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Subcutaneous versus intramuscular administration of human chorionic gonadotropin during an in vitro fertilization cycle

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Objective: To confirm that hCG levels in follicular fluid and serum would be comparable between IM and SC administration of purified hCG.

Design: In a prospective study, serum and follicular fluid levels of hCG after an IM or SC injection of 10,000 IU of hCG were evaluated 36 hours after injection, that is, at the time of oocyte retrieval.

Setting: This study was carried out in a university-affiliated IVF program.

Patient(s): Forty women undergoing oocyte retrieval were entered into the study at the time of egg retrieval, that is, 36 hours after hCG administration.

Intervention(s): SC or IM injection of hCG.

Main Outcome Measure(s): Serum and follicular fluid concentrations of hCG were evaluated 36 hours after injection at the time of oocyte retrieval.

Result(s): There was a significantly higher serum hCG level in the SC group (348.6 ± 98 IU/L) vs. the IM group (259.0 ± 115 IU/L) and a significantly higher follicular fluid hCG level in the SC vs. the IM group (233.5 ± 85 vs. 143.4 ± 134 IU/L).

Conclusion(s): After purified hCG administration via the SC route, both serum and follicular fluid levels are greater compared with the IM route. (Fertil Steril® 2003;79:881–5. ©2003 by American Society for Reproductive Medicine.)

Key Words: hCG, subcutaneous, intramuscular, pharmacodynamics, follicular fluid

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Human chorionic gonadotropin has been used as a surrogate for the LH surge to induce the resumption of oocyte meiosis and follicular maturation for IVF. Currently, most IVF centers instruct their patients to administer the purified form of hCG by the IM route to trigger ovulation. However, the highly purified and recombinant gonadotropins are now used SC, requiring that patients learn how to correctly inject themselves by two techniques, IM and SC. This leads to patient confusion, discomfort, and an increased need for patient education. Despite the new SC forms of hCG available, many centers still use purified hCG, which is intended for IM use.

Subcutaneous injection of purified hCG has received very little attention to date. There are few studies that evaluate the pharmacodynamics of hCG injection. Recently, Nagata et al. (1) studied serum and follicular fluid levels of hCG administered IM. They concluded that the ratio of the level of hCG in the follicular fluid to the level of hCG found in the serum was a good marker for ovarian blood flow and therefore also a good marker for ovarian responsiveness and subsequent pregnancy. They reported that a follicular fluid level of 62 mIU/mL was the lowest level of hCG associated with pregnancy. They also found that the ratio of the level of hCG in follicular fluid to the level of hCG in serum must be at least 0.46 to be adequate for pregnancy (1). Saal et al. found that the serum levels required for normal follicular maturation are likely to be achieved through the SC route.

Men with hypogonadotropic hypogonadism have also been treated via the SC route with

TABLE 1

Patient characteristics at baseline and during the IVF cycle.

	Subcutaneous (n = 23)	Intramuscular (n = 17)	*P*
Age at cycle start (y)	35.5 ± 5.3	36.7 ± 5.4	NS
Body mass index (kg/m^2)	24.1 ± 4.5	24.1 ± 3.7	NS
Cycle length (d)	12.9 ± 1.8	13.8 ± 2.3	NS
Total gonadotropin usage (IU)	2,791.3 ± 1,312.0	2,611 ± 1,107.8	NS
Peak E_2 level (mIU/mL)	1,714.9 ± 718.9	1,987.9 ± 1,197.1	NS
No. of mature follicles (≥16 mm)	7.2	7.1	NS
No. of oocytes retrieved	11.78	9.78	NS
Percent with normal fertilization	55.8	56.4	NS
Follicular fluid/serum hCG ratio	0.67	0.55	NS
Percent pregnant	31.8	46.7	.36

Note: Means are presented ± SD. NS = not significant.

Stelling. Subcutaneous vs. intramuscular hCG. Fertil Steril 2003.

adequate testicular response (2, 3). Men receiving 5,000 IU of either SC or IM injected hCG achieved serum levels significantly greater than 100 mIU/mL (2). The published data in women, however, are limited. Despite the lack of data on the pharmacodynamics of hCG administered SC, many centers outside of the United States commonly use it for the induction of ovulation.

