day (P-hCG) predictive of no pregnancy.
Design: Observational study of prospectively collected data of the P-hCG levels of stimulated IVF cycles.
Setting: In vitro fertilization unit.
Patient(s): All cycles of IVF/intracytoplasmic sperm injection with fresh embryo transfer performed between January 2009 and March 2014.
Intervention(s): None.
Main Outcome Measure(s): Pregnancy rate.
Result(s): Clinical pregnancy rate per ET was 38.7% and live birth rate was 29.1%. The P-hCG concentration was positively correlated to E_2 on the hCG day, and the number of oocytes was negatively correlated to age. Progesterone on hCG day was higher among agonist- compared with antagonist-treated patients (mean ± SD: 1.13 ± 0.69 ng/mL vs. 0.97 ± 0.50 ng/mL) and among recombinant FSH compared with recombinant FSH + hMG stimulation (mean ± SD: 1.11 ± 0.58 ng/mL vs. 0.94 ± 0.50 ng/mL). Pregnancy rate was positively associated with the number of oocytes. There was no correlation between P-hCG value and pregnancy rate, overall or according to the type of treatment.
Conclusion(s): In our setting there is no P-hCG value differentiating a good from a poor cycle success rate.
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Key Words: Clinical outcomes, ovarian stimulation, pregnancy rate, progesterone levels

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For the last two decades, the influence of increased levels of P before hCG administration (P-hCG) on the probability of pregnancy in IVF has been periodically revisited since it was first observed in 1990 (1), with more than 60 studies published subsequently. In current protocols that widely use GnRH analogs, agonists, or antagonists to suppress endogenous LH secretion, the increased P found toward the end of stimulation only reflects the total amount of P secreted by the granulosa cells of mature follicles (2, 3).

Several authors have analyzed the impact of P rise on IVF pregnancy rates, with conflicting results (4–12). Even four meta-analyses recently published reach different conclusions (11,13–15). The most recent one included 63 studies and almost 60,000 IVF cycles and concluded that the probability of pregnancy decreased in IVF cycles in which P-hCG was high (15). This seemed to be the end of the debate. However, the authors admitted that a bias could not be ruled out because most studies had been retrospective.

One reason for these conflicting findings could be the varied cut-off values set by different authors (between 0.8 and 3.0 ng/mL), sometimes close to the sensitivity level of the assays used (15, 16). However, after the study by Bosch et al. (6), the most widely used cut-off value is 1.5 ng/mL. Moreover, a P-hCG level >1.5 ng/mL seems to be a turning point in the endometrial gene expression profile (17, 18). Notwithstanding, this cut-off value is now being questioned, because several

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factors are known to impact P concentrations: type of stimulation protocol, type of GnRH analogue, type and dose of gonadotropin, patient age, number of follicles, and others, as noted in three meta-analyses recently published (11, 14, 15). There seems to be a consensus that the detrimental effect of elevated P (EP), if it occurred, would be exerted through a negative impact on the endometrium, because no deleterious effect of EP has been documented in cryotransfer cycles or oocyte reception cycles (15). Alterations at the molecular level have been observed through genomic analyses of the stimulated endometrium in women with EP, compared with women with no EP, and up to 140 dysregulated gene expressions were identified in the group of women with EP (18, 19).

However, there is no convincing evidence about a P-hCG cut-off value capable of predicting the probability of pregnancy, and every medical center is left to define their cut-offs individually according to a strict assessment of local assays (20).

In a previous study, the impact of P-hCG concentrations was analyzed by evaluating the receiver operating characteristic (ROC) curve, and no cut-off value predictive of pregnancy in stimulated IVF cycles under suppression with GnRH agonists was identified (5), therefore in our IVF program no particular strategy based on P-hCG level is taken, although a serum determination is routinely performed for academic purposes. Because of the findings of the recent meta-analyses (15), we decided to re-evaluate in our setting the role of P-hCG. The objective of the study was to ascertain whether there is currently a P-hCG level predictive of no pregnancy and, if so, assess the need to adopt any of the strategies recommended in the literature.

