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Live-birth rates after HP-hMG stimulation in the long GnRH agonist protocol: association with mid-follicular hCG and progesterone concentrations, but not with LH concentrations

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The aim of this retrospective study was to investigate the impact of endogenous and exogenous luteinizing hormone (LH) activity on treatment outcome, when taking into consideration potential confounding variables. Data were derived from IVF patients (n = 358) stimulated with highly purified menotrophin (HP-hMG) in a long gonadotrophin-releasing hormone (GnRH) agonist protocol. Simple retrospective logistic regression analysis showed that the mid-follicular exogenous concentrations of human chorionic gonadotrophin (hCG) (p = 0.027), provided by the HP-hMG preparation, and female age (p = 0.009) were significantly associated with live-birth rate, while the mid-follicular progesterone concentration (p = 0.075), the estradiol concentration on last stimulation day (p = 0.075) and number of embryos transferred (p = 0.071) were borderline significant. Endogenous LH was not associated with live-birth rate; neither at start of stimulation (p = 0.123), nor in the mid-follicular phase (p = 0.933) or on the last day of stimulation (p = 0.589). In the multiple regression analysis of life birth, mid-follicular hCG (p = 0.016) was identified as a positive predictor, and age (p = 0.004) and mid-follicular progesterone (p = 0.029) as negative predictors. In conclusion, mid-follicular concentrations of exogenous hCG and progesterone, but not endogenous LH, are associated with live-birth rate in IVF patients treated with HP-hMG in a long GnRH agonist cycle.

Keywords: Assisted reproduction, highly purified menotrophin, human chorionic gonadotrophin, luteinizing hormone, progesterone

Introduction

The concentration of circulating luteinizing hormone (LH) during the follicular phase of a controlled ovarian stimulation (COS) cycle is influenced by many factors such as the type of gonadotrophin-releasing hormone (GnRH) analogue, the protocol used as well as the type of gonadotrophin and timing of the last administration [1–6]. The evaluation of the impact of circulating LH concentrations on clinical outcome is complex as the published studies have diversities in patient selection criteria, down-regulation protocols and gonadotrophin preparations. Furthermore, there are differences among studies in LH assay methods and frequency of assessments as well as in the definition of what constitutes a low serum LH concentration.

A systematic review of trials in normo-ovulatory and anovulatory WHO II patients undergoing COS with recombinant follicle stimulating hormone (rFSH) activity only indicated that suppression of the endogenous LH concentration in the mid-late follicular phase does not affect pregnancy rates [7]. This meta-analysis excluded several studies which have reported a negative influence of low LH during stimulation on pregnancy rates [5,8–10]. A substantial reduction in the serum LH concentration from start of COS to the mid-late follicular phase resulted in significantly lower live-birth rates in patients stimulated with FSH activity following the long GnRH agonist protocol [11].

When COS is performed with gonadotrophin preparations containing both FSH and LH activity, interpretation of the impact of endogenous LH on outcome is complicated by the difficulty of differentiating the relative contributions of exogenous and endogenous LH activities. However, this obstacle applies only to supplementation with LH molecules, but not to supplementation with human chorionic gonadotrophin (hCG) molecules. In patients treated with a highly purified menotrophin preparation (HP-hMG), which contains hCG as the almost exclusive source of LH activity rather than LH [12], it is possible to separate the associations between outcome variables and the exogenous and endogenous components of LH activity.

A significant association between circulating hCG concentrations, but not LH concentrations, in the mid-follicular phase and ongoing pregnancy rates has been reported in IVF/ICSI patients stimulated with HP-hMG in the long GnRH agonist protocol (13). The aim of the present study was to confirm these associations between treatment success and serum concentrations of LH and hCG when following the long GnRH agonist protocol. In this evaluation, other potential confounding variables were also included.

