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Human chorionic gonadotropin levels in serum and follicular fluid are correlated with body mass index rather than the route of administration of purified hCG in ART cycles

Aim: To investigate hCG levels in follicular fluid and serum after intramuscular (IM) or subcutaneous (SC) administration of purified hCG, and their association with oocyte maturation and body mass index (BMI) in women undergoing IVF-ET.

Materials and Methods: The study included 160 infertile women that were recruited between April and June 2007. Standard-dose long IVF protocols were used for ovulation induction. SC or IM injections were used to administer hCG. BMI, oocyte maturity, and serum and follicular fluid hCG levels were the main outcome measurements.

Results: hCG levels in serum and follicular fluid in the 2 groups were similar. A negative correlation was observed between BMI and intrafollicular serum hCG levels. Mature oocyte counts were similar in the 2 groups. No correlation was observed between BMI and oocyte maturation. A negative correlation between BMI, and serum and follicular fluid hCG levels was more prominent in the IM group than in the SC group. Pregnancy rates were lower in the IM group.

Conclusions: Similar hCG levels were observed in the 2 groups. SC administration should be preferred over IM injection, as it is less painful for the patient and is easily administered. Serum and follicular fluid hCG levels were correlated with BMI, rather than the route of hCG administration.

Key Words: Ovulation induction, IVF cycles, purified hCG, BMI, SC injection of hCG

ART sikluslarında, intrafolliküler ve serum hCG Düzeyleri, purifiye hCG'nin veriliş yolundan çok hastaların vücut–kitle indeksi ile koreledir

Amaç: IVF-ET uygulanan hastalarda intramuskuler (IM) veya subkutan (SC) uygulanan pürifiye human koryonik gonodotropin`in (hCG) serum ve follikuler sıvı düzeylerinin oosit matürasyonu ve vücut kitle indeksi (body mass index - BMI) ile korelasyonunu değerlendirmektir.

Yöntemler: Nisan - Haziran 2007 tarihleri arasında Yardımcı Üreme Teknikleri Ünitesine başvuran 160 infertil kadın çalışmaya alındı.Tüm indüksiyon protokollerinde standart doz uzun protokol uygulandı. Ovulasyonu tetiklemek amacıyla alt abdomene SC veya kalçadan IM yolla hCG uygulandı. İntra folliküler ve serum hCG düzeyleri, oosit matüritesi ve BMI takip parametreleri olarak belirlendi.

Bulgular: IM ve SC grupların serum ve intrafolliküler hCG düzeylerinde fark izlenmedi. BMI ile serum ve intrafolliküler hCG düzeyleri arasında negatif korelasyon izlendi.Her iki grupta benzer düzeyde matür oosit izlendi. BMI ile oosit matürasyonu arasında korelasyon izlenmedi. BMI ile serum ve intrafolliküler hCG düzeyleri arasındaki negatif korelasyon IM grupta daha yüksek olarak izlendi. IM grup SC gruptan daha düşük gebelik oranlarına sahipti.

Sonuç: IM ve SC grupları arasında hCG düzeyleri yönünden benzer sonuçlar elde edilmiştir. SC yol kulanım kolaylığı ve daha az ağrılı olması nedeniyle hastalar için tercih sebebi olabilir. İntra folliküler ve serum hCG düzeyleri ilacın kullanım seklinden çok BMI ile koreledir.

Anahtar Sözcükler: Ovulasyon indüksiyonu, IVF siklusları, pürifiye hCG, vücut kitle indeksi, subkutan hCG enjeksiyonu

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Introduction

The mid-cycle luteinizing hormone (LH) surge is necessary for maturation of the oocyte and initiation of follicular luteinization. During IVF, a supra-physiological dose (10,000 IU) of hCG is given to mimic the effects of the natural LH surge. The administration of hCG at the end of a stimulation phase of gonadotropins triggers maturation of the cumulus-oocyte complex and allows the resumption of meiosis in the oocyte. Decreased periovulatory hCG concentrations are reported to be associated with lower fertilization rates (1). The purified form of hCG is usually given via the intramuscular (IM) route, but subcutaneous (SC) administration has also been described (2).