MATERIALS AND METHODS

This was an observational study of prospectively collected data of the P-hCG levels of stimulated IVF cycles. All cycles of IVF/intracytoplasmic sperm injection (ICSI) with fresh embryo transfer performed between January 2009 and March 2014 were included in the study. Patients who underwent retrieval but did not reach ET were not included because we aimed to assess the effect of P-hCG levels on pregnancy rate in fresh IVF/ET cycles (15).

During the study period, day-5 transfer and genetic diagnosis techniques were not a routine in our IVF program, rather they were our policy for recurrent implantation failure or specific indication. Therefore, to have a more homogeneous population and to avoid bias, only day-3 ETs were included.

Patients requiring GnRH agonist to trigger ovulation owing to the risk of ovarian hyperstimulation syndrome were excluded from the analysis, because they required modified luteal support (21).

Patients were stimulated with recombinant FSH (rFSH) (Gonal F, Serono; Puregon, MSD) and/or hMG (Menopur, Ferring) in the antagonist protocol (Cetrotide, Serono; Orgalutran, Organon) with a daily SC injection, after the administration of a contraceptive pill, or with suppression with agonists as of the mid-luteal phase of the previous cycle (Procrin, Abbot) in the long protocol. Response was monitored with transvaginal ultrasound scan and serum E_2 every 2 days, from day 5 of gonadotropin administration, and E_2 and P from the observation of a follicle of 18 mm until the day of hCG trigger. Recombinant hCG was used for ovulation induction in all cases (250 μg Ovitrelle, Serono) when at least three follicles $\geq$18 mm in diameter were observed. After oocyte retrieval and the usual IVF/ICSI procedures, the transfer of one to three embryos was performed on days 2–3 of the cycle, according to the number of good-quality embryos available and patient age. The luteal phase was supported with 200 mg, three times a day, of micronized vaginal P (Utrogestan, Seid) for 14 days, until serum β-hCG determination and, in case of a positive result, was maintained until confirmation of the pregnancy by the presence of fetal heartbeat by ultrasound scan in week 6 of gestation.

Hormone determinations of E_2 and P were performed in our laboratory with Roche's Cobas reagents in the Cobas e-411 analyzer, an electrochemiluminescence immunoassay. For E_2, the lower limit of detection was 5 pg/mL, with intra- and interassay variation of 2.4%–4.6% and 4.3%–9.9%, respectively. For P, the lower limit of detection was 0.03 ng/mL, with intra- and interassay variation of 1.5%–2.7% and 3.7%–5.5%, respectively. Antimüllerian hormone (AMH) determination was measured with Beckman Coulter reagents, an immunoenzymatic assay, with a lower limit of detection of 0.16 ng/mL, intra-assay variation of 3.4%–5.4%, and interassay variation of 4.0%–5.6%.

All data were included in the patient's electronic record, which is recorded in a Microsoft SQL Server 2005 database.

Continuous variables between the group of patients achieving and not achieving pregnancy were compared using the nonparametric Mann-Whitney test.

Progesterone levels were normalized with their transformation to a natural logarithm. This transformation was used for all analyses.

The correlation between continuous variables and log-transformed P was analyzed with a Spearman correlation coefficient.

The comparison between density function of the log-transformed P levels between pregnant and nonpregnant patients was performed with the "sm" package. This package uses kernel methods to construct nonparametric estimates of density functions (22).

Analysis of variance was used to compare the log-transformed P levels means, depending on the stimulation protocol, gonadotropins, and the interaction of both, and adjusted for patient age, E_2 level, hCG day, and oocytes retrieved.

The relationship between the log-transformed P concentrations and the probability of pregnancy was graphically evaluated with a generalized additive model (23).

The discriminating power of P was assessed with ROC curves.

The statistical analysis was performed with the R (R Core Team, 2014) (24) statistical software and the IBM SPSS Statistics 22.0 package.

This work was authorised by our institutional review board (Cátedra de Investigación en Obstetricia y Ginecología) (NCT02323347).