Methods

This study is a retrospective evaluation of patients in the HP-hMG (Menopur, Ferring Pharmaceuticals A/S) treated arm (n = 363) of a randomized controlled trial conducted in IVF patients following a long GnRH agonist protocol. The population characteristics and treatment protocol have been described elsewhere [14]. Main inclusion criteria were women with tubal-factor or unexplained infertility including endometriosis stage I/II or partners with mild semen abnormalities, 21–37 years of age, a body mass index

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(BMI) of 18–29 kg/m^2, FSH 1-12 IU/L, and regular menstrual cycles of 21–35 days. Women with polycystic ovary syndrome, endometriosis stage III/IV or partners with severe male factors requiring ICSI and poor responders were excluded. Triptorelin acetate, 0.1 mg/day (Decapeptyl; Ferring Pharmaceuticals), was initiated 5–7 days before the estimated start of next menses and continued until the end of gonadotrophin administration. After confirming pituitary desensitization, COS was initiated at 225 IU for the first 5 days and then adjusted according to individual response. Recombinant hCG, 250 μg (Ovitrelle, Merck Serono), was administered within 1 day of observing three or more follicles of ≥17 mm. Oocyte retrieval was performed 36 ± 2 h later. Vaginal progesterone gel, 90 mg/day 8% (Crinone, Merck Serono), for luteal support was given from the day of embryo transfer till confirmation of clinical pregnancy (5–6 weeks after embryo transfer) or negative βhCG test (13–15 days after embryo transfer). Transfer of one or two embryos was performed on day 3 after oocyte retrieval. A live birth cycle was defined as a cycle that resulted in at least one live-born neonate.

Blood samples were taken prior to start of stimulation, on stimulation day 6 and last day of stimulation. Blood was collected at least 8 h after the previous gonadotrophin dose. Serum was analyzed by a central laboratory using electrochemiluminescence immunoassays (FSH, LH, hCG), chemiluminescent immunometric assays (estradiol, progesterone) and radioimmunoassays (androstenedione, total testosterone). The lower detection limits (total imprecision, CV) were as follows: FSH 0.10 IU/L (<6%); LH 0.10 IU/L (<6%); hCG 0.10 IU/L (<8%); estradiol 55 pmol/L (<10%), progesterone 0.6 nmol/L (<8%), androstenedione 0.08 nmol/L (<10%) and total testosterone 0.17 nmol/L (5%).

Statistical analysis

The association between demographics, endocrinological variables and clinical outcome variables and live birth was assessed by means of simple regression models. The analyses were restricted to patients with endocrine data available for stimulation day 6, and three patients with outlier observations were excluded, leaving a total analyzable population of 358 IVF patients. A multiple logistic regression model was developed including all variables with $p \leq 0.1$ in the simple analyses, followed by a stepwise backwards selection until all terms were significant at the 5% level.

Results

The mean serum LH concentration was 2.2 ± 1.4, 1.4 ± 0.8 and 1.8 ± 0.9 IU/L on stimulation days 1, 6 and last day, respectively. Forty-two percent of the patients had a low LH level (<1.2 IU/L) at any time during COS. The mean serum hCG concentration was non-detectable, 2.5 ± 0.8 and 2.9 ± 1.2 IU/L on stimulation days 1, 6 and last day, respectively.

The simple logistic regression analysis identified two variables significantly associated with live-birth rate; the age was negatively associated (p = 0.009) and the serum hCG concentration on stimulation day 6 was positively associated (p = 0.027) (Table I). The serum concentrations of progesterone on stimulation day 6 (p = 0.075) and estradiol on last stimulation day (p = 0.075) as well as the number of embryos transferred (p = 0.071) were borderline significantly associated. There was no association between the endogenous LH concentration and live-birth rate; neither at baseline (p = 0.123), nor on day 6 (p = 0.933) or last day of stimulation (p = 0.589). There was no relationship between live-birth rate and body weight or the number of oocytes retrieved. When stratifying the patients into three subgroups based on the serum hCG concentration on stimulation day 6, the live-birth rates were15%, 29% and 32% in patients with low (≤1.9 IU/L, ≤25th percentile; n = 87), medium (>1.9–2.9 IU/L, >25th–75th percentile; n = 178) and high hCG (>2.9 IU/L, >75th percentile; n = 90), respectively.

