European Journal of Obstetrics & Gynecology and Reproductive Biology 203 (2016) 44–48

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

The impact of premature progesterone rise on the outcome of intrauterine insemination cycles with controlled ovarian hyperstimulation in unexplained infertility

Mehmet Firat Mutlu [a,*], Mehmet Erdem [b], Ahmet Erdem [b], Ilknur Mutlu [c], Ismail Guler [b], Erhan Demirdağ [d]

[a] Department of Obstetrics & Gynecology, Yuksek Ihtisas University Faculty of Medicine, Ankara, Turkey
[b] Department of Obstetrics & Gynecology, Gazi University Faculty of Medicine, Ankara, Turkey
[c] IVF Unit, Novaart IVF and Women Health Center, Ankara, Turkey
[d] Department of Obstetrics &Gynecology, Etlik Zubeyde Hanım Women's Health Education and Research Hospital, Ankara, Turkey

ARTICLE INFO

Article history:
Received 7 January 2016
Received in revised form 23 February 2016
Accepted 13 May 2016

Keywords:
Progesterone
Live birth rate
Ovarian hyperstimulation
Insemination

ABSTRACT

Objective: To ascertain the incidence of premature progesterone P rise and its impact on outcomes in controlled ovarian hyperstimulation and intrauterine insemination (COH–IUI) cycles, and also to identify variables related with premature P rise.

Study design: Four hundred sixty cycles of 460 couples with unexplained infertility having COH–IUI treatment with a starting dose of 75 IU recombinant FSH enrolled in this prospective study. Serum P levels were determined on the day of hCG trigger. Premature P rise was defined as progesterone ≥1 ng/mL. The primary outcome measure was live birth per cycle with regard to P levels of ≥1 ng/mL and ≥1.5 ng/mL. Secondary outcome measures were cycle characteristics associated with P rise.

Results: The incidence of premature P rise was 22.0%. P levels on hCG day were significantly lower in cycles with live birth as compared to cycles without live birth 0.49 ± 0.51 vs. 0.73 ± 0.82 ng/mL. Live birth rates were significantly lower in cycles with hCG day P levels ≥1.0 ng/mL (%7.9 vs. %22.6) and ≥1.5 ng/mL (%6.4 vs. %20.8). Among age, number of dominant follicles, estradiol, LH and P levels on the day of hCG trigger, it was found that P levels was the only significant variable to predict live birth on multivariate analysis. The number of dominant follicles on hCG day and premature LH surge were the only significant variables related with premature P rise.

Conclusion: Premature P is a frequent feature of COH–IUI cycles and associated with decreased live birth rates.

Introduction

Controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI) is widely used in first line treatment of unexplained and male factor infertility before In Vitro Fertilization (IVF) treatment. There are numerous factors that might influence the success rates in COH–IUI cycles as women's age, etiology and duration of infertility, semen parameters, sperm preparation methods, IUI timing, ovarian hyperstimulation protocol, number of pre-ovulatory follicles and premature LH surge [1–8].

Addition of COH to IUI increases the number of oocytes available for fertilization and the risk of premature LH and progesterone (P) rise as well [9]. Most of the data with regard to the impact of premature LH and P rise was acquired from COH cycles in IVF and it was shown that different cutoff levels of premature P rise ranging between 1 and 1.5 ng/mL on the day of hCG has detrimental effect of IVF outcome [10–17]. However, there were a few studies which investigate the incidence and the impact of early P rise in COH–IUI cycles [18,19]. The incidence of early P rise was between 8.7 and 22% when cut-off levels of 1, 1.1 and 1.6 ng/mL were used [18,19]. It was recently shown in a retrospective study that early P rise was associated with decreased ongoing pregnancy rates in IUI cycles [18]. Further prospective data are required to investigate the impact of P rise in IUI cycles.

In this prospective study we aimed to ascertain the incidence of premature P rise on the day of hCG administration, and its impact

* Corresponding author at: Department of Obstetrics & Gynecology, Yüksek Ihtisas University, Koru Hospital, Kızılırmak Mah. 1450. Sokak No: 13 Cukurambar, Ankara, Turkey. Tel.: +90 532 325 77 90.
E-mail address: firatmutlu78@hotmail.com (M.F. Mutlu).

http://dx.doi.org/10.1016/j.ejogrb.2016.05.013
0301-2115/

on cycle outcomes in terms of live birth in COH–IUI cycles. We also aimed to identify clinical and hormonal variables which were related to premature P rise in COH–IUI cycles.

Materials and methods

Patients and study design

This was a single-center prospective trial that included first cycles of 460 couples with unexplained infertility having COH–IUI treatment between 2008 and 2013 in an infertility clinic of a university-based tertiary care hospital. All of the patients underwent a complete infertility evaluation including mid-luteal progesterone levels, hysterosalphingography (HSG), and semen analysis. Inclusion criteria were as follows: failure to conceive for 12 months of unprotected regular intercourse, female age between 20 and 42 years, regular spontaneous menstrual cycles ranging from 24 to 35 days with mid-luteal P levels of >3 ng/mL, basal FSH levels ≤15 IU/l, basal LH levels <10 IU/l, bilateral tubal patency confirmed with HSG and normal semen features according to World Health Organization criteria [20]. Patients with endocrine disorders (polycystic ovarian syndrome, abnormal thyroid and prolactin hormone levels, hypogonadotropic hypogonadism), moderate to severe endometriosis (American Fertility Society, stage III or IV), patients with contraindications for one of the investigated drugs, patients with persistent ovarian cysts (>19 mm and >2 months) were excluded from the study. The study protocol was approved by Ethics Committees of our Faculty. Written informed consent was taken from all patients.

