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Human chorionic gonadotropin administration is associated with high pregnancy rates during ovarian stimulation and timed intercourse or intrauterine insemination

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Abstract

Background: There are different factors that influence treatment outcome after ovarian stimulation and timed-intercourse or intrauterine insemination (IUI). After patient age, it has been suggested that timing of insemination in relation to ovulation is probably the most important variable affecting the success of treatment. The objective of this study is to study the value of human chorionic gonadotropin (hCG) administration and occurrence of luteinizing hormone (LH) surge in timing insemination on the treatment outcome after follicular monitoring with timed-intercourse or intrauterine insemination, with or without ovarian stimulation.

Methods: Retrospective analysis of 2000 consecutive completed treatment cycles (637 timed-intercourse and 1363 intrauterine insemination cycles). Stimulation protocols included clomiphene alone or with FSH injection, letrozole (an aromatase inhibitor) alone or with FSH, and FSH alone. LH-surge was defined as an increase in LH level ≥200% over mean of preceding two days. When given, hCG was administered at a dose of 10,000 IU. The main outcome was clinical pregnancy rate per cycle.

Results: Higher pregnancy rates occurred in cycles in which hCG was given. Occurrence of an LH-surge was associated with a higher pregnancy rate with clomiphene treatment, but a lower pregnancy rate with FSH treatment.

Conclusions: hCG administration is associated with a favorable outcome during ovarian stimulation. Awaiting occurrence of LH-surge is associated with a better outcome with CC but not with FSH treatment.

Background

Ovarian stimulation with timed-intercourse or intrauterine insemination (IUI) has been empirically applied alone or in combination for treatment of unexplained infertility, male-factor infertility, anovulatory infertility as well as other cases of infertility. This treatment modality is used when the female partner has at least one open tube in addition to some ovarian function and the male partner has motile sperm [1]. In infertile couples meeting the

above criteria, combining ovarian stimulation with IUI is an effective means of achieving pregnancy [2,3].

There are different factors that influence treatment outcome after ovarian stimulation and timed-intercourse or IUI [4,5]. These include women's age, ovarian stimulation protocol, semen parameters and method of semen preparation [6-8], number of inseminations [9,10] as well as number of preovulatory follicles, length and cause of infertility and number of prior treatment cycles [11,12]. Another important factor is timing of intercourse or insemination. It has been suggested that timing of insemination in IUI cycles in relation to ovulation is probably the most important variable affecting the success of treatment [3].

With the introduction of IUI into infertility management, timing of insemination was initially based on past cycle length and basal body temperature charts [13]. Later, timing insemination according to LH-surge was found to be associated with improved outcome [14]. However, with the development of human chorionic gonadotropin (hCG) and its application to trigger ovulation and time insemination, controversy has arisen as to the best method of timing intercourse or IUI to achieve optimal pregnancy rates. There is no consensus whether timing of insemination by waiting for detection of LH-surge, or by administering hCG without waiting for LH-surge, or by waiting for LH-surge and then adding hCG, leads to the best pregnancy rates [15-20].

In this study we looked at treatment outcome (achievement of clinical pregnancy) according to the three different methods of timing intercourse and insemination currently applied in infertility practice: 1-hCG administration without waiting for LH-surge, 2-waiting for LH-surge plus hCG administeration, or 3-waiting for LH-surge without administering hCG.

Methods

Approval was obtained from the Research Ethics Board of University of Toronto and Mount Sinai Hospital to review charts of infertile couples who underwent cycle monitoring for timed-intercourse or IUI. The study was conducted at Reproductive Biology Units (RBU) located at Toronto General Hospital before mid-2000 and at Mount Sinai Hospital after mid-2000, and at Toronto Center for Advanced Reproductive Technology (TCART). These clinics are academic tertiary referral centers affiliated with Reproductive Sciences Division, Department of Obstetrics and Gynecology, University of Toronto, Canada. Charts were reviewed for treatment cycles completed between January 1997 and March 2001. The same clinical team including five reroductive endocrinologists work in both centers (RBU and TCART) applied the same ovarian stimulation protocols with similar management and follow up plans in both centers.