The multiple logistic regression model of live-birth rate included the mid-follicular hCG concentration (p = 0.016) as positive predictor, and female age (p = 0.004) and the mid-follicular progesterone concentration (p = 0.029) as negative predictors (Table II). In addition, the mid-follicular LH concentration was forced into the prediction model despite being non-significant (p = 0.759), as it was the main objective of the study to evaluate its role versus exogenous hCG activity. The predictive ability of the model measured by the area under the receiver operating characteristics (ROC) curve was 0.645. Figure 1 displays predicted chances of a live-birth corresponding to the multiple logistic regression model.

Discussion

The present analysis shows that, when using HP-hMG for COS, the exogenous hCG concentration in the mid-follicular phase is positively associated with the live-birth rate in IVF patients following a long GnRH agonist protocol, independent of the

Table I. Simple logistic regression analysis of the association between demographics, endocrinological variables and clinical outcome variables and live birth in IVF patients treated with HP-hMG in a long GnRH agonist protocol.

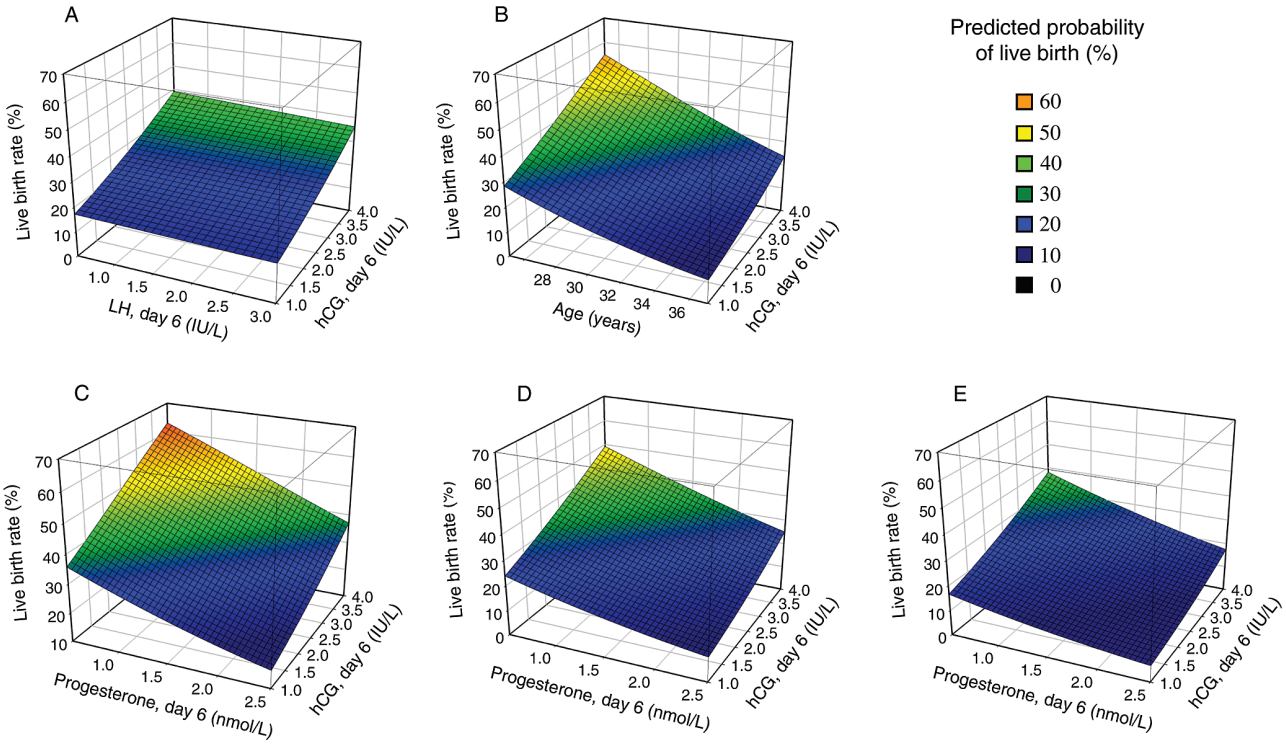
Variables	OR[a]	95% CI[b]	p value
Demographics			
Age (years)	0.91	0.84–0.98	0.009
Weight (kg)	1.01	0.98–1.03	0.658
BMI (kg/m^2)	0.99	0.91–1.09	0.891
Start of stimulation			
LH (IU/L)	1.13	0.97–1.33	0.123
FSH (IU/L)	1.13	0.96–1.33	0.150
Day 6 of stimulation			
LH (IU/L)	0.99	0.74–1.31	0.933
hCG (IU/L)	1.39	1.04–1.86	0.027
Estradiol (nmol/L)	1.19	0.94–1.52	0.159
Progesterone (nmol/L)	0.74	0.48–1.13	0.075
Last stimulation day			
LH (IU/L)	1.07	0.83–1.39	0.589
hCG (IU/L)	1.09	0.89–1.33	0.399
Estradiol (nmol/L)	1.06	0.99–1.14	0.075
Progesterone (nmol/L)	0.93	0.78–1.10	0.342
Oocyte retrieval			
Number of oocytes retrieved	1.04	0.99–1.08	0.108
Embryo transfer			
Number of embryos transferred	1.63	0.95–2.81	0.071

