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ASSISTED REPRODUCTION TECHNOLOGIES

Human chorionic gonadotropin serum levels following ovulation triggering and IVF cycle outcome

Yossi Mizrachi[1,2] · Eran Horowitz[1,2] · Jacob Farhi[1,2] · David Levran[1,2] · Arieh Raziel[1,2] · Ariel Weissman[1,2]

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Abstract

Purpose The clinical significance of serum hCG levels after ovulation triggering was studied previously with conflicting results. Our aim was to study the correlation of hCG levels on the day after ovulation triggering using recombinant hCG (r-hCG) with treatment outcome.

Methods A prospective observational study of all fresh IVF/ICSI cycles in a single medical center, between January 2015 and June 2016, was performed. hCG serum levels were obtained 10–12 h following ovulation triggering with 250 mcg r-hCG. Clinical and laboratory outcome parameters were compared between cycles with serum hCG above and below median level. A multivariate regression analysis was performed in order to study the association between hCG levels and live birth rate, after controlling for confounders.

Results Overall, 326 cycles were included. Median serum hCG level was 91.35 IU/L. hCG levels were lower as age and BMI were higher ($p = 0.004$, $p < 0.001$, respectively). The study groups did not differ with regard to clinical pregnancy rate ($p = 0.14$), live birth rate ($p = 0.09$), fertilization rate ($p = 0.45$), or metaphase II oocyte rate ($p = 0.68$). On multivariate regression analysis, hCG level was not associated with live birth (aOR 0.99, 95% CI 0.98–1.005), after controlling for patient's age and BMI.

Conclusions hCG levels on the day after ovulation triggering with 250 mcg r-hCG are inversely correlated with patient age and BMI. However, they are not correlated with any clinical or laboratory outcome parameter. Therefore, testing for hCG levels after ovulation induction seems futile and cannot be recommended.

Keywords Human chorionic gonadotropin · IVF · BMI · Outcome

Introduction

For more than five decades, human chorionic gonadotropin (hCG) has been widely used for triggering the final stage of follicular maturation in IVF and in ovulation induction treatment cycles [1]. Due to its high degree of homology with luteinizing hormone (LH), hCG efficiently mimics the mid-cycle LH surge, inducing ovulation, resumption of meiosis in the oocyte, and formation of the corpus luteum. Furthermore, hCG plays a critical role in the complex process of implantation, contributing to the receptivity of the endometrium [2]. It has been therefore postulated that serum levels of hCG following ovulation triggering may be correlated with reproductive outcome [3–6].

The clinical significance of serum hCG levels after ovulation triggering has been studied previously in a very limited manner, and conflicting results have been obtained. Studies have been conducted in two time points: either on the morning after hCG administration (12–14 h after triggering), or on the time of oocyte retrieval (after 34–36 h). Adding further to the confusion, both the subcutaneous (SC) and intramuscular (IM) routes, as well as recombinant and urinary preparations in different doses, have been used. While Zhou et al. [3] have found that higher levels of hCG 12 h after IM urinary hCG (u-hCG) administration were associated with a higher clinical pregnancy rate, Shapiro et al. [7] failed to find such a correlation. In addition, Matorras et al. [5] studied hCG levels 36 h after SC recombinant hCG (r-hCG) triggering and also found that they were not associated with treatment outcome.

✉ Yossi Mizrachi
mizrachi.yossi@gmail.com

[1] IVF Unit, Department of Obstetrics and Gynecology, The Edith Wolfson Medical Center, 62 Halochamim St, POB 58100, Holon, Israel

[2] Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel

The hCG dose and route of administration, as well as body mass index (BMI), have been previously recognized as affecting serum hCG levels following ovulation triggering [8–11]. High BMI was found to be correlated with lower post injection hCG serum concentrations [10, 12], as well as lower hCG concentrations, in follicular fluid at the time of oocyte retrieval [13].