In fact, SC administration of hCG has been used in both Europe and North America for ovulation induction and IVF treatment. The SC route of administration, which allows self-administration by the patient, has previously been used (3). This is especially relevant when hCG administration, which is usually timed, is to be given late at night and nursing staff must be available outside normal office hours to administer an IM injection.

Drug distribution and metabolism in the body are dependent on the amount of adipose tissue, as well as the route of administration and rate of plasma clearance (4). The pharmacokinetic behavior of hCG may also be affected by obesity. In general, a larger distribution volume results in a lower serum concentration (5). The body mass index (BMI) is widely used in epidemiological studies as a good indicator of adiposity (6). In a prospective cohort study, Salha et al. concluded that a high BMI is detrimental to the success of IVF treatment and has a significant influence on the distribution and metabolism of hCG (7). Elkind-Hirsch et al. also reported that the highest levels of hCG were measured in women with the lowest BMI (3).

Although the pharmacokinetics following both routes of administration have been compared (3,6,8-10), the results obtained are inconsistent. Studies to date have been inconclusive as to the effect of BMI on serum concentrations of hCG in predicting the outcome of IVF treatment, in terms of biochemical and clinical pregnancy rates (4).

The aim of the present prospective study was to evaluate and compare the effects of SC and IM administration of hCG on serum and follicular fluids hormone levels, oocyte maturation, and IVF outcome, and their association with BMI in women undergoing IVF-ET using r-FSH and ICSI.

The study was based on the following questions:

1. Is there any difference in serum and follicular fluid hCG levels between IVF patients that receive purified hCG via the IM and SC route (Pregynl 10,000 IU) to stimulate ovulation?

2. Does the administration of hCG via IM and SC routes have any effect on parameters such as oocyte maturation, fertilization rate, embryo grade, and pregnancy outcome?

3. Is there any correlation between BMI, and serum and follicular fluid hCG levels in terms of drug distribution?

4. Is SC administration of hCG preferable in terms of patient compliance and ease of administration, and are there potential side-effects?

Methods

The study included 113 women aged 19-39 years recruited from the Zekai Tahir Burak Women's Hospital Assisted Reproduction Clinic that were undergoing the first or second IVF cycle between April 2007 and June 2007. Infertility among the patients was attributable to tubal factors (including endometriosis) (n = 13), unexplained infertility (n = 64), sub-fertile male factor infertility (n = 36) (≥ 5 total progressive motile spermatozoa per milliliter). Ethical approval was obtained from the local research ethics committee prior to commencement of the study and written informed consent was obtained from all the participants.

The exclusion criteria were as follows:

- Patients older than 39 years old;
- Patients with severe male factor infertility (< 5 total progressive motile spermatozoa per milliliter and allowing for TESE);
- Patients with an endocrine disorder (hyperthyroidism or hypothyroidism, hyperprolactinemia, or premature ovarian failure);

- Diminished ovarian reserve (FSH > 10 IU/ml);
- Any evidence of any clinically relevant systemic disease (e.g., IDDM);
- More than 3 previous failed IVF cycles or an IVF cycle canceled because of poor response to gonadotropins;
- Prior documentation of intolerance or allergy to any gonadotropin;
- A uterine anomaly or uterine fibroids and hydrosalpinges.

Superovulation Protocol (Figure 1)

All patients were pretreated with 50 mg estradiol + 500 mg norgestrel as oral contraceptive (Desolett, Schering-Plough) for 18 days, starting day 3 of the cycle. Pituitary suppression with a GnRH-agonist–Lucrin flakon (Abbott, Cedex, İstanbul)–was initiated on cycle day 18 at the dose of 1 mg/day SC injection into the thigh or arm. On day 2 of menses a baseline ultrasound (US) was performed to document that the ovaries were quiescent. Documentation of pituitary down-regulation was indicated by an estradiol level < 50 pg/ml and an LH level < 5 IU/ml.