After reviewing over 600 fresh IVF cycles, we reported that hCG may be given by SC administration with an efficacy similar to IM injection (4). There were no statistically significant differences between groups in the number of oocytes retrieved, number of mature oocytes retrieved, fertilization rate, embryo quality, or pregnancy rate. To further study the effectiveness of SC administration of purified hCG we sought to compare serum and follicular fluid levels of hCG after either IM or SC injection. We hypothesized that both methods of administration would produce adequate serum and follicular fluid levels to allow full follicular and oocyte maturation.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval from Beth Israel Deaconess Medical Center and informed consent from each patient, 40 women undergoing vaginal oocyte retrieval in a university-affiliated IVF program were prospectively entered into the study at the time of egg retrieval. Patients undergoing IVF procedures were typically given GnRH agonists. Some patients were treated with a "flare" approach, while others were treated by luteal phase downregulation. Patients were given recombinant FSH for ovulation induction. When a minimum of three follicles exceeded 16 mm in average diameter, an ovulatory dose of purified hCG (10,000 IU) was given by IM or SC injection to all patients. The route of purified hCG administration, IM or SC, was determined before entry in the study at the patient's attending physician's preference based on the practice site location. Vaginal oocyte retrieval was performed under ultrasound guidance with general anesthesia 36 hours after hCG injection. Serum was collected at the time of IV catheter placement before induction of anesthesia. Follicular fluid was collected from the first mature follicle aspirated, using media-free collection tubes. Embryos were transferred on day 3 after retrieval. Luteal phase support was prescribed in varying dosages (50–400 mg) and routes (IM and vaginally) beginning on the day after egg retrieval. Luteal support was then continued until 14 days after retrieval when a quantitative measurement of the hCG level was obtained.

Serum and follicular fluid hCG levels were measured using an automated, immunoassay analyzer, the DPC Immulite (Diagnostic Product Corporation, NJ), with an analytical sensitivity of 0.4 mIU/mL and an interassay precision of 8.8%. Statistical analysis was then performed using unpaired *t*-tests and χ^2 tests for comparison.

RESULTS

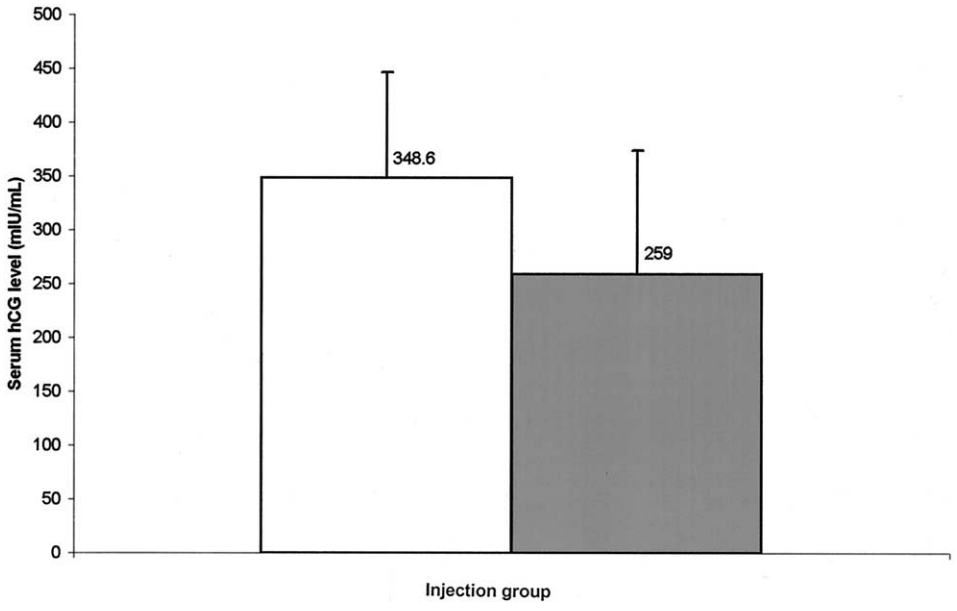
There were 17 women in the IM group and 23 women in the SC group. Baseline and cycle characteristics between groups are depicted in Table 1. There were no significant differences between groups in patient age, body mass index (BMI), cycle length, total gonadotropin usage, peak E_2 level before hCG injection, number of mature follicles on day of hCG, number of oocytes retrieved, percent of oocytes with normal fertilization, or pregnancy rates.