Because of the limited and conflicting data available, the clinical significance of serum hCG levels post ovulation triggering and the way it is affected by the patients' BMI is currently unresolved. Since serum levels and bioavailability of hCG following ovulation triggering may be clinically relevant and have the potential to be personalized by individualization of the ovulatory dose as well as by supplemental dose adjustments, there is a definite interest in the subject. Our aim was to study the factors that influence hCG levels following ovulation triggering with special focus on BMI and the correlation between hCG serum levels on the day after ovulation triggering by r-hCG and clinical and laboratory outcome parameters.

Materials and methods

A prospective observational study of all IVF/ICSI cycles was conducted in a single university-affiliated medical center between January 2015 and June 2016. During that time, it was our standard policy to monitor our patients in the morning after ovulation triggering. Women were included in the study if they were under the age of 45 and underwent fresh IVF treatment with embryo transfer. Exclusion criteria included cycles using donor oocytes, preimplantation genetic diagnosis, banking or freeze-all cycles, dual triggering with hCG and gonadotropin-releasing hormone (GnRH) analogue, and triggering with doses other than 250 mcg r-hCG. Data were retrieved from the patients' medical records. The primary outcome measure was the live birth rate (LBR). Secondary outcomes included clinical pregnancy rate (CPR), defined as fetal cardiac activity on transvaginal sonography; number of oocytes retrieved; fertilization rate; metaphase II oocyte rate; and implantation rate. The institutional review board approved the study.

IVF protocols

Our IVF protocols have been previously described [14, 15]. Either the long GnRH agonist protocol with mid-luteal start, the short agonist, or the GnRH antagonist protocol was used. Controlled ovarian stimulation (COS) was performed using recombinant FSH (Gonal F, Merk Serono, Germany; or Puregon, MSD, USA) or highly purified urinary menopausal gonadotropins (Menopur, Ferring, Germany). Monitoring of follicular and endometrial growth and development consisted of serial transvaginal ultrasound scans and measurements of plasma estradiol (E2) and progesterone (P) levels. r-hCG (Ovitrelle 250 mcg, Merck-Serono) was administered when ≥ 2 follicles were 18 mm in diameter with serum E2 levels within the acceptable range for the number of mature follicles present. Transvaginal ultrasound-guided oocyte retrieval was performed 36 h after hCG administration under general anesthesia with a single-lumen 18 gauge needle.

After retrieval, oocytes were fertilized by either conventional insemination or intracytoplasmic sperm injection (ICSI), as indicated. Embryo transfer was performed 72 h after egg retrieval under ultrasound guidance. A single embryo transfer was preferred in young good prognosis patients, and up to four embryos could be transferred otherwise according to the guidelines of the Israeli Fertility Society. Luteal support was provided by vaginal P preparations (Utrogestan, Besins Iscovesco, France, Endometrin, Ferring, or Crinone, Merk-Serono) and oral E2 2 mg two times per day (Estrofem, Novo Nordisk).

Serum E2 and P were measured by means of the automated Elecsys Immunoanalyser (Roche Diagnostics, Mannheim, Germany). Intra-assay and inter-assay coefficients of variation were < 5 and < 10% for E2 and < 3 and < 5% for P, respectively. Serum hCG levels were measured using a commercial immunoassay test (hCG STAT, Fisher healthcare, USA). The detection limit of the test was 5 IU/L.

Statistical analysis

Statistical analysis was performed using SPSS software v23 (IBM, USA). Spearman's correlation coefficient test was used to study the correlation between hCG levels, age, and BMI. Clinical and laboratory outcome parameters were compared between cycles with hCG serum levels above and below median level. Continuous variables were compared using Student's *t* test. Categorical variables were compared using the chi-square test. A multivariate regression analysis was performed in order to study the association between hCG levels, CPR, and LBR, after controlling for confounders.

Using a preliminary analysis, we assumed that the LBR per transfer in women with low and high serum hCG levels would be 15 and 28%, respectively. Using these assumptions, together with a 5% alpha and using the chi-square test, we calculated that 156 subjects in each group would provide 80% power to detect a true, between-group difference of this size. Additional 7 patients were added to each group to preserve study power in the event of patient loss.