The stimulation cycle began by using r-FSH (Gonal-F, Serono, İstanbul) at the dose of 225 IU/day, which was administered for 3 days. After starting r-FSH, the Lucrin flakon dose was decreased to 0.5 mg/day (Figure 1). Estradiol monitoring and US were performed according to standard IVF clinical practice. When a minimum of 3 follicles exceeded 16 mm in average diameter, an ovulatory dose of purified hCG ((Profasi 5000 IU, Serono, İstanbul) was given by IM or SC injection to all the patients (Figure 1).

Subjects were assigned, using a computer-generated random numbers table, to receive IM or SC hCG on the day after the last dose of gonadotropins. The SC injection of hCG was self-administered in the lower abdomen with a 5/8-inch 27-gauge needle. The volume of diluent was 1 ml for both the SC and IM injections. Vaginal oocyte retrieval was performed under US guidance 36 h after hCG injection. The oocytes were then fertilized using ICSI technology.

All serum samples and follicular fluids were collected on the same day as oocyte retrieval. Follicular fluid was collected from the first mature follicle aspirated, using media-free collection tubes. The number of cells of each embryo and embryo qualities were documented. Embryos were transferred 3 days after retrieval and a maximum of 3 embryos were replaced into each patient's uterus. Luteal phase support was prescribed vaginally beginning on the day after egg retrieval (Crinone 8%; Serono, İstanbul, 400 mg/day) and continued until 14 days after retrieval, at which time a quantitative measurement of the hCG level was obtained.

Data regarding the number of oocytes obtained, serum hCG level, follicular fluid hCG level, fertilization rate, number of embryos transferred, pregnancy rate (+ hCG/ET), and hCG ratio (follicular fluid hCG/serum hCG) were recorded for each patient. BMI was calculated for each patient using her weight and height (kg/m^2).

Hormone Assays

Serum and follicular fluid aspirates were stored at –20 °C after 10 min of centrifugation at 3000 RPM. Estradiol and hCG levels were measured using an automated, electrochemiluminescence (ECLIA E-

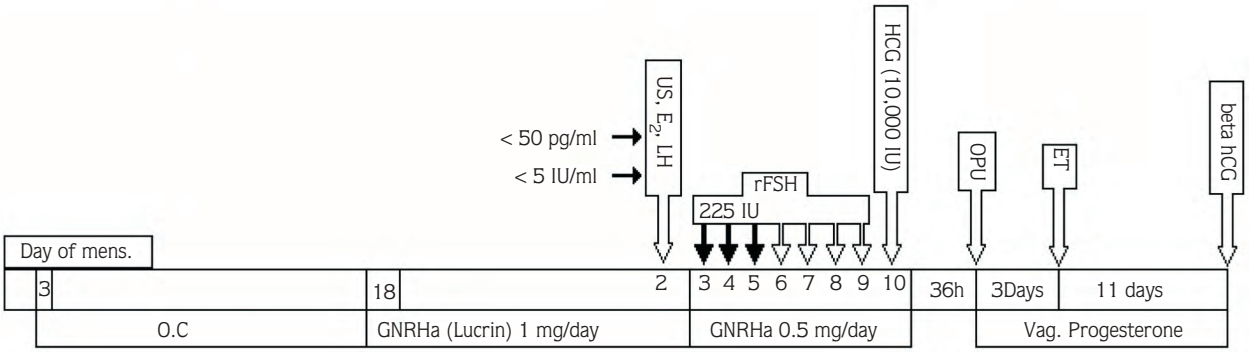

Figure 1.Superovulation protocol.

170, ROCHE) system with a sensitivity for hCG < 0.1 mIU/ml and linear interassay precision of 0.1-10,000 mIU/ml.

Statistical Analyses

To compare differences in age, BMI, hormone measurements (serum hCG 36 h after administration, serum estradiol levels on the day of hCG measurement), duration and total r-FSH treatment dose, number of oocytes retrieved, and oocyte maturation between the SC and IM groups, unpaired t tests were used. Spearman's and Pearson's product-moment correlation tests were used to determine the relationships between BMI, and serum and follicular hCG concentration, and then linear regression analysis was used for positive correlations. The chi-squared test was used to determine the difference between the presence and absence of outcome variables (e.g., clinical pregnancy). A P value < 0.05 was regarded as statistically significant.

