Serum human chorionic gonadotropin level after ovulation triggering is influenced by the patient's body mass index and the number of larger follicles

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Objective: To identify determinants of the serum concentration of hCG levels after triggering of ovulation with exogenous hCG during controlled ovarian stimulation cycles for in vitro fertilization with or without intracytoplasmic sperm injection.
Design: Retrospective cohort study.
Setting: University Medical Center.
Patient(s): One hundred-fifteen women who underwent conventional in vitro fertilization/intracytoplasmic sperm injection cycles from March 2003 to March 2005.
Intervention(s): All patients underwent ovarian hyperstimulation with gonadotropins and GnRH-antagonist for pituitary downregulation. Patients were started on oral contraceptives 1 month before the stimulation. Gonadotropins were administered from stimulation day 1 until the day of the hCG trigger, and GnRH-antagonist was added from the day when at least one follicle reached 14 mm in diameter and continued until hCG administration. The hCG was administered in 5,000-IU, 10,000-IU, or 15,000-IU doses on the day of ovulation triggering.
Main Outcome Measure(s): We performed a stepwise multiple regression analysis to predict which variable would influence the serum concentration of hCG when measured the day after the administration of exogenous hCG.
Result(s): Body mass index (kg/m^2) and number of follicles >14 mm were the only determinants of the hCG concentration (cumulative $R^2 = 0.30$; $P<.001$). Patient age, estradiol peak, number of oocytes retrieved, length of stimulation, and length of GnRH-antagonist administration in days were not associated with serum hCG levels.
Conclusion(s): Knowing that the number of larger follicles and the patient's BMI are the major determinants of the hormone's clearance in the body can help in the hCG dose titration during ovarian stimulation. (Fertil Steril® 2007;88:152–5. ©2007 by American Society for Reproductive Medicine.)

Key Words: hCG, ovulation induction, in vitro fertilization, BMI, serum level

Human chorionic gonadotropin, normally produced by the trophoblastic tissue for the maintenance of pregnancy, has been used for ovulation induction in animal models since the 1950s, and in infertile patients since the 1960s (1–3). It subsequently became the routine oocyte maturation trigger in in-vitro fertilization cycles in the 1970s (4).

Human chorionic gonadotropin has been shown to have multiple effects on the gonads as well as in extragonadal tissues acting at the level of the LH receptors (LH/hCG receptors), because it shares most of the molecular composition with the endogenous LH (5). In the ovary, LH/hCG receptors are expressed in the thecal cells of small preovulatory follicles, but they have also been found in the granulosa cells of the larger preovulatory follicles (>10 mm). It has been shown that follicular maturation does not progress in LH/hCG receptor knockout mice, even if they show normal prenatal ovarian development (6). In the uterus, the endometrium expresses LH/hCG receptors during the implantation period (7). Moreover, it has been seen that LH/hCG and progesterone receptors in the uterus show a mutual enhancement of expression during this period (8, 9). The hCG was shown to improve the uterine receptivity by enhancing endometrial decidualization and stimulating endometrial neoangiogenesis by upregulating vascular-endothelial growth factor function (8). This endometrial maturation is also enhanced during the follicular phase by administration of LH (and, similarly, administration of hCG) in ovulation induction cycles characterized by a regimen of gonadotropin–releasing hormone agonist (GnRH-a) plus human menopausal gonadotropins (10).

Recently, hCG has been shown to be effective in continuing ovulation induction after a shortened gonadotropin priming, and before the routine high-dose hCG triggering that is administered 35 to 36 hours before the oocyte retrieval (11). The hCG shows

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TABLE 1

Characteristics of the study population subdivided into three groups based on hCG ovulation trigger dose.