Results

During the study period, 326 treatment cycles met the inclusion criteria and had a valid serum hCG test available. Median serum hCG level was 91.35 IU/L (range 18–322 IU/L). The

median age of the patients was 37 (range 22–44). Fresh embryo transfer was performed in 273 (83.7%) cycles. Of these, a single embryo was transferred in 26.1% of cycles, two embryos were transferred in 38.3% of cycles, three embryos were transferred in 17.8% of cycles, and four embryos were transferred in 1.5% of cycles.

Serum levels of hCG did not differ between women who did and did not become pregnant (90.8 ± 44.2 vs. 99.0 ± 43.9 IU/L; $p = 0.20$, respectively). Serum hCG levels were inversely correlated with patient's BMI (Spearman's test, $r = -0.50$, $p < 0.001$) (Fig. 1). Although statistically significant, the correlation between hCG levels and patient's age was weak (Spearman's test, $r = -0.15$, $p = 0.006$). Compared to women with hCG levels above median level, women with hCG levels below median level were older (36.3 vs. 34.5 years, respectively, $p = 0.004$) and had a higher BMI (26.8 vs. 22.3, respectively, $p < 0.001$). They also had a slightly lower progesterone level on the day of ovulation triggering (Table 1). The number of oocytes obtained, the rate of mature metaphase II (MII) oocytes, fertilization rate, pregnancy rate, and live birth rate did not differ between the study groups (Table 2).

On multivariate logistic regression analysis, hCG levels were not associated with CPR (adjusted OR 0.99, 95% CI 0.98–1.004, $p = 0.28$), or LBR (adjusted OR 0.99, 95% CI 0.98–1.005, $p = 0.43$), after controlling for patient's age, BMI, and infertility diagnosis (Table 3). As most cycles included a GnRH antagonist protocol (66.9% of cycles), we performed a post hoc analysis examining only these cycles. hCG levels were not associated with LBR (aOR 1.001, 95% CI 0.99–1.01) or CPR (aOR 0.99, 95% CI 0.99–1.008), when analyzing only GnRH antagonist cycles, and adjusting for the above variables.

Discussion

The results of our study indicate that hCG levels on the day after ovulation triggering with 250 mcg of r-hCG are inversely correlated with patient's age and BMI, but have no correlation with any of the reproductive outcome variables that were studied.

Although hCG has been commercially available for more than 50 years, few studies have been performed to address dose optimization in female patients [6, 16–18]. While many studies in reproductive medicine have been carried out on hormone characteristics of the day of hCG administration, "the morning after" has been clearly neglected and studied in a very limited way. For example, it took many years and multiple studies with conflicting results, until the adverse effects of late follicular phase P elevation have been fully recognized [19]. Likewise, "the morning after" (or 12 h after triggering) should be further studied, as is an excellent time point to assess the ongoing effects of the ovulatory trigger. If clinically significant correlations between serum hCG levels on "the morning after" and reproductive outcome are found, additional doses of hCG might be given at this time point to optimize its serum levels. This is the reason why "the morning after" or 12 h following the hCG trigger was chosen in our study design.

