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Evaluation of whether Using hCG to Stimulate Oocyte Release Helps or Decreases Pregnancy Rates following Intrauterine Insemination

Key Words

Cervical factor
Human chorionic gonadotropin
Intrauterine insemination
Luteinized unruptured follicle

Abstract

The study's objective was to determine if using human chorionic gonadotropin (hCG) as a timing method for intrauterine insemination (IUI) in patients who make mature follicles but have cervical factor problems has a negative effect on pregnancy rates (PRs) (possibly by releasing an immature oocyte), or increases the rate of luteinized unruptured follicles (LUF). Patients were offered hCG or natural release after an explanation of the theoretical advantages and disadvantages. Intrauterine insemination was performed 36-40 h after hCG; timing of IUI with hCG was based on day of luteinizing hormone (LH) surge modified by serum progesterone (P). Incidence of LUF in those taking hCG - 5/116 (4.3%); 0/33 without hCG. Pregnancies - 24/116 (20%) with hCG; 3/30 (10%) without hCG. No statistical differences in these rates were found. Thus, using hCG for more convenient timing for IUI in nonsuperovulated cycles does not decrease the PR or cause a high incidence of LUF.

Introduction

The luteinizing hormone (LH) surge has been defined in different ways using a radioimmunoassay (RIA) method of detection. One study found that when the LH reached 60 mIU/ml, ovulation occurred approximately 27 h later [1] and with a level of 50 mIU/ml ovulation would probably occur 36 h later [2], while others have suggested ovulation occurs 36-38 h from the initiation of the LH surge [3, 4].

The LH surge extends for 48 h [2]. Thus, if the LH exceeds 50 mIU/ml on the second of two consecutive days, the physician cannot determine whether the LH surge occurred 1 h after the blood was obtained on the

previous day or 1 h before the blood was obtained on the succeeding day, or, somewhere in between.

One clue that ovulation may have occurred many hours before the second blood level might be provided by measuring the serum progesterone (P) level; a serum P approaching 1 ng/ml usually suggests that the LH surge occurred approximately 12-20 h before.

Once out of the seminal plasma the sperm may not be capable of fertilizing for more than 4 h, unless it reaches the cervical mucus. The oocytes, once in the fallopian tube, may not be able to be fertilized beyond 8 h. Thus, the window of fertilization may extend only 12 h. Obtaining urinary LH levels every 3 h once the follicle approaches sonographic maturity (18-24 mm diameter)

Table 1. Incidence of LUF and pregnancy rates

| | Group 1 (n = 21) | Group 2 (n = 32) | Group 3 (n = 9) | Group 4 (n = 84) |
|------------------------------|---------------------|---------------------|--------------------|---------------------|
| Ultrasound results | | | | |
| Released | 21 (100) | 29 (90.6) | 9 (100) | 76 (90.4) |
| Inconclusive | 0 (0) | 1 (3.1) | 0 (0) | 5 (5.9) |
| LUF ^a | 0 (0) | 2 (6.3) | 0 (0) | 3 (3.6) |
| Pregnancy rates ^b | 2 (9.5) | 4 (12.5) | 1 (11.1) | 20 (23.8) |

Percentages in parentheses.

^a $p = 0.61$; ^b $p = 0.29$.

may be the most accurate method, but then the clinician is faced with performing the intrauterine insemination (IUI) 36–40 h later, which may be late at night or very early morning.

For convenience, human chorionic gonadotropin (hCG) is frequently given and the IUI is performed a certain number of hours later, e.g., 36–40 h later; thus hCG may be given late at night and the IUI performed 2 mornings later. Theoretical concern about the use of hCG is that the release of the oocyte may be from an immature follicle or that the follicle may not be ready to release the oocyte, leading to a luteinized unruptured follicle (LUF).

The study presented herein compared pregnancy rates (PRs) and the incidence of LUF in patients having IUI with or without hCG.

Materials and Methods

This study included all patients ($n = 153$) having an IUI from the time period of January 1990 to January 1992. Patients were offered hCG to allow more convenient timing, but were advised of the theoretical problem of releasing an oocyte from an immature follicle or LUF syndrome. The option of taking hCG was chosen by 122 patients (79%) and rejected by 31 (21%).

Intrauterine insemination was performed for either male factor or cervical factor. Entry into the study was denied if there were any sperm demonstrable in the cervical mucus with progressive linear motion 8–12 h following intercourse. For this study all patients (male or female) with an antisperm antibody level $> 50\%$ (as determined by immunobead test, in semen or mucus), were excluded.

There were no attempts for purposeful superovulation and IUI; those patients taking follicle maturing drugs did so either because they were anovulatory or had a luteal phase defect related to releasing an oocyte from an immature follicle [5].

Transvaginal sonography with a 5 MHz vaginal probe was performed beginning 16–17 days prior to expected menses. As soon as the follicle reached a minimum 18 mm average diameter, daily sera

estradiol (E_2), P and LH samples were obtained. E_2 was assayed by solid phase RIA (Diagnostic Products Corporation, Los Angeles, Calif.); P and LH were also measured by RIA (Amersham Corporation, Arlington Heights, Ill.). The LH surge was defined as the first level exceeding 50 mIU/ml.

Hoff et al. [2] previously presented data suggesting that the serum P reaches a level of approximately 0.5 ng/ml at the time of the LH surge and reaches approximately 1 ng/ml 24 h from the LH surge. For this reason, for patients whose P level reached 0.8 ng/ml and who still received hCG, insemination was performed 26–28 h later.