Variable	hCG 5,000 N = 21	hCG 10,000 N = 19	hCG 15,000 N = 75	Significance
Age (y)	31.5 ± 4	35 ± 6	33 ± 4	NS
Body mass index (kg/m^2)	26 ± 5	24 ± 4	26 ± 6	NS
No. days on antagonist	5.0 ± 1.0	4.9 ± 1.0	4.7 ± 1.0	NS
Length of stimulation (d)	12.0 ± 1.2	11.8 ± 1.5	11.3 ± 1.7	NS
Total gonadotropin dose (IU)	3,537 ± 1,499	6,254 ± 4,856	4,994 ± 4,019	NS
E_2 on hCG day (pg/mL)	4,049 ± 775	2,860 ± 943	2,046 ± 668	$P<.05$[a]
Total no. follicles >14 mm	17 ± 5	10 ± 5	9 ± 4	$P<.05$[b]
hCG levels after hCG trigger (mIU/mL)	113 ± 27	229 ± 116	361 ± 210	$P<.05$[a]
Normalized hCG levels (mIU/mL)[c]	113 ± 27	115 ± 58	120 ± 70	Ns
No. oocytes retrieved	28 ± 12	15 ± 8	13 ± 7	$P<.05$[b]

Note: Data are reported as mean ± SD. Ns = not significant.

[a] All groups are different.

[b] 5,000-IU group different from 10,000-IU and 15,000-IU groups.

[c] Normalized to 5,000 IU.

Detti. BMI and larger follicles impact serum hCG level. Fertil Steril 2007.

a higher receptor affinity and a longer half-life (24 hours) as compared with endogenous LH, which has a half-life of only approximately 60 minutes (12). Because hCG has shown promising ovulation induction properties and because little of its pharmacokinetics is known, the aim of the current study was to identify the major determinants of the level of serum hCG levels after midcycle single-dose administration.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board at Wayne State University. In this retrospective study, we evaluated 115 consecutive women who underwent conventional IVF/intracytoplasmic sperm injection (ICSI) cycles from March 2003 to March 2005. All patients underwent controlled ovarian hyperstimulation with gonadotropins and GnRH-a for pituitary downregulation. Patients were started on oral contraceptives approximately 1 month before the stimulation. Gonadotropins (mainly recombinant FSH [r-FSH] and preparations containing an equal amount of FSH and LH) were administered from stimulation day 1 until the day of the hCG trigger, and GnRH-a was added when at least one follicle reached 14 mm in diameter and continued daily until the day of hCG ovulation triggering dose. The hCG was administered in a 5,000-IU, 10,000-IU, or 15,000-IU dose depending on the combination of number of follicles and estradiol level. In the presence of more preovulatory follicles and higher serum estradiol levels (≥3,000 pg/mL), a lower hCG dose would decrease the risk of ovarian hyperstimulation syndrome (OHSS). However, the minimum requirement to administer hCG was the presence of at least two follicles measuring >18 mm in diameter. In the presence of fewer ovarian follicles and lower serum estradiol levels, a higher hCG dose was administered (10,000 or 15,000 IU). We then measured the serum hCG level the day after the administration of exogenous hCG, about 10 to 14 hours after the intramuscular injection (7:30 PM to 12:30 AM, median time 9:30 PM). This approach allowed us to detect those patients who did not self-administer the intramuscular injection and cancel or delay the oocyte retrieval, thus eliminating the surgical risks of a procedure when the yield of obtaining mature oocytes would be poor and a high risk of no oocyte or immature oocytes exists (hCG triggers oocyte maturation with the completion of the first meiotic division).

To adjust for the exogenous hCG dose administered, the serum hCG concentration obtained the day after the hCG trigger was divided by 2 or 3 if the patient received 10,000 IU or 15,000 IU of hCG, respectively. This allowed us to evaluate the patients as if they all had received the normalized dose of 5,000 IU of hCG.

We performed Pearson product moment correlations and stepwise multiple regression analyses to determine which variables would influence the serum hCG level after a single administration. The variables evaluated were: age, body mass index (BMI, in kg/m^2), estradiol peak, number of follicles >14 mm, number of oocytes retrieved, length of stimulation, and length of GnRH-a administration in days. A significance level of $P<.05$ was considered statistically significant. All statistical analyses were conducted with SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL).