No statistically significant difference (P=.36) was observed when comparing pregnancy rates in the IM group (46.7%) to pregnancy rates in the SC group (31.8%), although our sample size is not large enough to exclude a small difference.

There was a significantly higher (P=.014) serum hCG level in the SC group (348.6 ± 98 mIU/mL) compared with

FIGURE 1

Serum hCG level at time of oocyte retrieval in SC and IM groups.

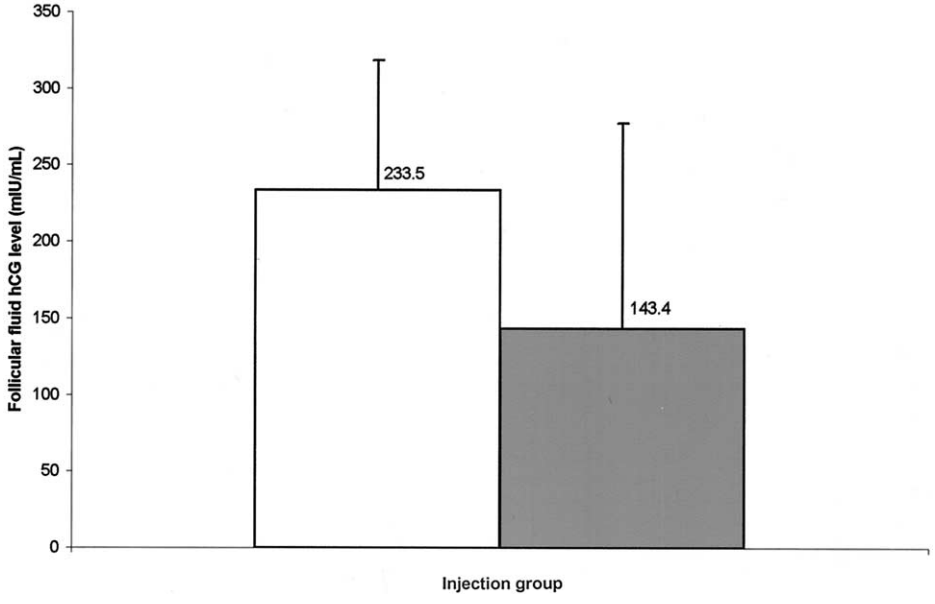


Stelling. Subcutaneous vs. intramuscular hCG. Fertil Steril 2003.

the IM group (259.0 ± 115 mIU/mL), as shown in Figure 1. There was also a significantly higher follicular fluid hCG level in the SC vs. the IM group (233.5 ± 85 vs. 143.4 ± 134 mIU/mL; $P=.021$), as shown in Figure 2. Serum levels ranged from 66 to 478 mIU/mL. Follicular fluid levels ranged from 34 to 745 mIU/mL. With regard to the ratios of

FIGURE 2

Follicular fluid hCG level at time of oocyte retrieval in SC and IM groups.



Stelling. Subcutaneous vs. intramuscular hCG. Fertil Steril 2003.

follicular fluid hCG levels to serum hCG levels, we did not find a significant difference for pregnant (0.58) and nonpregnant patients (0.65). For pregnant patients in the SC group, the ratio was 0.60, while the value for patients in the IM group was 0.55. For nonpregnant patients, the SC ratio was 0.71 and the IM ratio was 0.56.

Without regard to administration route, there was a correlation between serum hCG levels and follicular fluid levels, approximated by the line $y = 188.3 + 0.62x$, $r^2 = 0.451$ ($P<.0001$). There was a trend for decreasing serum hCG levels with increasing BMI ($P=.075$). There was no correlation between BMI and follicular fluid hCG levels ($P=.91$). There was a slight nonsignificant increase in the number of oocytes retrieved with increasing follicular fluid hCG levels ($P=.18$). There does not appear to be a correlation between hCG levels and age, peak E_2 levels, or total gonadotropin dosage.