This retrospective study included 2000 consecutive completed treatment cycles (637 timed-timed-intercourse cycles and 1363 IUI cycles) in 860 infertile women, 250 with polycystic ovarian syndrome (PCOS) and 610 with unexplained infertility. PCOS was diagnosed according to the National Institutes of Health consensus criteria [21] and unexplained infertility was diagnosed by exclusion of tubal factor infertility (hysterosalpingography and laparoscopy), anovulation (by luteal phase progesterone > 5 nM) and male factor by semenalysis according to WHO criteria [22].

Criteria for patient inclusion included completed cycles in which there was only one infertility factor (PCOS or unexplained infertility) with comparable semen parameters meeting the minimum WHO criteria as explained above.

Stimulation protocols included clomiphene citrate (CC) alone (771 cycles) or with FSH injection (132 cycles), letrozole (an aromatase inhibitor) alone (146 cycles) or with FSH (143 cycles), FSH alone (515 cycles). LH-surge was defined as an increase in LH level ≥200% over mean of preceding two days LH levels. When given, hCG was administered at a dose of 10,000 IU, single subcutaneous or intramuscular injection (Profasi®, Serono, Oakville, Ontario, Canada or Pregnyl®, Organon, Scarborough, Ontario, Canada, respectively). All cycles received luteal phase support with progesterone in the form of vaginal suppositories 100 mg twice daily. In 293 treatment cycles, patients received no ovarian stimulation before timed-intercourse or insemination.

CC was given orally at a dose of 50–100 mg daily from day 3 to day 7 of menstrual cycle. The aromatase inhibitor, letrozole, was given orally at a dose of 2.5 mg daily from day 3 to day 7 of menstrual cycle as previously described for ovulation induction [23-25]. FSH injections were given in the form of highly purified FSH (Fertinorm®, Serono, Oakville, Ontario, Canada) or recombinant FSH, (Gonal-F® Serono, Oakville, Ontario, Canada or Puregon®, Organon, Scarborough, Ontario, Canada) at a dose of 50–300 IU/day. When given alone, FSH injections started on day 3 of menstrual cycle. When given in conjunction with CC or letrozole, injections started on day 7 of menstrual cycle.

The managing physician decided the choice of the ovarian stimulation protocol with the patient based on her clinical profile (mainly the age, duration of infertility and prior treatment history). An algorithm usually is followed starting with a natural cycle (no treatment in unexplained infertility) followed by ovarian stimulation with

clomiphene citrate. When pregnancy is not achieved after about three cycles of clomiphene or if a thin endometrium is seen, the clomiphene is considered failed and then the aromatase inhibitor or FSH (alone or in combination with clomiphene or aromatase inhibitor, empirically decided) was used.

The development of ovarian follicles was monitored by transvaginal ultrasound measurement of mean follicular diameter and serial assays serum LH and estradiol levels. This was done on a daily basis during the last few days of stimulation immediately before insemination and less frequently in the early part of follicular phase. hCG (10,000 IU) was given to trigger ovulation when mean diameter of an average of two ovarian follicles was ≥18 mm. IUI was done 38 hours after hCG administration if no LH-surge occurred. If LH-surge was detected, IUI was done on the following day and at 38 hours. Intercourse was recommended exactly like IUI. Patients called to confirm the encounter of intercourse on the following day for documentation.

The decision to give hCG was made by the physician on call for the infertility unit. The timing of insemination was based on the achievement of average mean diameter of 18 mm or larger for two or more follicles (one follicle in no-medication cycles). After reviewing the serum LH level, the treating physician decided whether an endogenous LH surge occurred or not. If an endogenous LH surge occurred a decision was made to give hCG or not based on the physician preference (no specific guidelines existed). If an LH surge did not occur, hCG was given to trigger ovulation. This algorithm of hCG administration contributed to the homogeneous structure among the different study groups and absence of significant differences in any of the variables that might affect the achievement of pregnancy e.g. age and infertility diagnosis. In the no-medication group, there was a tendency towards avoiding the use of any medications to trigger ovulation, often at patient request. Thus, hCG administration was avoided in most of the non-stimulated cycles. In the gonadotropin group, there was a tendency to give hCG to trigger ovulation in most of the cycles due to general belief among physicians that hCG is needed because LH-surge achieved during gonadotropin stimulation might be inadequate as reviewed by Macklon and Fauser [26].