RESULTS

The demographics of the patients are described in Table 1. Of the 115 patients evaluated, an exogenous hCG dose of 5,000 IU was self-administered by 21 patients, 10,000 IU by 19 patients,

TABLE 2

Characteristics of the patients in whom OHSS developed.

Variable	No. 1[a]	No. 2[a]	No. 3[a]	No. 4[a]	No. 5[b]	No. 6[a]
Age (y)	38	36	35	25	30	30
Body mass index	27	36	33	24	22	28
No. days on antagonist	5	4	7	4	6	4
Length of stimulation (d)	12	12	12	11	10	10
E_2 on hCG day (pg/mL)	5,539	4,280	4,550	3,759	2,773	3,512
Total no. follicles >14 mm	19	12	19	29	11	18
hCG levels after hCG trigger (mIU/mL)	122	67	86	129	741[c]	68
No. oocytes retrieved	15	29	53	31	13	37

[a] Patients received 5,000-IU hCG dose for ovulation trigger.
[b] Patient received 15,000-IU hCG dose.
[c] Normalized hCG level was 247.

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and 15,000 IU by 75 patients. Six of 115 patients (5.2%) who developed OHSS and did not undergo embryo transfer were included in our analysis. Five of them received 5,000 IU hCG as ovulation trigger; they had a mean estradiol level of 4,069 pg/mL (3512 to 5539 pg/mL). One received 15,000 IU hCG when the estradiol peak was 2,773 pg/ml (Table 2).

As expected, serum hCG levels after the 15,000-IU triggering dose were higher than the levels after the two lower dosages ($P<.05$). After adjusting the serum hCG level for the dose administered, the Pearson correlation identified that BMI, total number of follicles >14 mm on the day of hCG administration, and total number of oocytes retrieved are all negatively correlated with the serum hCG level ($r = -0.54$, -0.22, and -0.21, respectively; $P<.05$).

Stepwise logistic regression identified BMI and total number of follicles >14 mm on the day of hCG administration as the only predictors of the hCG serum level ($R^2 = 0.30$), with the BMI representing the largest contributor (BMI $R^2 = 0.26$; $P<.001$; total number of follicles $R^2 = 0.04$, $P<.05$) (Fig. 1). In particular, a higher BMI and a higher number of larger follicles were related to a lower serum hCG after 10 to 14 hours. Patient age, estradiol peak, number of oocytes retrieved, length of stimulation, and length of GnRH-a administration in days were not correlated with the serum concentration.

