Gn-RH antagonists in intrauterine insemination: the weekend-free protocol

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Objective: To compare the results of intrauterine insemination (IUI) when GnRH antagonist was added—to avoid IUI on weekend—with those obtained with the standard IUI protocol.

Study design: In an IUI program under ovarian stimulation with gonadotropins when one or more follicles of 15–16 mm were seen, if it was not possible for logistic reasons (weekend) to perform the insemination 72 h later, GnRH antagonist was administered until human chorionic gonadotropin (hCG) administration. The IUI was performed on Monday. We compared the results of this IUI “weekend-free” group with our results in standard IUI cycles, where IUI was performed 36–38 h after reaching optimal follicular growth.

Results: Both groups were comparable regarding the main demographic parameters, except for higher estradiol levels, due to the prolonging ovarian stimulation. The per cycle pregnancy rate (PR) were very similar in both groups: 15.7% in the weekend-free IUI versus 16.5% in standard IUI. The multiple pregnancy rate and the hyperstimulation rate were also similar. A non-significant trend to higher high-order multiple pregnancy was observed in the weekend-free IUI.

Conclusions: In IUI cycles under ovarian suprastimulation with gonadotrophins, the use of GnRH antagonist allows the manipulation of the follicular development in such a way that it is possible to avoid inseminations on the weekends, without apparently reducing the PR.

KEY WORDS: GnRH antagonist; intrauterine insemination; ovarian stimulation; pregnancy rates; weekend.

INTRODUCTION

Intrauterine insemination (IUI) with the husband's sperm is a widely performed technique. There is some controversy regarding a number of methodological questions concerning IUI management that include indications, ovarian stimulation, number of inseminations per cycle, IUI timing, the number of

cycles to perform and the sperm preparation method. Stimulated IUI cycles have considerably higher pregnancy rates (PR) than unstimulated cycles (1,2). In IUI cycles stimulated with gonadotropins, higher PR have been reported than in clomiphene stimulated cycles (3–5).

Although not well studied, it is usually accepted that when a single insemination is performed per cycle, it should be timed 34–38 h after hCG (6). On the other hand, a number of centers perform two inseminations per cycle to increase the possibilities of finding an open oocyte fertilization window, specially if a premature ovulation occurs (7,8).

GnRH antagonists have been recently introduced in IVF methods, showing an effectivity similar to

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GnRH agonists in avoiding the premature surge of luteinizing hormone (LH) (9,10). However, as far as we know, there is no published report of GnRH antagonists in IUI.

MATERIALS AND METHODS

The period of study was from February 1, 2002 till March 1, 2003. During this time 417 IUI cycles were performed, corresponding to 198 couples. Main IUI indications were: (a) mild-moderate male factor (b) idiopathic infertility (c) failure of ovarian stimulation and programmed intercourse cycles (d) female infertilities with at least one normal patent tube.

Our standard IUI management has been previously published (11,12). Ovulation stimulation consisted of 150 IU of rec FSH (Gonal F, Laboratorios Serono, Madrid), starting on the second day of the menstrual cycle, and adjusting the dose thereafter according to vaginal ultrasound and estradiol determinations. When at least two follicles >17 mm were obtained, the estradiol levels being >500 pg/mL, 250 mcg of rec hCG (Ovitrelle, Serono Laboratories, Spain) were given. When such conditions were not obtained, the cycle was cancelled. When six or more follicles >16 mm were seen or when the estradiol levels were >2000 pg/mL, the cycle was transformed into an IVF or cancelled, if IVF was rejected. Only one insemination per cycle was performed (36–38 h after hCG).

Semen samples for IUI were prepared with Pure-sperm (NidaCom Laboratories, Sweden), as previously described (11–13). Luteal phase was supplemented with urinary hCG (HCG Lepori, Laboratorios Lepori; Madrid) (2500 IU on day +1, +3, +5, and +7 following insemination) and with vaginal myronized progesterone (Utrogestan, Laboratoires Besins-Iscovesco, Paris, France) (200 mg/12 h for the 15 days following insemination) for cases with estradiol levels <1500 pg/mL. In those cases with estradiol levels >1500 pg/mL, only vaginal progesterone, at the aforementioned dose, was given. A maximum of six insemination cycles were performed if pregnancy was not reached beforehand.

Due to logistic conditions, it was not possible either to perform inseminations on Saturdays and Sundays, or ultrasound or estradiol determinations. During the aforementioned period of study, when the follicular development indicated that the optimal day for insemination was going to be the next Saturday or Sunday, GnRH antagonist was added. This

happened when one or more follicles of 15–16 mm were seen, and if it was not possible for logistic reasons to perform the insemination 72 h later. GnRH antagonist (Cetrotide 0.25, Laboratorios Serono) was administered 0.25 mg every day, starting in the afternoon of the day when the ultrasound criteria were met, and continuing for the next days in the morning, until hCG was given. IUI was performed on Monday, 36–38 h after hCG administration. In such cases the blood sample was taken on the day of hCG administration, but the analysis itself was done on Monday.

We compared the results of standard IUI with those obtained with the “weekend-free IUI.” In all cases, pregnancy was defined by the visualization of a gestational sac at the 6th week of amenorrhea.

Statistical analysis was performed by means of chi square, Fisher exact test, and Student’s *t*-test following the standard criteria of applicability. Statistical significance limit was defined as $\alpha = 0.05$.