The dose and duration of FSH treatment were adjusted during monitoring of follicular development according to patient's response including the number of growing follicles and estradiol levels. The goal of ovarian stimulation was to achieve an average of two ovarian follicles with a mean diameter of ≥18 mm on the day of hCG administration.

All insemination cycles included IUI with partner semen. The same method of semen preparation [sperm wash] was applied in all insemination cycles. All men had normal semen analysis by WHO criteria and there was no significant difference in the semen parameters of the partners in the different patients groups as regards sperm number, motility and strict criteria for morphology (data not shown). The same 2 infertility nurses performed intrauterine inseminations in all patients.

Pregnancy was diagnosed by quantitative β-hCG two weeks after timed-intercourse or insemination. Clinical pregnancy was confirmed by observing fetal cardiac activity on transvaginal ultrasound four weeks after a positive pregnancy test.

Intercourse or insemination was timed according to the administration of hCG, or the occurrence of LH-surge. Hence there were three study groups: group 1: "hCG-only group" included cycles in which patients received hCG [without LH-surge], group 2: "hCG plus LH-surge" group included cycles in which patients received hCG on the day of the detected LH-surge, and group 3: "LH-only" group included cycles in which patients did not receive hCG [LH-surge occurred].

Two more groups are formed from combinations of the above three groups. Group 4: "all hCG", include all cycles in which patients received hCG irrespective to occurrence of LH-surge [hCG ± LH-surge]. This group is the sum of groups 1 and 2 [hCG-only group and hCG plus LH group]. Group 5: all LH-surge group, included all cycles in which patients had LH-surge whether received hCG or not [LH ± hCG]. This group is the sum of groups 2 and 3 [hCG plus LH-surge group and LH-surge-only group]. Box 1 summarizes the five different patients groups.

Group 1: hCG-only group, no LH-surge occurred

Group 2: hCG plus LH-surge group, both hCG was given and LH-surge occurred on the same day

Group 3: LH-surge-only group, LH-surge occurred but no hCG was given

Group 4: All hCG group, all cycles in which hCG was given whether alone or on the day of hCG (sum of groups 1 and 2)

Group 5: All LH-surge group, all cycles in which LH-surge occurred whether hCG was given or not (sum or groups 2 and 3)

Analysis of data

To look at the effect of hCG administration and ocuurrence of LH-surge on the treatment outcome, clinical pregnancy rates per cycle were compared among the first three study groups. To look at the effect of hCG administration on treatment outcome, clinical pregnancy rates per cycle were compared between cycles in which hCG was given, group 4, [hCG alone or with LH-surge] and cycles in which hCG was not given, group 3 (LH-surge-only group). Then we confined the comparison on the cycles in which LH-surge occurred by comparing cycles in which hCG was given, group 2 (hCG plus LH-surge) with the cycles in which hCG was not given, group 3 (LH-surge-only cycles).

To look at the effect of LH-surge on the treatment outcome we compared all cycles in which LH-surge occurred, group 5, (whether alone, LH-surge-only or LH-surge plus hCG cycles) with all cycles in which LH-surge did not occur, group 1, (hCG-only cycles).

The various factors known to affect the outcome of ovarian stimulation and insemination treatment [4-12,27,28] including age, number of inseminations, number of prior treatment cycles (table 1) as well as type of insemination and infertility diagnosis (table 2) have been compared among the diferent study groups. There was no statistically significant difference in any of these variables among the study groups. There was no significant difference among the study groups for other important variables that might have affected the outcome (achievement of pregnancy) including the number of follicles, dose of ovarian stimulation medication (CC and letrozole dose and FSH, total number of units) as well as estradiol level on the day of hCG administration. We ran the statistical analysis applying multiple regression analysis considering the following as important confounding factors: age, number of prior treatment cycles, infertility diagnosis and insemination type (intercourse or IUI). When all cycles were considered together, hCG administration was found to be an independent factor associated with a higher pregnancy rate. When sub-grouped according to stimulation type, the sample size was not large enough with all types of stimulation to draw the same conclusion although the trend was maintained for a higher pregnancy rate in association with hCG administration.