Results

The IM group contained 56 women and 57 women were in the SC group. Baseline and cycle characteristics in the 2 groups are depicted in Table 1. Mean age and mean BMI were similar in the 2 groups (mean age: 30 years; mean BMI: 25.5). All BMIs were between 19 and 36. There were no significant differences between the groups in terms of cycle length, number of antral follicles, total gonadotropin usage, peak E_2 level before hCG injection, number of oocytes retrieved, percentage of oocytes with normal fertilization, or pregnancy rates (Table 1).

Serum and follicular hCG levels in the SC group were higher than in the IM group, but the differences were not significant (279.3 ± 231. vs. 222.4 ± 103.3 mIU/ml, P = 0.10 and 151.3 ± 108.2 vs. 134.9 ± 85.4 mIU/ml, P = 0.37, respectively). With regard to the ratio of follicular fluid hCG level to serum hCG level, there was not a significant difference between the pregnant (P = 0.63) and non-pregnant patients (0.58) (P = 0.417).

A statistically significant difference (P = 0.14) was not observed between the pregnancy rates in the IM group (35.7%) and the SC group (49.1%) (Table 1).

A negative correlation between BMI, and intrafollicular and serum hCG levels (r = –0.27, r = –0.24) was observed in all the patients in both groups.

Table 1. Basal hormone levels and demographic characteristics of the patients.

Baseline and cycle characteristics between groups				
Variable	IM (n=56)	SC (n = 57)	(p)	(t)
Age (years)	30.0 ± 5.4	30.6 ± 4.7	0.571	–0.6
BMI (kg/m^2)	25.4 ± 4.0	25.6 ± 3.0	0.572	–0.6
Duration of infertility (years)	7.8 ± 5.0	9.5 ± 5.2	0.843	–0.2
Baseline E^2 levels (pg/ml)	45.7 ± 18.6	41.2 ± 12.7	0.500	–0.7
Baseline FSH levels (mIU/ml)	6.7 ± 1.9	6.9 ± 1.9	0.499	–0.7
Total number of antral follicles	9.4 ± 4.1	10.4 ± 4.1	0.089	–1.7
Duration of r-FSH (d)	9.6 ± 1.3	9.7 ± 1.7	0.089	–1.7
Total dose of r-FSH (IU)	2349.9 ± 1059.3	2266.4 ± 930.8	0.845	–0.2
Serum E_2 (pg/ml) day of hCG	2182.4 ± 913.2	2132.9 ± 818.8	0.844	–0.2
Serum hCG levels (mIU/ml) on day of OPU	222.4 ± 103.4	279.3 ± 237.1	0.194	-1.3
Total number of oocytes retrieved	10.2 ± 5.2	9.2 ± 4.2	0.750	-0.3
% of oocytes suitable for ICSI (fert. rate)	77.0± 30.7	72.7 ± 27.4	0.657	0.4
Total number of mature oocytes (m^2)	8.0 ± 4.8	7.4 ± 3.8	0.657	0.4
Total number of embryos	5.1 ± 3.2	5.1 ± 3.6	0.763	0.3
Follicular fluid hCG level (mIU/ml) on day of OPU	134.9 ± 85.4	151.3 ± 108.2	0.102	–1.6
Biochemical pregnancy outcome (+hCG/ET)	20/56 (35.7%)	28/57 (49.1%)	0.140	
hCG ratio (fol. hCG/serum hCG)	0.58 ± 0.2	0.63 ± 0.3	0.454	0.4

*A P value < 0.05 was regarded as statistically significant.

As BMI increased, serum and follicular fluid hCG levels decreased (P = 0.008, P = 0.003) (Table 2).