DISCUSSION

We have demonstrated that SC administration of purified hCG during IVF for follicular and oocyte maturation achieves higher serum and follicular fluid levels than the IM route at the time of oocyte retrieval, that is, 36 hours after injection. There does not appear to be a large influence of other cycle parameters, such as E_2 level or gonadotropin dosage, on these levels. This study may or may not be consistent with Nagata et al.'s observation that increasing follicular fluid levels may be a marker of ovarian blood supply as shown by the trend toward an increased number of oocytes retrieved (1). We found that the lowest ratio of follicular fluid hCG to serum hCG for pregnancy was 0.54, while Nagata et al. found that a ratio of 0.62 was necessary for pregnancy. Although we did not find a significant correlation between serum or follicular fluid levels with pregnancy rates, our sample size does not possess adequate power to exclude a small difference. We found a small, nonsignificant difference in pregnancy rates between the SC and IM groups, and we anticipate that with a larger sample size, the pregnancy rates between the two groups would be equal. In our earlier large retrospective study evaluating 600 cycles, no difference in pregnancy rates was observed (4).

Increasing BMI was correlated with decreasing hCG levels in the serum, but it did not have a great effect on follicular fluid levels. Elkind-Hirsch et al. found that the highest hCG levels were measured in the women with the lowest BMI and that the patient's body size, rather than the method of administration of hCG, determined hCG levels (5). Jones et al. also found an inverse correlation between BMI and follicular fluid levels of hCG 36 hours after injection and concluded that hCG concentration was significantly decreased in patients with a BMI greater than 30 (6). In contrast, our lowest levels seemed to be in patients with a normal BMI. It is possible that this discrepancy is due to the fact that our standard dosage of 10,000 IU of purified hCG is at least adequate and quite possibly overwhelming for any BMI that we studied. Further research is clearly necessary to address this topic.

The pharmacodynamics of SC hCG administration has received little attention. Saal et al. has compared SC and IM routes of 5,000 IU hCG in 24 men (7). They found a delay in peak levels of hCG, a drop in magnitude of the peak, and a prolonged half-life for the SC route. They concluded that this was secondary to delayed absorption from the SC injection site compared with the IM injection site. They, however, found no difference in testicular response as measured by serum T levels and hypothesized that the delayed resorption may help prevent Leydig cell desensitization (7). Our results are somewhat discrepant from these results because our SC group had higher levels in both serum and follicular fluid. The differences could be explained by several factors. We evaluated women as compared with men, and no formal studies comparing sex differences in hCG dynamics have been performed. We used a higher dose of hCG, 10,000 IU vs. 5,000 IU. We also only looked at one time point, 36 hours after hCG injection. The longer half-life when administered via the SC route, combined with the higher dose of hCG, could explain the discrepancies. Later peak levels may be achieved with SC compared with IM, but this remains beyond the scope of this study.

Despite the slight pharmacodynamic differences that appear to exist between administration routes, there does not appear to be a clinically significant difference in IVF outcomes. We found no relation between hCG levels, either serum or follicular fluid, and clinical outcome. Even the lowest hCG levels measured in serum (66 IU/L) and follicular fluid (34 IU/L) had adequate effectiveness, as measured by the number of oocytes retrieved, percent normal fertilization, and pregnancy rates. Our previous retrospective study evaluating the clinical parameters in more detail also failed to find clinically significant differences in IVF outcomes in greater than 600 cycles (4).

The purpose of this study was not to look at clinical outcomes, but to show that levels of hCG after SC injection are adequate to produce similar results when compared with hCG levels after IM injection. This paper also serves as a reference guide for normal serum and follicular fluid levels after hCG administration. Our large (>2,000 fresh IVF cycles per year) university-affiliated IVF center has switched to SC administration of hCG for the trigger of ovulation in IVF and ovulation induction cycles without ill effect. This has enabled us to simplify patient education and help prevent significant patient discomfort. When comparing SC and IM levels, one can see that both serum and follicular fluid hCG levels, when measured 36 hours after injection, are higher when administered SC than when administered IM. It can then be concluded that SC administration achieves serum and follicular fluid levels adequate to obtain the desired clinical effects with less patient inconvenience.

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