Table 1: Various patients characteristics (age, number of treatment cycles and infertility duratin) among the different patients groups. Data presented as Mean ± SD (range).

	All groups	Group 1 HCG-only	Group 2 hCG plus LH-surge	Group 3 LH-onlysurge only	Group 4 All hCG (sum of groups 1 and 2	Group 5 All LH-surge cycles Sum of groups 2 and 3
No. of cycles	2000	1146	548	306	1694	854
Age	34.3 ± 4.3 (20–45)	34.2 ± 4.3 (20–45)	34.7 ± 4.1 (24–45)	33.95 ± 4.3 (23–45)	34.36 ± 4.2 (20–45)	34.44 ± 4.2 (23–45)
No. of inseminations	1.1 ± 0.3 (1–2)	1.12 ± 0.32 (1–2)	1.39 ± 0.5 (1–2)	1.24 ± 0.42 (1–2)	1.28 ± 0.45 (1–2)	1.28 ± 0.5 (1–2)
No. of prior treatment cycles	2.9 ± 2.2 (1–7)	2.8 ± 2.1 (1–7)	3.1 ± 2.2 (1–6)	2.71 ± 2.4 (1–6)	2.9 ± 2.14 (1–7)	2.96 ± 2.3 (1–6)

There was no statistically signbificant difference among the different groups as regards the age, number of inseminations or prior treatment cycles.

Table 2: The percentage of insemination cycles and infertility diagnosis among the different patients groups. Data are presented as number (% from total cycles).

	All groups	Group 1 HCG-only	Group 2 hCG plus LH-surge	Group 3 LH-surge-only	Group 4 All hCG (sum of groups 1 and 2	Group 5 All LH-surge Sum of groups 2 and 3
No. of cycles	2000	1146	548	306	1694	854
IC	637 (31.9%)	364 (31.8%)	157 (28.6%)	116 (37.9%)	521 (30.8%)	273 (32%)
IUI	1363 (68.2%)	782 (68.2%)	391 (71.4%)	190 (62.1%)	1173 (69.2%)	581 (68%)
No. of patients	860	439	315	106	754	421
PCOS	250 (29.1%)	127 (28.9%)	95 (30.2%)	28 (26.4%)	222 (29.4%)	123 (29.2%)
Unexplained infertility	610 (70.9%)	312 (71.1%)	220 (69.8%)	78 (73.6%)	532 (70.6%)	298 (70.8%)

There was no statistically signbificant difference among the different groups as regards the number of timed-intercourse or IUI cycles, or the infertility diagnosis.

Table 3: Clinical pregnancy rates per cycle according to method applied for timing insemination or intercourse (hCG-only, hCG plus LH-surge or LH-surge-only) among the different ovarian stimulation protocols. Results are expressed as rate (number of pregnancy cycles/total number of cycles).

	HCG-only (group 1)	hCG + LH-surge (group 2)	LH-surge-only (group 3)	All Cycles
All stimulation cycles	10.2% (109/1068)	14.3% (69/483)	2% (5/256)	10.7% (183/1707)
CC	6.3% (34/539)	15.9% (20/126)	1.9% (2/106)	7.3% (56/771)
CC+FSH	15% (16/108)	30% (6/20)	0 (0/4)	16.7% (22/132)
Letrozole	9% (6/66)	20.3% (14/69)	9% (1/11)	14.4% (21/146)
Letrozole+FSH	17% (14/82)	17.2% (8/58)	0 (0/3)	17.5% (22/143)
FSH	14% (39/273)	10% (21/210)	6.3% (2/32)	12.2% (62/515)
No medication	6.5% (5/78)	12.7% (8/65)	8.8% (13/150)	8.9% (26/293)

Statistical analysis

The following statistical tests were used where appropriate to analyze various data among the study groups: ANOVA was used to compare between the three groups (hCG alone, HcG plus LH and LH only groups), Student's t-test, Chi square test and Bonferroni t-test when comparing between each two groups (hCG versus no hCG and LH surge versus no LH surge) in addition to multiple regression analysis as explained above, considering P value < 0.05 statistically significant. The statistical tests were performed with SigmaStat for Windows Version 1.0 software (SigmaStat Software HighEdit Professional Copyright® 1993, MicroHelp Inc and HeilerSoftware GmbH, San Rafael, CA, USA).