A significant negative correlation between BMI, and serum and follicular fluid hCG levels was observed in the IM group (IM group: n = 56, Spearman's correlation: r = –0. 34, P = 0.009; r = –0. 36, P = 0.006 vs. SC group: n = 57; Spearman's correlation: r = –0.12, P = 0.37; r = –0.17, P = 0.20) (Table 3). A significant correlation was not observed between BMI and oocyte maturation (r = –0.05; P = 0.53) (Table 3). There was a strong negative correlation between BMI and follicular fluid hCG level in the IM group, but in the SC group there was a weak negative correlation (Figure 2).

There was a statistically significant trend in decreasing serum and follicular fluid hCG levels with increasing BMI in IM group in the linear regression analysis (P = 0.001) (Table 4).

Significant local adverse effects were not observed in the SC group; only 2 patients experienced inflammation at the injection site and 9 patients had skin tenderness in the SC group compared to 6 in the IM group. All the observed symptoms disappeared within 24 h.

Table 3. Correlation between BMI in the 2 groups based on Spearman's correlation test. There was a significant negative correlation between BMI, and serum and follicular fluid hCG levels in the IM group. There were no significant correlations between BMI, and oocyte maturation, fertilization rate, or pregnancy rate in either group.

	BMI			
	IM GROUP (n = 56)		SC GROUP (n = 57)	
	(r)	(P)	(r)	(P)
Foll hCG	–0.36	0.006	–0.12	0.37
Serum hCG	–0.34	0.009	–0.17	0.20
M2 oocytes	–0.10	0.44	–0.11	0.41
Fert. ratio	0.045	0.74	–0.03	0.77
Pregnancy	–0.05	0.68	–0.19	0.88

*Correlation was significant at the 0.01 level (2-tailed).

Discussion

The complex process of oocyte maturation and ovulation requires a timely LH surge in the natural cycle. In the stimulated cycle, hCG is administered to provide this stimulus. There have been several studies on the pharmacokinetics of hCG administration (3,6,8-10). Weissman et al., studying the pharmacokinetics of a single IM versus SC dose of hCG, observed a similar profile, with the highest hCG concentrations achieved with a dose of 10,000 IU administered subcutaneously. They concluded that SC injection of hCG for induction of ovulation is a simple and safe method, which might result in higher patient tolerance of infertility treatment (10). The advantages of SC injection of hCG are obvious. The International Recombinant Human Chorionic Gonadotropin Study

Table 2. When we look at the correlations between BMI and serum and follicular hCG levels, a negative correlation was found between BMI with intrafollicular and serum hCG levels in all patients, regardless of adminstration route. And these correlations are statistically significant (p=0.008;p=0.003).

		bmi	opuhcg	folhcg
bmi	Pearson Correıation	1	-0.247(**)	-0.273(**)
	Sig. (2-tailed)		0.008	0.003
	N	113	113	113
Serum hcg	Pearson Correlation	-0.247(**)	1	0.559(**)
	Sig. (2-tailed)	0.008		0.000
	N	113	113	113
folhcg	Pearson Correıation	-0.273(**)	0.559(**)	1
	Sig. (2-tailed)	0.003	0.000	
	N	113	113	113