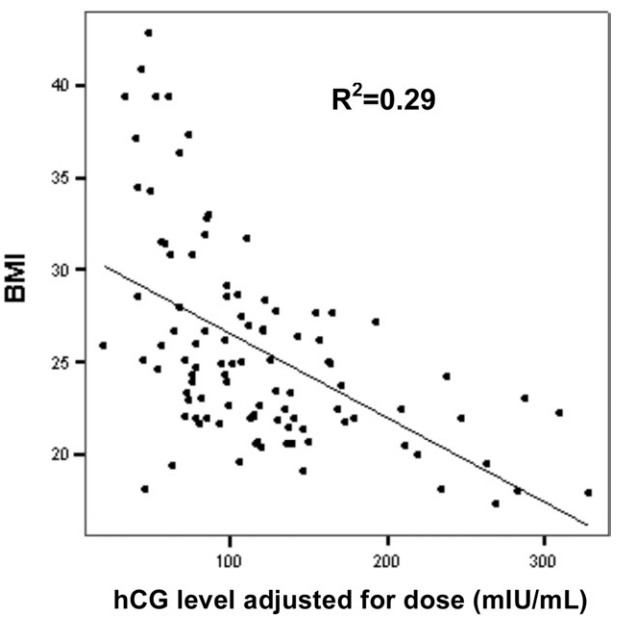
CONCLUSIONS

Patient BMI and total number of follicles >14 mm were the only predictors of the hCG concentration in the body when measured 10 t 14 hours after exogenous hCG administration. We did not evaluate serum hCG decrement over time because this was beyond the scope of our clinical inquiry. However, BMI likely reflects the volume of distribution, although other mechanisms such as modified enzymatic transportation and binding cannot be excluded in explaining this phenomenon. Our findings will help in deciding the correct hCG trigger dose based on the patient's BMI, because leaner patients will reach higher serum hCG levels than overweight patients with comparable ovulation induction characteristics; as previously suggested, this might make these women more susceptible to developing OHSS (13). Future studies will be needed to determine whether titration of the hCG trigger dose based on the patient's BMI and number of bigger follicles could help prevent the development of OHSS.

We do not have an explanation for why a more successful stimulation (i.e., higher number of follicles >14 mm in diam-

FIGURE 1

Scatterplot of adjusted hCG serum level and body mass index.



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eter) would be related to a lower hCG level after single-dose administration, even if in our results this accounts for a minimal relative risk ($R^2 = 0.04$). Moreover, a higher number of bigger follicles is strictly related to a higher serum estradiol level; although our study confirmed this highly significant correlation ($P<.001$), it is surprising that we failed to find a relationship between serum hCG concentration and estradiol level similar to the one shown for the total number of follicles >14 mm. In our study population, women with a higher number of bigger follicles (more than 10 follicles − mean) and a lower serum hCG concentration (<116 mIU/mL − mean) were also those with a greater BMI (26 ± 6 kg/m^2), compared with the BMI of the patients with <10 bigger follicles and a higher hCG concentration (23 ± 3 kg/m^2). We could speculate that BMI, being such a big predictor of the serum hCG concentration on its own, might falsely make the number of follicles >14 mm appear as another predictor in our analysis.

The purified gonadotropins that are used to induce follicle maturation may contain traces of hCG, which is naturally present in the postmenopausal urine from which the gonadotropins are extracted (14). In our analysis, we did not control for this parameter. However, even considering the long half-life of hCG compared with LH, the amount of serum hCG reached during ovulation induction would be very modest (and comparable among the patients) compared with the high dose used for ovulation trigger.

Early reports described the use of multiple hCG doses sequentially or overlapping the standard ovulation induction with gonadotropins (15). Recently there has been a revitalized interest in hCG function and its promising role in ovulation induction cycles. A pioneering study by Filicori et al. (11) on the use of hCG as the substance of choice for complete ovulation induction regimens described a single daily dose of 200 IU for the last 3 to 5 days of the cycle after pretreating the patients with standard regimens of recombinant FSH or of hMG for a few days until a threshold estradiol value and a fixed number of follicles reached 12 mm in diameter. The hCG daily dose was not titrated during the stimulation period, and it was followed by the administration of a standard ovulation-triggering hCG dose of 10,000 IU. The mean serum hCG level reached during the days of hCG administration was 8.1 ± 0.5 IU/L. The 200-IU daily hCG dose was arbitrarily chosen based on a previous prospective randomized study on ovarian stimulation with different hCG doses in various combinations with r-FSH after an initial stimulation with r-FSH alone (16). However, all of the patients in both studies were lean with minimal variation in the BMI (22.7 ± 0.3 kg/m^2, range 21 to 25 kg/m^2). Although in this study hCG was administered subcutaneously, it has been shown that this route gives analogous responses when compared with the intramuscular administration (17).

Our study shows that patients of different BMIs will have different serum hCG levels when treated with a single hCG dose. In a nonhomogeneous patient population, the final outcome of a fixed regimen could be very dissimilar, even considering the long half-life of hCG. In the United States, patient weight is more varied than it is in Europe, as can be readily envisioned by the BMI reported in our study (25 ± 5 kg/m^2, cumulative for the 3 groups of patients, range 17 to 42 kg/m^2). Knowing that the concentration of hCG in the body is dependent on the patient's BMI can help the endocrinologist in titrating the hCG trigger or daily dose when the patient population is not homogeneous.

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