RESULTS

IUI indications were similar in both groups. There were no differences concerning demographic parameters, except for a longer duration of ovarian stimulation as well as the increased estradiol levels in the weekend-free IUI (due to prolonging gonadotrophin stimulation in order to delay IUI).

Per cycle pregnancy rates were similar in both groups (15.7% in the weekend-free IUI versus 16.5% in standard IUI) (Table I). There were no significant differences concerning multiple pregnancy rate

Table I. Comparison of the “Weekend-Free IUI” with Standard IUI

	Weekend-free IUI (n = 89)	IUI general population (n = 328)	P
Wife’s age (years)	36.1 ± 2.5	35.1 ± 3.6	ns
Husband’s age (years)	37.4 ± 4.2	36.8 ± 2.9	ns
Duration of infertility (years)	4.6 ± 2.1	4.4 ± 1.8	ns
Days of stimulation	12.0 ± 1.8	10.5 ± 2.2	<0.001
Estradiol the day of hCG (pg/mL)	1151 ± 558	969 ± 438	<0.01
Per cycle pregnancy rate (%)	15.7 (14/89)	16.5 (54/328)	ns
Multiple pregnancy (%)	28.6 (4/14)	20.4 (11/54)	ns
Triplets or more (%)	14.3 (2/14)	3.7 (2/54)	ns

Note. Values are expressed by mean ± SD, except pregnancy rates, expressed in percentages.

Multiple pregnancy rates are expressed in regard to the total number of pregnancies.

(28.6% versus 20.4%). The frequency of triplets or other multiplets was somewhat higher in the weekend-free IUI (one triplet and one quadruplet, amounting to 14.3% of pregnancies) than in the standard IUI (one triplet and one quadruplet, amounting to 3.7% of pregnancies), but the differences lacked statistical significance.

There was no case of severe ovarian hyperstimulation syndrome in any of the two groups. There was a 1.1% rate of moderate ovarian hyperstimulation in the weekend-free IUI ($n = 1$) versus 0.8% in standard IUI ($n = 3$).

In one case, a presumed adverse effect to GnRH antagonist was reported, consisting of moderate generalized edema, appearing on the second day of GnRH antagonist therapy. There was no smarting, nor other symptoms. The edema improved when GnRH antagonist was stopped, and disappeared 7 days later.

When we compared, among the weekend-free IUI patients, the characteristics of conceptional and non-conceptional cycles, no difference was observed, except for the fact that conceptional cycles had a lower ordinal number (Table II).

DISCUSSION

The method employed in IUI differs widely among the different groups. There is lack of agreement concerning indications, ovarian stimulation, number of inseminations per cycle, IUI timing, number of cycles to perform and sperm preparation. In a recent meta-analysis a non-significant trend of higher PR was observed when two inseminations per cycle were performed (6). One could speculate that this could be due to a better covering of the oocyte fertilization window. The IUI timing is also controversial, and although few have studied, most authors

recommend performing IUI 34–38 h after hCG (6). Performing IUI after this time would be less efficient.

Thus it could be expected that when follicular development was achieved, in some cases the spontaneous surge of LH might happen, and thus performing IUI 24–48 h after the theoretical optimal time (on Monday) would be too late. The benefits of avoiding premature LH surge in IVF, by means of GnRH agonist, are well known. However, in IUI, the systematic administration of GnRH agonists have shown no benefits (14).

In our study, we observed a PR almost identical to that observed in the standard IUI group (15.7 versus 16.5%). Thus, from our preliminary data, administering a GnRH antagonist and avoiding inseminations on the weekend does not reduce the PR.

Concerning side effects, the hyperstimulation rate was also similar in both the groups. The higher order multiple pregnancy rate was very high in the weekend-free population, almost four times that of standard IUI, but was not statistically significant. If such a trend were confirmed in further studies, it would represent a serious argument against this practice.

We are aware that our study has some methodological shortcomings. It is not a randomized study, with their well-known limitations. However, it should be emphasized that the main characteristics of this study and control populations were very similar, except for those parameters related with prolonging ovarian stimulation. On the other hand, it could be argued that there were no differences in the PR, not because of the use of GnRH antagonist, because that delaying IUI for 24–48 h is not important.

Thus until more data are available from our experience, it can be concluded that in IUI cycles under ovarian suprastimulation, the use of GnRH antagonist allows manipulating the follicular development in such a way that it is possible to avoid inseminations on the weekends, without apparently reducing the PR.

Table II. Comparison of Conceptional and Non-Conceptional Cycles in GnRH Antagonist Treated IUI patients

	Non-conceptional cycles	Conceptional cycles	<i>P</i>
Wife's age (years)	36.3 ± 2.4	35.2 ± 2.6	ns
Husband's age (years)	37.4 ± 4.2	37.4 ± 4.1	ns
Infertility duration	4.7 ± 2.0	4.2 ± 1.9	ns
Cycle number	3.01 ± 1.2	2.0 ± 1.1	<0.05
GnRH ampoules	3.7 ± 1.0	3.8 ± 1.6	ns
Estradiol (pg/mL)	1108 ± 539	1309 ± 641	ns
Follicles ≥ 16 mm	4.7 ± 1.7	5.0 ± 1.2	ns

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