** Corelation is significant at the 0.01 level (2 tailed)

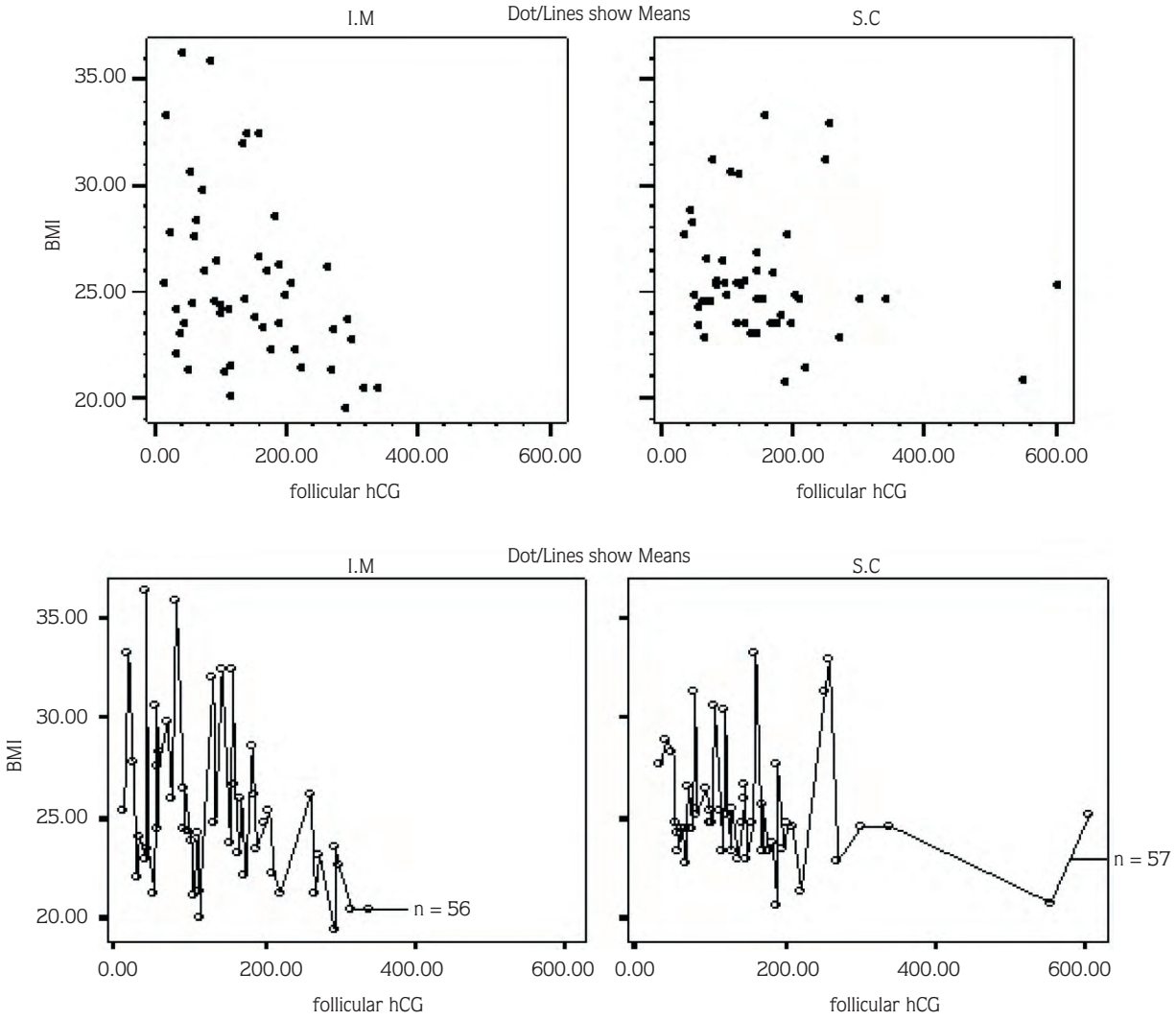

Figure 2. There was a strong negative correlation in the IM group between BMI and follicular fluid hCG level, whereas in the SC group there was a weak negative correlation.

Group suggested that both urinary hCG and recombinant hCG were effective in ovulation induction when administered via the SC route and that no statistically significant differences were observed between the treatment groups in terms of the primary efficacy endpoints (12). With SC hCG administration there is no need for the patient to visit a clinic or have a partner be responsible for injections. Jones et al. reported that SC self-administered hCG in males with hypogonadotropic hypogonadism is safe and produces comparable levels of serum and salivary testosterone to that administered via the IM route (13).

The present study showed that 36 h after IM or SC injection of purified hCG (10,000 IU) serum and follicular fluid hCG concentrations were similar and that there were no differences between the 2 groups' cycle length, total gonadotropin usage, peak E_2 level before hCG injection, number of oocytes retrieved, number of M2 oocytes, fertilization rates, or pregnancy rates. Serum and follicular fluid hCG levels in the SC group were slightly higher than in the IM group, but the difference was not statistically significant. Stelling et al. demonstrated that SC administration of purified hCG during IVF for

Table 4. Linear Regression Analysis. There was a statistically significant trend in decreasing serum and follicular fluid hCG levels with increasing BMI in IM group (P = 0.001).