Ovarian stimulation protocol

All patients underwent baseline transvaginal ultrasonography (TVU) on day 3 of the menstrual cycle and were then treated with a starting dose of 75 IU recombinant FSH (Gonal-F, Serono, Turkey and Puregon, Organon, Turkey). Ovarian response and endometrial thickness were assessed with TVU starting from day 7 to 8 of cycles. Gonadotropin dose was increased by 50% if the diameter of leading follicle was <10 mm on day 8 of the stimulation. The gonadotopin dose remained the same until the day of hCG trigger after the leading follicle reached to 12 mm diameter. Cycles were triggered with 250 μcg recombinant hCG (Ovitrelle, Serono, Turkey) when at least one dominant follicle had reached 18 mm in diameter. Cycles with more than three dominant follicles and/or estradiol levels >1500 pg/ml were canceled. A single insemination was performed 36 h after hCG administration with a disposable IUI catheter. The patient rested in a supine position for 15 min after the procedure. Luteal support was supplemented with vaginal progesterone gel (Crinone 8% vaginal gel, Serono, Turkey) once a day starting 2 days after insemination and carried on until a pregnancy test was performed.

Serum LH and P levels were analyzed on the day of hCG trigger. Serum samples were analyzed by using the chemoluminescence with the Architect analyzer (Abbot Diagnostics). The analytical sensitivity of P assay was 0.1 ng/mL with intra and inter-assay coefficients of 6.9 and 3.9%, respectively. The analytical sensitivity of LH assay was 0.1 mIU/mLwith intra and inter-assay coefficients of 6.8 and 4.7%, respectively. P levels were blinded to investigators until pregnancy test not to effect cycle management. Premature LH rise was defined as LH ≥10 mIU/mL, and premature P rise as progesterone ≥1 ng/mL. Patients were categorized to have premature luteinization when there was premature P rise in addition to premature LH.

Patients had pregnancy test on 14 post-insemination day by measuring serum β-hCG levels and intrauterine pregnancy was confirmed by using TVU, 2 weeks after a positive pregnancy test. Patients that were pregnant continued to receive luteal support up until the 8th week of gestation. Pregnancy testing was performed by determining the quantitative serum hCG level at 14 days after hCG administration. A clinical pregnancy was defined as the presence of a gestational sac on TVU. Live birth was defined as birth of an infant after 24 weeks of pregnancy who was alive 1 week after birth. Miscarriage was defined as pregnancy loss before 20 weeks.

Outcome measures and statistical analysis

The primary outcome measure was live birth per cycle with regard to P levels. P levels of 1 and 1.5 ng/mL were used for comparisons. The incidence of LH and P rise on the day of hCG trigger were also evaluated. Secondary outcome measures were cycle characteristics associated with live birth and P rise. The Statistical Program for Social Sciences (SPSS, version 11.5, SPSS Inc., Chicago, IL) was used for statistical analysis. A priori power analysis was performed. For an expected pregnancy rate of 5% for cycles with P rise and 15% for cycles without P rise, a sample size of 400 patients was required for a statistical power of 90% at a level of .05. Data were expressed as mean ± SD. Parametric distribution of data was confirmed by the Kolmogorov–Smirnov test before further analysis. The continuous demographic variables of patients and cycles were compared with Student's *t* test. Mann–Whitney *U*-test was used for independent samples without a normal distribution. Categorical variables were compared with Chi square test. Multivariate logistic regression analysis was used to assess the effect of different variables on live birth and premature P rise prediction. A p value of 0.05 was considered statistically significant.

Results

The first cycles of 460 couples were included in the study. The incidence of premature LH rise was 27.3%. The incidence of premature P rise was 22.0% for P level of ≥1 ng/mL and 10.2% for P level of ≥1.5 ng/mL. The incidence of premature luteinization was 11.5%.

The demographic characteristics of patient population, including age (28.2 ± 5.9 vs. 29.6 ± 5.0 years), duration of infertility (2.8 ± 1.8 vs. 3.4 ± 2.4 years), basal FSH (7.4 ± 3.8 vs. 8.0 ± 4.9 IU/mL), body mass index (24.8 ± 3.4 vs. 24.1 ± 4.1 kg/m^2) were comparable in patients with and without live birth. The cycle characteristics of study group with regard to live birth were demonstrated in Table 1. There were no significant differences between two groups in terms of duration of stimulation, total gonadotropin dose, E_2 levels, LH levels and endometrial thickness on hCG day and sperm parameters. P levels

Table 1
The cycle characteristics of study group with regard to live birth rate.

	Cycles with live birth (n = 89)	Cycles without live birth (n = 371)	p
Duration of stimulation (days)	9.7 ± 3.6	9.0 ± 2.6	NS
Total gonadotropin dose (IU)	870 ± 285	790 ± 350	NS
LH levels on the day of hCG (IU/mL)	8.0 ± 10.7	8.5 ± 8.4	NS
Progesterone levels on the day of hCG (ng/mL)	0.49 ± 0.51	0.73 ± 0.82	<0.01
E_2 Levels on the day of hCG (pg/mL)	685 ± 620	536 ± 462	NS
Endometrial thickness on hCG day (mm)	11.3 ± 2.3	11.0 ± 2.2	NS
Dominant follicle number on hCG day	1.6 ± 0.9	1.4 ± 1	NS
Basal sperm concentration (×10^6)	47.5 ± 31.1	46.3 ± 34.1	NS
Basal sperm motility (%)	57.5 ± 14.1	54.2 ± 16.2	NS
Sperm concentration after preparation (×10^6)	65.6 ± 54.2	59 ± 52.1	NS
Sperm motility after preparation (%)	78.6 ± 14.1	79.4 ± 20.0	NS

NS, non-significant.