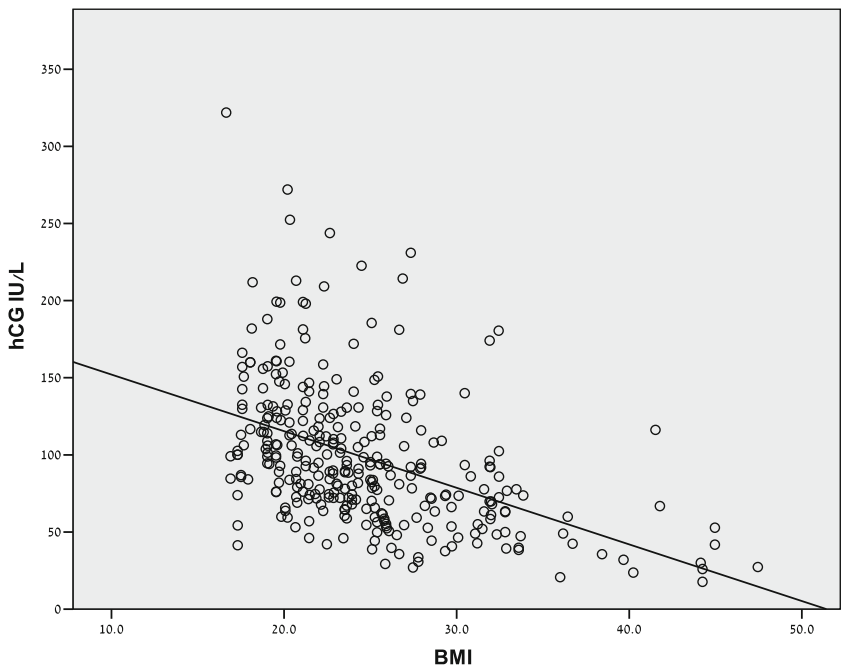

Fig. 1 Correlation between hCG levels on the day after ovulation triggering and patients BMI ($r = -0.50$, $p < 0.001$)

Table 1 Baseline characteristics of treatment cycles with hCG serum levels above and below median level

	hCG level below median < 91.35 IU/L $n = 163$	hCG level above median > 91.35 IU/L $n = 163$	p value
Age (years)	36.3 ± 5.6	34.5 ± 5.4	0.004
BMI (kg/m^2)	26.8 ± 6.1	22.3 ± 3.9	< 0.001
Infertility diagnosis			
Male factor	50 (30.7)	40 (24.5)	0.21
Mixed male and female factors	35 (21.5)	32 (19.6)	0.68
Low ovarian reserve	29 (17.8)	23 (14.1)	0.36
Unexplained	31 (19.0)	24 (14.7)	0.30
Mechanical factor	7 (4.3)	34 (20.9)	< 0.001
No. of previous IVF cycles	1.78 ± 1.6	1.75 ± 1.1	0.93
Infertility duration (years)	2.7 ± 2.0	2.6 ± 1.9	0.52
AMH < 1 ng/mL	93 (57.1)	90 (55.2)	0.73
E2 level on triggering day (pmol/L)	5897 ± 2774	5974 ± 3178	0.81
P level on triggering day (nmol/L)	2.7 ± 1.4	3.0 ± 1.7	0.04
Endometrium thickness on triggering day (mm)	9.8 ± 2.3	9.4 ± 2.3	0.06

Data are presented as mean ± SD, or n (%)

AMH anti-mullerian hormone, *E2* estradiol, *P* progesterone

The clinical significance of hCG serum levels after ovulation triggering has been studied previously with inconsistent results. Zhou et al. [3] have found that higher levels of hCG 12 h after the administration of 10,000 IU of u-hCG were associated with a higher clinical pregnancy rate. Salha et al. [10] have demonstrated a significant association between serum hCG concentration 35–37 h after the IM administration of 5000 IU of u-hCG and the number of oocytes aspirated. In contrast, Wikland et al. [6] prospectively randomized patients to receive 5000 or 10,000 IU u-hCG SC or IM for ovulation triggering and found no difference in any of the reproductive outcome parameters studied irrespective of the dose or route of administration. Shapiro et al. [7] retrospectively evaluated the correlation between serum hCG levels 12–16 h after IM u-hCG administration and reproductive outcome, including the incidence of ovarian hyperstimulation syndrome (OHSS). They used an individualized approach in prescribing the ovulatory dose of hCG, using doses ranged from 2500 to 20,000 IU, depending on each patient's weight and OHSS risk. No significant relationships were observed between