[a]Odds ratio. [b]Confidence interval.

Table II. Multiple logistic regression model for prediction of probability of live birth in IVF patients treated with HP-hMG in a long GnRH agonist protocol.

Predictor	OR[a]	95% CI[b]	p value
Age (years)	0.89	0.83–0.96	0.004
Serum hCG (IU/L), stimulation day 6	1.45	1.07–1.97	0.016
Serum progesterone (nmol/L), stimulation day 6	0.59	0.37–0.95	0.029
Serum LH (IU/L), stimulation day 6	0.95	0.71–1.29	0.759

[a]Odds ratio. [b]Confidence interval.



Age (years)	hCG (IU/L), day 6	Predicted probability of live birth, % (95% prediction limits)		
		Progesterone (nmol/L), day 6		
		0.8[a]	1.4[b]	2.2[c]
26[a]	1.5[a]	36 (24-51)	29 (20-41)	21 (12-34)
	2.4[b]	44 (32-57)	37 (28-47)	28 (18-40)
	3.5[c]	55 (39-69)	47 (35-59)	36 (24-50)
31[b]	1.5[a]	24 (17-33)	19 (14-26)	13 (8-22)
	2.4[b]	31 (24-39)	25 (20-30)	18 (12-26)
	3.5[c]	41 (29-53)	33 (25-42)	25 (16-35)
35[c]	1.5[a]	17 (11-26)	13 (8-20)	9 (4-17)
	2.4[b]	22 (15-31)	17 (12-24)	12 (7-21)
	3.5[c]	30 (20-44)	24 (16-35)	17 (10-29)

[a]10th percentile; [b]50th percentile; [c]90th percentile

Figure 1. Predicted chances of live birth based on a multivariate logistic regression model for patients treated with HP-hMG in a long GnRH agonist protocol. (A) The predicted live-birth rate using the explanatory factors 'endogenous serum LH concentration' and 'exogenous serum hCG concentration on day 6 of stimulation', where the variables 'female age' and 'progesterone concentration on day 6 of stimulation' are set to the median values of 31 years and 1.4 nmol/L, respectively. (B) The predicted live-birth rate versus 'female age' and 'exogenous serum hCG concentration on day 6'; concentrations of progesterone and endogenous LH (1.4 IU/L) are set to the median values. (C–E) The predicted live-birth rate versus 'exogenous serum hCG concentration on day 6' and 'serum progesterone concentration on day 6' for patients aged 26, 31 and 35 years, respectively; the concentration of endogenous LH are set to the median value. The tabulation shows the predicted live-birth rates (and 95% prediction limits) at various female ages and mid-follicular concentrations of hCG and progesterone.