Results

Table (3) shows clinical pregnancy rates per cycle among the three main study groups (hCG-only, hCG plus LH-surge and LH-surge-only) according to the stimulation protocols. When all treatment cycles were combined together, the hCG plus LH-surge group had a significantly higher clinical pregnancy rate when compared to the other two groups, hCG-only group ($P < 0.05$) and LH-surge-only group ($P < 0.01$). hCG plus LH-surge group had a significantly higher clinical pregnancy rate compared to the other two groups in CC treatment cycles. However, this difference was statistically insignificant with other ovarian stimulation protocols (CC+FSH, letrozole, and letrozole + FSH) or the no stimulation cycles. In FSH treatment cycles, there was a trend for the hCG-only group to be associated with a higher, though statistically insignificant, clinical pregnancy rate compared to the other two groups. The same trend was maintained when the analysis was done after subgrouping the cycles acording to type of insemination i.e. timed-intercourse (figure 1-a) or IUI (figure 1-b). However, the differenece was smaller in the IUI cycles. Also, after subgrouping the patients according to infertility diagnosis (PCOS or unexplained infertility), the same trend was maintained (data are not presented).

When all hCG cycles were combined together, the administration of hCG was associated with higher clinical pregnancy rates among all stimulation protocols (figure 2-a). The difference was statistically significant with CC ($P < 0.01$), CC + FSH ($P < 0.01$), and letrozole + FSH treatment ($P < 0.05$). To look at the effect of LH-surge on the clinical pregnancy rate, all cycles in which LH-surge occurred were compared to the cycles without LH-surge (hCG-only). LH-surge was associated with a significantly higher pregnancy rate among the different stimulation protocols that utilized CC, alone or with FSH ($P < 0.05$). On the other hand, with FSH treatment (alone or with letrozole), LH-surge was associated with lower clinical pregnancy rates that was statistically significant ($P < .05$) in FSH-only cycles (figure 2-b).

Discusion

Three important findings of interest arise from results in this retrospective study. The first is the association of hCG treatment with higher clinical pregnancy rates irrespective of stimulation protocol, insemination types (timed-intercourse or IUI) or infertility diagnoses (PCOS or unexplained infertility). The second finding was the trend for a significantly higher clinical pregnancy rate associated with LH-surge in CC treatment, either alone or with FSH. This trend was maintained after sub-grouping according to insemination type and infertility diagnoses. The third finding was a significantly lower clinical pregnancy rate associated with LH-surge in FSH treatment cycles.

To maximize the chance of success, timing of intercourse and intrauterine insemination should be closely related to the time of ovulation [1]. Early studies reported discrepancies in the time of ovulation after the onset of LH-surge. A multicentred collaborative study from the World Health Organization, found that ovulation occurred 24–56 hours from the onset of LH-surge and between 8–40 hours after its peak [29]. Garcia et al, reported that ovulation occurred after a mean time of 27.3 h from onset of LH-surge [30]. In IVF cycles, oocytes retrieved 36–38 h from the start of LH-surge achieved good fertilization rates [31]. Nowa-