Table 2 Treatment outcome parameters in cycles with hCG serum levels above and below median level

	hCG level below median < 91.35 IU/L $n = 163$	hCG level above median > 91.35 IU/L $n = 163$	p value
No. of oocytes retrieved	7.7 ± 4.9	8.2 ± 5.4	0.35
No. of metaphase II oocytes (ICSI cycles)	5.3 ± 3.9	5.7 ± 4.1	0.44
No. of fertilized oocytes	3.9 ± 3.1	4.5 ± 3.7	0.10
Fertilization rate	0.52 ± 0.28	0.55 ± 0.28	0.45
Metaphase II oocyte rate	0.74 ± 0.28	0.75 ± 0.24	0.68
Cycles reaching embryo transfer (%)	138 (84.7)	135 (82.8)	0.65
Implantation rate	0.15 ± 0.29	0.14 ± 0.31	0.73
Clinical pregnancy rate per cycle (%)	34 (21.4)	24 (15.1)	0.14
Clinical pregnancy rate per transfer, n/N (%)	34/138 (24.6)	24/135 (17.8)	0.16
Live birth rate per cycle (%)	31 (19.5)	20 (12.6)	0.09
Live birth rate per transfer, n/N (%)	31/138 (22.5)	20/135 (14.8)	0.10

Data are presented as mean ± SD, or n (%)

Table 3 Factors associated with live birth rate and clinical pregnancy rate—multivariate regression analysis

	aOR (95% CI) for LBR	aOR (95% CI) for CPR
Serum hCG level (IU/L)	0.99 (0.98–1.005)	0.99 (0.98–1.004)
Age (years)	0.87 (0.81–0.92)	0.87 (0.82–0.92)
BMI	1.08 (1.01–1.14)	1.05 (0.99–1.11)
Infertility diagnosis	0.94 (0.78–1.13)	0.94 (0.79–1.12)

Odds ratios are adjusted for the variables listed in the table

aOR adjusted odds ratio, *CI* confidence interval, *LBR* live birth rate, *CPR* clinical pregnancy rate

serum hCG and the proportion of follicles yielding oocytes, fertilization rate, blastulation rate, or the probabilities of embryo transfer, implantation, or clinical pregnancy. The incidence of OHSS (all types) and OHSS requiring transvaginal paracentesis was predicted by hCG concentration. Al-Hassan et al. [4] obtained three samples of blood: 12 h, 36 h (during oocyte retrieval), and 84 h (at the time of ET) following 10,000 IU of u-hCG IM administration to 404 patients. The percentage of MII oocytes at different blood levels ranged from 84 to 88%, and no significant increase in percentage of MII oocytes in association with an increasing serum hCG concentration was found. Likewise, Matorras et al. [5] have found that hCG levels 36 h after the SC administration of 250 mcg of r-hCG were not associated with treatment outcome.

It has been previously shown that there is a negative correlation between hCG levels and BMI, after ovulation triggering with urinary hCG [3, 9, 12, 20] and r-hCG [5]. In contrast, Stefanis et al. [21] measured serum hCG concentrations at 12 and 36 h following a SC injection of 5000 IU u-hCG in correlation to BMI in 149 patients undergoing IVF/ICSI. There was no correlation between BMI and hCG levels at 12 and 36 h following administration. In addition, no correlation was found between serum hCG levels and the number of oocytes retrieved or fertilized. While there are numerous reports suggesting an adverse effect of increased BMI on reproductive outcome [22, 23], whether this effect is mediated through post triggering serum hCG levels has not been specifically investigated.

Higher BMI likely reflects higher volume of distribution, resulting in lower serum levels. Chan et al. [9] have demonstrated that 10,000 IM dosing of u-hCG provided better bioavailability than SC dosing, but bioavailability was significantly less in obese women than in non-obese women. Salha et al. [10] compared serum hCG levels at the time of oocyte retrieval following the IM administration of 5000 u-hCG in 50 normal (18–25 kg/m^2) and 50 high (≥ 26 kg/m^2) BMI patients. Patients with a high BMI had a significantly lower mean serum hCG concentration compared with controls, as well as significantly fewer oocytes aspirated. They also demonstrated a significant decrease in the oocyte:follicle ratio compared with controls, and the fertilization rate and clinical pregnancy rate per cycle were also lower in patients with high BMI compared with those with normal BMI. It was suggested that high BMI is detrimental to IVF treatment outcome and has an important influence on the distribution and metabolism of hCG, although the relative roles of hCG levels and BMI in the outcome have not been clearly delineated.