Only those patients whose follicles reached an average diameter of 18 mm, with an E_2 level of at least 200 pg/ml, were included in the study. Sera samples were collected in the morning and the results were obtained later in the afternoon; hCG was given between 6 and 10 p.m. that evening and the IUI performed at 11 a.m., 36–40 h later; the decision on whether the timing was 36 or 40 h later depended on the LH – if < 50 mIU/ml, then 40 h later and if > 50 mIU/ml, then 36 h later. A P level ≥ 0.8 ng/ml but < 1 ng/ml modified IUI so that the timing was 24–28 h later. An ultrasound was performed, if the follicle was intact, IUI was repeated 12 h later.

The timing of IUI in patients not using hCG was based on the sera levels of P on the day of the LH surge. A P level of ≥ 1 ng/ml would lead to an IUI that evening, whereas, a level > 0.8 but < 1 ng/ml resulted in an IUI 26–28 h later, for those whose P levels were < 0.5 ng/ml, the IUI was planned for 36–40 h from that morning's sera levels. Once again, an intact follicle, demonstrated by sonography, would lead to repeating the IUI 12 h later.

Three days from the LH surge, another pelvic ultrasound was performed. If the follicle failed to decrease by at least 5 mm and the serum P level was > 2 ng/ml, a diagnosis of LUF was made.

There were four groups evaluated: group 1 – no medications; group 2 – no follicle-maturing drugs (FMD) but given hCG for release; group 3 – clomiphene citrate (CC) for FMD but no hCG; group 4 – CC with hCG. χ^2 analysis with Yates correction for continuity was used to test for differences in the PRs and incidence of LUF in the four groups. All statistical tests were done at the 0.05 level of significance.

Results

Of the 153 patients in the study, 122 (79%) opted to take hCG for timing of IUI, 31 (21%) chose not to. To the best of our knowledge, there was no bias in presentation to the patient, influencing their choice of one option over the other. CC had been used in 89 of 122 (73%) patients taking hCG vs. 8 of 27 (30%) not taking hCG.

Sonographic confirmation of release 3 days post-LH surge was not available for 7 patients. They were therefore excluded from the statistical analysis. The final sample sizes in the four groups were 21, 32, 9 and 84, respectively. The incidence of LUF and PRs in the four groups are presented in table 1. There were no statistically significant differences in the incidence of LUF in any of the four groups ($\chi^2 = 1.8$, d.f. = 3, $p = 0.606$). Luteinized unruptured follicle was confirmed in 5 of 116 (4.3%) of patients

taking hCG and in 0 of 30 (0.0%) patients not receiving hCG ($\chi^2 = 0.353$, d.f. = 1, $p = 0.553$). There were no statistical differences found in the PRs by medication group ($\chi^2 = 3.4$, d.f. = 3, $p = 0.286$, table 1). Pregnancies occurred in 24 of 116 patients where hCG was used vs. 3 of 33 (9.0%) when hCG was not given ($\chi^2 = 1.31$, d.f. = 1, $p = 0.252$). A male factor problem was seen in 53 of 122 (43%) patients receiving hCG vs. 18 of 31 (58%) not given hCG.

Discussion

There are insufficient data to conclude that giving hCG improves the PR following IUI for cervical factor. Nevertheless, it seems safe to conclude that the overall PR of 24 of 105 (22.9%) following hCG for IUI timing does not reduce the efficacy of IUI. A previous randomized

study comparing intercourse to IUI for cervical factor found a 21.2% PR per cycle, but these patients were not corrected for LUF [6]. If we include all patients, regardless of release criteria, the PR was 24 of 116 or 20.7%.

If the LH surge occurred between the time of obtaining morning sera levels and the time of hCG injection, there still would be an 8-hour extended time for fertilization in the fallopian tube; these patients had IUIs at 40 h, but those with a rise in LH but low sera P levels were assumed to have had a more recent surge, therefore, the earlier 36 h time was used.

There have been several reports suggesting poor PRs with IUI without superovulation [7, 8]. The data presented herein corroborate our previous study suggesting that with properly timed IUI, superovulation is not necessary. The possibility exists that the superovulation helped suppress spontaneous LH surge, and, since hCG was given, merely allowed for more accurate timing.

References

- 1 Garcia JE, Jones GS, Wright GL: Prediction of the time of ovulation. *Fertil Steril* 1981;36:308-315.
- 2 Hoff JD, Quigley ME, Yen SSC: Hormonal dynamics at mid-cycle: A reevaluation. *J Clin Endocrinol Metab* 1983;57:792-795.
- 3 Testart J, Frydman R, Feinstein MC, Thibault A, Roger M, Scholler R: Interpretation of plasma luteinizing hormone assay for the collection of mature oocytes from women: Definition of a luteinizing hormone surge initiating rise. *Fertil Steril* 1981;36:50-54.
- 4 Taymor ML, Seibel MM, Smith D, Levesque L: Ovulation timing by luteinizing hormone assay and follicle puncture. *Obstet Gynecol* 1983;62:191-195.
- 5 Check JH, Nowroozi K, Wu CH, Adelson HG, Lauer C: Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. *Int J Fertil* 1988;33:252-256.
- 6 Check JH, Chase JS, Spirito P: Efficacy of intrauterine insemination versus sexual relations versus intracervical insemination for treatment of cervical factor infertility. *Am J Gyn Health* 1991;59:11-17.
- 7 Corson SL, Batzer FR, Gocial B, Maislin G: Intrauterine insemination and ovulation stimulation as treatment of infertility. *J Reprod Med* 1989;34:397-406.
- 8 Kemmann E, Bohrer M, Shelden R, Fiasconaro G, Beardsley L: Active ovulation management increases the monthly probability of pregnancy occurrence in ovulatory women who receive intrauterine insemination. *Fertil Steril* 1987;48:916-920.