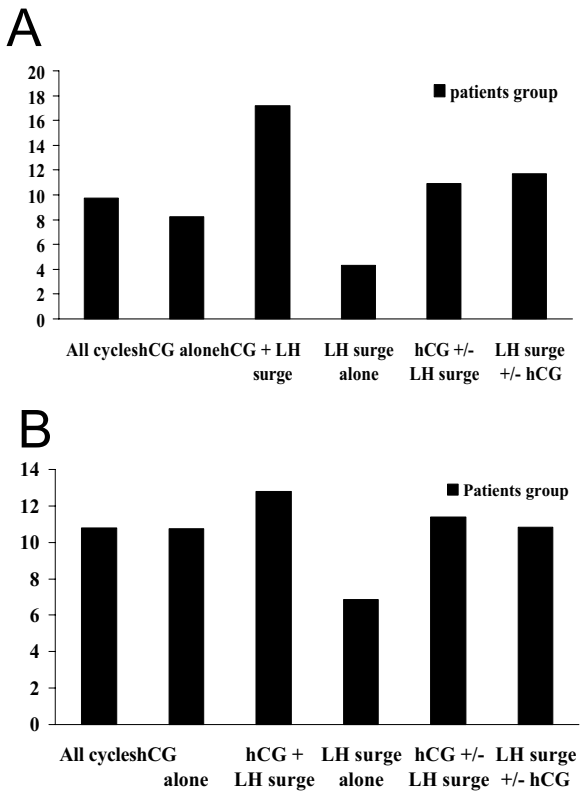

Figure 1
Clinical pregnancy rate per cycle among different patients groups according to method of insemination (timed-intercourse or IUI). A) Clinical pregnancy rate per cycle among the different patients groups, timed-intercourse cycles only. The same pattern was maintained as for all cycles combined (timed-intercourse and IUI cycles, table 3). Higher pregnancy rates were observed in group 2 (hCG + LH-surge) when compared to the other two groups: group 1, hCG-only ($P < 0.05$) and group 3, LH-surge-only ($P < 0.01$). Also, all hCG cycles (group 4) was associated with higher clinical pregnancy rate when compared to the no hCG i.e. LH-surge-only cycles $P < 0.01$). **B**) Clinical pregnancy rate per cycle among the different patients groups, IUI cycles only. The same pattern was maintained as for all cycles (timed-intercourse and IUI cycles, table 3). Higher pregnancy rates were observed in group 2 (hCG + LH-surge) when compared to the other two groups: group 1, hCG-only (not statistically significant) and group 3, LH-surge-only ($P < 0.05$). Also, all hCG cycles (group 4) was associated with higher clinical pregnancy rate when compared to the no hCG i.e. LH-surge-only cycles $P < 0.05$).

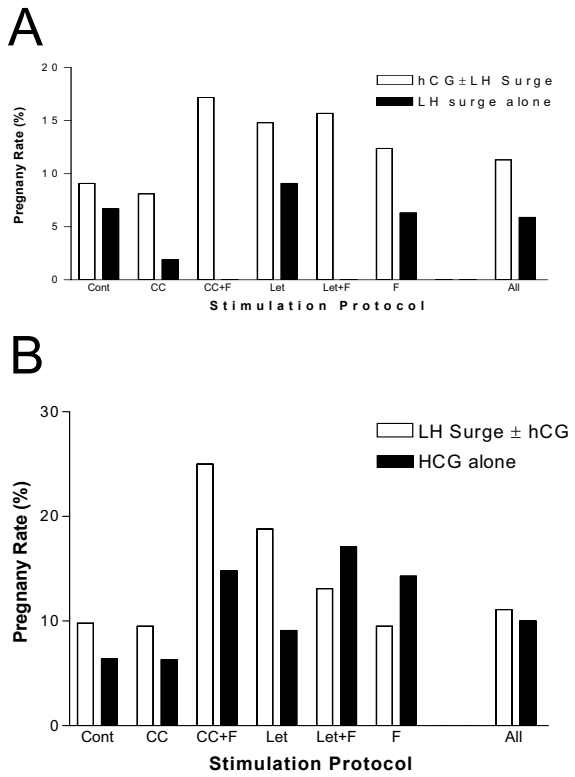

Figure 2
Clinical pregnancy rates according to hCG administeration and occurrence of LH-surge among different stimulation protocols. A) Comparison between clinical pregnancy rate in cycles in which hCG was given with or without an LH-surge versus cycles in which hCG was not given (LH-surge alone). Combined intrauterine insemination and timed-intercourse cycles, both polycystic ovarian syndrome and unexplained infertility patients. Control (Cont), clomiphene citrate (CC), FSH (F), and letrozole (Let). **B**) Comparison between clinical pregnancy rates in cycles in which an LH-surge occurred (with or without hCG administration) versus cycles in which LH-surge did not occur. Combined intrauterine insemination and timed-intercourse cycles, both polycystic ovarian syndrome and unexplained infertility patients. Control (Cont), clomiphene citrate (CC), FSH (F), and letrozole (Let).

days, hCG is used to trigger ovulation and time insemination which is a common practice among many infertility centers worldwide. Follicular rupture and ovulation usually occur ~36–48 h after hCG injection [32].