In the majority of studies mentioned above, u-hCG preparations were used. Urinary hCG preparations were first available and were associated with a number of disadvantages, including an uncontrolled source, lack of purity, and increased batch-to-batch variation in activity that may affect clinical results [24, 25]. Furthermore, the low purity of urinary preparations restricted them mostly to IM injections. Recombinant hCG formulas have the advantage of high purity, resulting less adverse effects and no risk of disease transmission, and excellent batch-to-batch consistency compared to urinary hCG [26]. Subcutaneous self-administration of r-hCG became possible, thus increasing patients' convenience and compliance. Studies comparing doses of 500 and 250 mcg of r-hCG have found a similar number of oocytes and MII oocytes retrieved, but a higher number of fertilized oocytes and cleaved embryos with the higher dose [17, 18]. Overall, hormone dynamics following r-hCG administration have been rarely studied, and the available information is therefore fragmentary and incomplete [5]. With the growing use of r-hCG in clinical practice, there is a clear need for more such data.

Our results are in contrast with those reported by Zhou et al. [3]. In their study, hCG levels were obtained 12 h after ovulation triggering, and clinical pregnancy rate was significantly higher across increasing quartiles of hCG. This discrepancy may result from inherent differences in study design and patient population. In their study, Zhou et al. included a selected group of good prognosis patients, who were ≤ 35 years old, suffered from tubal factor infertility, had a normal ovarian reserve, and had ≥ 2 good-quality embryos available for transfer. In addition, 10,000 IU of IM urinary hCG were used rather than SC r–hCG. Nevertheless, taking into account the differences in the study populations and the overall limited size of both studies, the conflicting results simply call for more in-depth observations into "the morning after."

How can the results of our study be explained? We hypothesize that beyond a certain threshold, even very low levels of serum hCG are sufficient to induce effective oocyte maturation and ovulation. Thus, higher serum levels do not improve

treatment outcome. This is supported by a previous study in which hCG levels were obtained before oocyte retrieval after triggering with u-hCG. Low hCG levels (< 100 IU/L) were as effective as higher levels regarding the percentage of MII oocytes [27]. In our study, the lowest serum hCG level after which a pregnancy was achieved was 24.0 IU/L.

Our cohort consists of relatively poor prognosis patients with a mean of 1.7 ± 2.4 previous failed attempts. According to the Israeli heath care system, poor prognosis patients have an almost unlimited access to IVF as long as embryos are available for transfer, irrespective of the number of previous failed cycles. This along with the high age range (22–44 years) explains the relatively low implantation rate, CPR, and LBR that we have observed.

Our study has several limitations. First is the relatively small sample size. The LBR per transfer was only 15.6%, considerably lower than we had assumed. Thus, we were underpowered to detect this difference (43% power). Second, we have included a heterogeneous group of patients with a wide range of indications for treatment, age groups, and past treatment histories. Nevertheless, by means of multivariate logistic regression analysis, we controlled for these baseline differences and the results failed to show a correlation between serum hCG levels and reproductive outcome. The strengths of the current study include the inclusion of women with a wide age range including those with advanced maternal age. Most studies have not included patients over the age of 40. Moreover, we also include live birth rates in our report, which are lacking from most previous studies.

In conclusion, hCG levels on the day after ovulation triggering with SC 250 mcg r-hCG are inversely correlated with patient age and BMI. However, they are not correlated with any substantial clinical or laboratory outcome parameter. From a clinical point of view, neither routine testing for serum hCG levels after ovulation triggering nor hCG supplementation based on the testing results can be recommended at the moment. The paucity of data on hormone characteristics following the ovulatory trigger highlights the need for more studies on this topic.