endogenous LH concentrations prior to or during COS. These findings replicate the positive association between mid-follicular hCG and treatment success in women stimulated with HP-hMG in a long GnRH agonist protocol [13]. Moreover, the serum concentration of exogenous hCG at end of stimulation has been found to be positively associated with live-birth rate in normogonadotropic anovulatory infertile women treated with HP-hMG, while endogenous LH concentrations were not [15].

The present study provide reassurance that supplementation of LH activity in the form of hCG will not lead to deteriorated cycle outcomes *per se* in IVF patients undergoing COS with HP-hMG in a long GnRH agonist protocol. On the contrary, patients with a high mid-follicular hCG concentration had actually the highest live-birth rate. Since there was no relationship between body weight (or BMI) and live-birth rate in the present study, the mid-follicular hCG concentration was likely not only a reflection of hCG bioavailability associated with body weight.

There are scarce data in the literature on the associations between endogenous LH and exogenous hCG concentrations and outcome in patients stimulated with HP-hMG in GnRH antagonist protocols. The endogenous LH concentrations appear not to be associated with pregnancy rates in normogonadotropic

patients undergoing stimulation with rFSH in GnRH antagonist cycles [16]. Nevertheless, a retrospective study in patients stimulated with rFSH supplemented with urinary hCG, 50 IU or 100 IU daily, in a GnRH antagonist protocol reported that the patients with LH concentrations below 0.5 IU/L after start of the GnRH antagonist had significantly higher live-birth rates than the patients treated with rFSH alone [17].

Some of the effects of exogenous hCG on treatment outcome have been suggested to be mediated by a modification of the intra-follicular balance of endocrine/paracrine factors and the cytokine profile associated with oocyte and embryo quality as well as endometrial characteristics [18–20]. The association between hCG concentrations and ongoing pregnancy/live-birth rate has been observed in studies with early initiation of LH activity supplementation. Low-dose hCG additions to the final stages of COS have been associated with reduced FSH consumption or full FSH replacement, without affecting the pregnancy rates [21–24].

The findings in the present study do not argue against the concept that high mid-follicular endogenous LH concentrations may potentially be associated with lower pregnancy and live-birth rates [10,25]. If no exogenous LH molecules are added during stimulation, the circulating LH concentration in a long GnRH agonist protocol should provide an indication of the patient's pituitary response to the down-regulation as well as the follicular development and estradiol concentration associated with the gonadotrophin stimulation. A high serum LH concentration in the mid-follicular phase may be reflective of a hypothalamic-pituitary-gonadal axis refractory to down-regulation by the GnRH agonist or direct or indirect effects of gonadotrophin administration.

The serum progesterone concentration in the mid-follicular phase was found as a negative predictor of live birth. A modest elevated progesterone concentration during the mid-late follicular phase has been proposed to have a negative impact on embryo implantation and pregnancy rates in both long GnRH agonist and GnRH antagonist cycles by affecting primarily endometrial receptivity [14,26–30].

In conclusion, mid-follicular concentration of exogenous hCG is positively associated with the live-birth rate in patients stimulated with HP-hMG following the long GnRH agonist protocol, independently of the endogenous LH concentration prior to or during COS. The patient's age and mid-follicular progesterone concentration are confounding variables that are negatively associated with the live-birth rate. Although the available data do not provide evidence of a causal relationship between exogenous hCG and positive treatment outcome, they warrant further exploration of the impact of exogenous hCG supplementation from start of stimulation on treatment outcome.

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