Whether to wait for LH-surge to occur or administer hCG to trigger ovulation is still a matter of controversy. Martinez et al [17,33] suggested that a beneficial effect would occur when the process of natural follicular maturation

and the spontaneous rise of LH was allowed to occur. In our study, we found similar findings of a higher clinical pregnancy rate in the group of hCG plus LH-surge. However, this improvement in clinical pregnancy rates was not found when FSH was used alone or with letrozole. Of interest, the findings with CC + FSH cycles are consistent with an earlier report, almost 15 years ago, that the occurrence of LH-surge was a favorable event, associated with higher pregnancy and live birth rates in IVF cycles in which the combination of CC + hMG was applied for controlled ovarian hyperstimulation [34].

As LH-surge can last for up to 2 days before ovulation in some patients [35], a treatment plan based on LH-surge alone can result in inaccurate timing of ovulation and insemination. When hCG is given before LH-surge there can be mistiming of follicle maturity. It is therefore reasonable to expect a better pregnancy rate when an ovulatory dose of hCG is administered after LH-surge [19].

The occurrence of LH-surge in CC treatment cycles may indicate a healthy hypothalamo-pituitary axis that has been released from the estrogen receptor antagonistic effect of CC and may indicate a rapid clearance of the antiestrogenic component of CC. LH-surge, therefore, may also reflect a lesser peripheral antiestrogen effect at the level of endometrium and cervix favoring the achievement of pregnancy.

With FSH treatment, the lower clinical pregnancy rate associated with LH-surge could be related to premature timing of LH-surge as a result of rapidly rising estrogen levels attained during the growth of multiple healthy follicles. This premature LH-surge may result in triggering the ovulation of immature oocytes. Premature LH-surges are well-known from experience with controlled ovarian hyperstimulation for assisted reproduction predating the use of GnRH analogue pituitary downregulation.

In a similar study design to ours, Awonuga and Govindbhai [36] did not find any difference in the pregnancy rate among the cycles in which hCG was administered or in which LH-surge occurred. LH-surge detection was, however, performed with urine kits. Urinary LH monitoring has its limitations that include false-negative results when peak LH concentrations are low [<40 IU/l]. This has been found in up to 35% of ovulatory cycles [37]. It is possible that up to a third of inseminations are timed incorrectly when LH kits alone are used to time IUI [38] and some women may even ovulate before LH can be detected in the urine [39]. In addition, the small size of the study may have limited the detection of a small but significant difference in outcome.

In a prospective, randomized, cross-over study that evaluated the benefit of hCG-timed versus LH-timed IUI in CC stimulated cycles [40], no statistically significant difference was seen in the pregnancy rate with the use of hCG (4.2%) versus LH monitoring (4.3%). The low pregnancy rat in this study suggests a different patient population to ours and such low pregnancy rate may have masked a difference in the two timing approaches.

Conclusions

The findings of this study support the practice of administering hCG to trigger ovulation and time insemination and to time its administration according to LH-surge. Waiting for LH-surge to happen before giving hCG might be associated with high pregnancy rates when CC is used (whether alone or in combination with gonadotropins). On the other hand, with FSH treatment the occurrence of LH-surge before administering hCG might be associated with lower pregnancy rates. It is important to mention that the retrospective design of our study may bias the results. A retrospective study is less likely to have clearly defined criteria for patient inclusion, and non-randomized trials have the potential to provide a distorted view of the problem. However, the large number of treatment cycles (2000 cycles) and the absence of significant difference in relevant confounding factors (age, fertility diagnosis and duration) among the study groups would allow drawing useful conclusions that consitiute the basis for future randomized trials. A prospective clinical trial in which the method for timing insemination is randomly determined before starting ovarian stimulation would help in achieving unequivocal conclusions.

Authors' contribution

MFMM and SSA have carried out the data collection including the charts review and data entry and preparing the manuscript. MFMM has done the statistics, prepared the tables and graphs. RFC has supervised and reviewed the study design, data collection, statistical analysis and writing the manuscript including the tables and figures preparation. All authors read and approved the final manuscript. The work has been presented in part at the 50th Annual Meeting of the Pacific Coast Reproductive Society", Rancho Las Palmas, California, April 2002.

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