Author contribution All authors contributed substantially to the concept and design, analysis and interpretation of data, drafting, and revisions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not requested by our LRB, because during the study period it was our standard policy to monitor hCG serum level in the morning after ovulation triggering.

References

1. Gemzell C. Induction of ovulation with human gonadotropins. Recent Prog Horm Res. 1965;21:179–204.
2. Tsampalas M, Gridelet V, Berndt S, Foidart JM, Geenen V, Perrier d'Hauterive S. Human chorionic gonadotropin: a hormone with immunological and angiogenic properties. J Reprod Immunol. 2010;85(1):93–8. https://doi.org/10.1016/j.jri.2009.11.008.
3. Zhou J, Wang S, Wang B, Wang J, Chen H, Zhang N, et al. The value of HCG serum concentrations after trigger in predicting pregnancy and live birth rates in IVF-ICSI. Reprod BioMed Online. 2015;30(6):667–73. https://doi.org/10.1016/j.rbmo.2015.02.013.
4. al-Hassan S, Fishel S, Fleming S, Thornton S. Low plasma levels of hCG after 10,000-IU hCG injection do not reduce the number or maturation of oocytes recovered in patients undergoing assisted reproduction. J Assist Reprod Genet. 1998;15(10):583–6.
5. Matorras R, Meabe A, Mendoza R, Prieto B, Ramon O, Mugica J, et al. Human chorionic gonadotropin (hCG) plasma levels at oocyte retrieval and IVF outcomes. J Assist Reprod Genet. 2012;29(10):1067–71. https://doi.org/10.1007/s10815-012-9826-7.
6. Wikland M, Borg J, Forsberg AS, Jakobsson AH, Svalander P, Waldenstrom U. Human chorionic gonadotrophin self-administered by the subcutaneous route to induce oocyte maturation in an in-vitro fertilization and embryo transfer programme. Hum Reprod. 1995;10(7):1667–70.
7. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Ross R, Morris S. Effects of the ovulatory serum concentration of human chorionic gonadotropin on the incidence of ovarian hyperstimulation syndrome and success rates for in vitro fertilization. Fertil Steril. 2005;84(1):93–8. https://doi.org/10.1016/j.fertnstert.2004.12.053.
8. Weissman A, Lurie S, Zalel Y, Goldchmit R, Shoham Z. Human chorionic gonadotropin: pharmacokinetics of subcutaneous administration. Gynecol Endocrinol. 1996;10(4):273–6.
9. Chan CC, Ng EH, Chan MM, Tang OS, Lau EY, Yeung WS, et al. Bioavailability of hCG after intramuscular or subcutaneous injection in obese and non-obese women. Hum Reprod. 2003;18(11):2294–7.
10. Salha O, Dada T, Sharma V. Influence of body mass index and self-administration of hCG on the outcome of IVF cycles: a prospective cohort study. Hum Fertil (Camb). 2001;4(1):37–42.
11. Shah DK, Missmer SA, Correia KF, Ginsburg ES. Pharmacokinetics of human chorionic gonadotropin injection in obese and normal-weight women. J Clin Endocrinol Metab. 2014;99(4):1314–21. https://doi.org/10.1210/jc.2013-4086.
12. Elkind-Hirsch KE, Bello S, Esparcia L, Phillips K, Sheiko A, McNichol M. Serum human chorionic gonadotropin levels are correlated with body mass index rather than route of administration in women undergoing in vitro fertilization–embryo transfer using human menopausal gonadotropin and intracytoplasmic sperm injection. Fertil Steril. 2001;75(4):700–4.
13. Carrell DT, Jones KP, Peterson CM, Aoki V, Emery BR, Campbell BR. Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome. Reprod BioMed Online. 2001;3(2):109–11.
14. Weissman A, Farhi J, Royburt M, Nahum H, Glezerman M, Levran D. Prospective evaluation of two stimulation protocols for low responders who were undergoing in vitro fertilization-embryo transfer. Fertil Steril. 2003;79(4):886–92.