Coefficients							
			Unstandardized Coefficients		Standardized Coefficiets		
Group	Model		B	Std. Error	Beta	t	Sig.
i.m	1	(Constand)	347.003	67.680		5.127	0
		bmi	-8.33	2.626	-0.396	-3.173	0.002
s.c.	1	(Constand)	307.191	122.016		2.518	0.015
		bmi	-6.022	4.736	-0.169	-1.272	0.209

Residuals Statsitics						
Group		Minimum	maximum	Mean	Std.deviation	N
i.m.	Predicted Value	44.537	187.5633	134.925	33.86662	56
	Residual		-132.424	164.05403	0	78.44414 56
	Std. Predicted Value	-2.669	1.554	0	1	56
	Std. Residual	-1.673	2.072	0	0.991	56
s.c.	Predicted value	106.4595	182.5179	153.0719	18.12031	57
	residual	-108.653	449.0593	0	105.67643	57
	Std.predicted value	-2.572	1.625	0	1	57
	Std. Residual	-1.019	4.211	0	0.991	57

a. Dependent Variable: folhcg

follicular and oocyte maturation achieves higher serum and follicular fluid hCG levels at the time of oocyte retrieval than the IM route. Their large retrospective study of 600 cycles reported no difference in pregnancy rates (6). Another group (8) studied hCG levels at 12 and 36 h after hCG injection to induce oocyte maturation during IVF cycles, and reported that serum levels of hCG were significantly higher in women that received IM injection than in those that received SC injection, especially at 12 h after injection. In contrast, using the same model, no difference in the serum concentration of hCG was observed at 12 h (3) or 24 h (9) after injection when the study was repeated. It was also noted that the difference in serum hCG level between the women that received IM and SC administration was smaller at 36 h.

Nagata et al. concluded that the ratio of the level of hCG in the follicular fluid to the level of serum hCG was a good marker for ovarian responsiveness and subsequent pregnancy. They reported that the ratio of the level of serum hCG must be at least 0.46 to be adequate for pregnancy (11). We observed that the mean hCG ratio in the SC group was 0.62 versus 0.58 in the IM group (P = 0.45). With regard to the ratio of follicular fluid hCG level to serum hCG level, we did not observe a significant difference between pregnant (0.63) and non-pregnant patients (0.58) (P = 0.417).

Obese women have a larger volume of distribution than non-obese women, and this may lead to a lower serum hCG concentration after drug administration (5). Elkind-Hirsh et al. (2001) observed a strong negative correlation between serum hCG levels and BMI. The highest levels of hCG were measured in women with the lowest BMI (3). Our results are consistent with studies that reported a negative correlation between BMI, and intrafollicular and serum hCG levels in all patients, regardless of the route of administration. As BMI increased in the present study, serum and follicular fluid hCG levels decreased. A correlation between BMI, and oocyte

maturation and fertilization rates was not noted in the present study. We also observed a significant negative correlation between BMI, and serum and follicular fluid hCG levels in the IM group; however, in the SC group we observed a weak correlation between BMI, and serum and follicular fluid hCG levels.

Carrel et al. (2001) reported an inverse correlation between BMI and intrafollicular hCG concentration (1). Their data clearly indicate a poor prognosis for IVF patients with a BMI > 30. Chan et al. noted generally higher bioavailability of the drug following IM administration; however, they also observed lower bioavailability of hCG in obese women, irrespective of the route of administration (2).

In conclusion, the advantages of self-administering hCG via the SC route are obvious; there is no need for women to visit a clinic or a nurse late at night, and a couple can now take care of all their hormone injections during a treatment cycle. In non-obese patients SC administration of purified hCG does not compromise cycle outcome, and increases convenience and flexibility in the treatment program, and it is more cost effective than recombinant forms of hCG. Based on the present study's results, BMI, rather than the route of hCG administration, determines circulating levels of hCG and, ultimately, oocyte exposure to gonadotropin for final maturation.

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