15. Tannus S, Weissman A, Boaz M, Horowitz E, Ravhon A, Golan A, et al. The effect of delayed initiation of gonadotropin-releasing hormone antagonist in a flexible protocol on in vitro fertilization outcome. Fertil Steril. 2013;99(3):725–30. https://doi.org/10.1016/j.fertnstert.2012.11.020.
16. Abdalla HI, Ah-Moye M, Brinsden P, Howe DL, Okonofua F, Craft I. The effect of the dose of human chorionic gonadotropin and the type of gonadotropin stimulation on oocyte recovery rates in an in vitro fertilization program. Fertil Steril. 1987;48(6):958–63.
17. Chan CC, Ng EH, Tang OS, Yeung WS, Lau EY, Ho PC. A prospective, randomized, double-blind study to compare two doses of recombinant human chorionic gonadotropin in inducing final oocyte maturity and the hormonal profile during the luteal phase. J Clin Endocrinol Metab. 2005;90(7):3933–8. https://doi.org/10.1210/jc.2004-2169.
18. Chang P, Kenley S, Burns T, Denton G, Currie K, DeVane G, et al. Recombinant human chorionic gonadotropin (rhCG) in assisted reproductive technology: results of a clinical trial comparing two doses of rhCG (Ovidrel) to urinary hCG (Profasi) for induction of final follicular maturation in in vitro fertilization-embryo transfer. Fertil Steril. 2001;76(1):67–74.
19. Venetis CA, Kolibianakis EM, Bosdou JK, Tarlatzis BC. Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles. Hum Reprod Update. 2013;19(5):433–57. https://doi.org/10.1093/humupd/dmt014.
20. Detti L, Mitwally MF, Rode A, Yelian FD, Kruger M, Diamond MP, et al. Serum human chorionic gonadotropin level after ovulation triggering is influenced by the patient's body mass index and the number of larger follicles. Fertil Steril. 2007;88(1):152–5. https://doi.org/10.1016/j.fertnstert.2006.11.124.
21. Stefanis P, Das S, Barsoum-Derias E, Kingsland C, Lewis-Jones I, Gazvani R. Relationship between serum human chorionic gonadotrophin levels and body mass index in women undergoing in vitro fertilisation cycles. Eur J Obstet Gynecol Reprod Biol. 2007;132(2):204–8. https://doi.org/10.1016/j.ejogrb.2006.08.017.
22. Provost MP, Acharya KS, Acharya CR, Yeh JS, Steward RG, Eaton JL, et al. Pregnancy outcomes decline with increasing recipient body mass index: an analysis of 22,317 fresh donor/recipient cycles from the 2008–2010 Society for Assisted Reproductive Technology Clinic Outcome Reporting System registry. Fertil Steril. 2016;105(2):364–8. https://doi.org/10.1016/j.fertnstert.2015.10.015.
23. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod BioMed Online. 2011;23(4):421–39. https://doi.org/10.1016/j.rbmo.2011.06.018.
24. Penarrubia J, Balasch J, Fabregues F, Creus M, Civico S, Vanrell JA. Recurrent empty follicle syndrome successfully treated with recombinant human chorionic gonadotrophin. Hum Reprod. 1999;14(7):1703–6.
25. Zegers-Hochschild F, Fernandez E, Mackenna A, Fabres C, Altieri E, Lopez T. The empty follicle syndrome: a pharmaceutical industry syndrome. Hum Reprod. 1995;10(9):2262–5.
26. Ludwig M, Doody KJ, Doody KM. Use of recombinant human chorionic gonadotropin in ovulation induction. Fertil Steril. 2003;79(5):1051–9.
27. Stelling JR, Chapman ET, Frankfurter D, Harris DH, Oskowitz SP, Reindollar RH. Subcutaneous versus intramuscular administration of human chorionic gonadotropin during an in vitro fertilization cycle. Fertil Steril. 2003;79(4):881–5.