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ORIGINAL ARTICLE

Day two post retrieval 1500 IUI hCG bolus, progesterone-free luteal support post GnRH agonist trigger – a proof of concept study

Sharon Vanetik[a], Linoy Segal[a], Tatiana Breizman[b] and Shahar Kol[a,b]

[a]Ruth and Bruce Rappaport Faculty of medicine, Technion – Israel Institute of Technology, Haifa, Israel; [b]Department of Obstetrics and Gynecology, IVF Unit, Haifa, Israel

ABSTRACT

Small dose of hCG (1500 IU) on the day of oocyte retrieval, followed by daily progesterone administration, is currently the preferred way to secure adequate luteal support following GnRH agonist trigger. In the current proof-of-concept study, we explored the possibility that a bolus of 1500 IU hCG, given two days after oocyte retrieval, may be sufficient to sustain adequate luteal support without additional progesterone treatment. From February 2015 to August 2016, we obtained 44 pregnancies following GnRHa trigger followed by day 2 hCG (1500 IU) support only (study group). Data from these 44 cycles were compared with the latest 44 pregnancies obtained following hCG (6500 IU) trigger followed by conventional progesterone luteal documented (control group). Mean progesterone levels (14 days postoocyte retrieval) in the study and control groups were 197 nmol/l and 173 nmol/l, respectively (NS). Mean E_2 levels (14 days post oocyte retrieval) in the study group was 6937 pmol/l, significantly higher ($p < .001$) than in the control group (3.276 pmol/l). We conclude that bolus of 1500 IU hCG, administered 2 days after retrieval, can provide excellent support, without the need to further supplement with progesterone.

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KEYWORDS
GnRH agonist; luteal phase support; hCG; controlled ovarian stimulation; progesterone

Introduction

GnRH agonist (GnRHa) trigger instead of hCG is currently widely practiced, primarily in the context of ovarian hyperstimulation syndrome (OHSS) prevention. In fact, as many as 36% of IVF GnRH antagonist cycles in Europe are triggered with GnRHa [1]. After the initial findings of poor reproductive outcome, when a standard luteal phase support (LPS) was used in relation to GnRHa trigger [2,3], the subsequent development of modified LPS policies – either hCG rescue or intensive steroid rescue [4] – resulted in a reproductive outcome comparable to that of hCG trigger. Thus, GnRHa trigger has become a viable alternative for the 'gold standard' hCG trigger [5].

GnRHa trigger causes luteolysis [6,7] if not counteracted by hCG, which is the reason why modifications of the standard LPS are necessary to obtain a good reproductive outcome after fresh embryo transfer. In this line, the concept of 'tailored,' ovarian response-based, luteal support was suggested. One bolus of hCG (1500 IU) on the day of oocyte retrieval, followed by a standard LPS in normal responders (<14 follicles >11 mm), yielded good clinical outcomes [4,5]. Finally, in OHSS risk patients (15–25 follicles >11 mm), a single bolus of 1500 hCG at the time of oocyte retrieval similarly resulted in excellent clinical outcomes and no OHSS development [4,5]. In all the above studies, additional progesterone supplementation was given.

In our previous publication [8], we showed that complete luteal rescue post-GnRHa trigger is possible even if the hCG bolus (1500 IU) is given a few days after oocyte retrieval ('luteal coasting'). Moreover, late hCG bolus resulted in high mid-luteal progesterone levels (window of implantation), leaving additional progesterone support redundant.

We therefore reasoned that, by shifting the 1500 IU hCG bolus from the day of oocyte retrieval to two days later, complete luteal rescue is possible, without any further need for progesterone support. Progesterone support is usually given vaginally or intramuscularly until week 9–12 of pregnancy. This treatment adds to patient discomfort and treatment burden, and therefore, a search for ways to alleviate it is indicated.

The aim of the current study is to compare pregnancy outcome in patients triggered with GnRHa followed by 1500 IU hCG bolus two days (day 2) postoocyte retrieval, with patients triggered with hCG followed by standard progesterone support.

Materials and methods

From February 2015 to August 2016, we obtained 44 pregnancies following GnRHa trigger followed by day 2 hCG (1500 IU) support only (study group). Data from these 44 cycles were compared with the latest 44 pregnancies obtained following hCG (6500 IU) trigger followed by conventional progesterone luteal support for which the clinical outcome was documented (control group).

Inclusion criteria

Patients with positive β-hCG test 14 days postoocyte retrieval, with concomitant measurement of E_2 and P.

Complete follow-up of pregnancy and delivery or miscarriage, after a viable pregnancy was ascertained.

Exclusion criteria

Patients with missing data on E_2 and p level 14 days postoocyte retrieval.

CONTACT Shahar Kol skol@rambam.health.gov.il IVF Unit, Rambam Heath Care Campus, POB 9602, Haifa, Israel 31096

Protocol

Controlled ovarian stimulation (COS) was performed with a GnRH antagonist 'short' protocol for the study group, in order to keep the option of GnRHa trigger in case of excessive ovarian response. Either the GnRHa 'long', or GnRH antagonist 'short' protocols were used for the control group. The cycles were monitored according to the policy of the clinic. In both groups, ovulation trigger (Decapeptyl 0.2 mg, Ferring, in the study group, Ovitrelle 250 μg, Merck, in the control group) was administered as soon as three leading follicles reached ≥17 mm mean diameter, oocyte retrieval was performed 34–36 h later. Oocytes were fertilized with conventional IVF or ICSI, according to individual patient criteria. In the study group, a bolus of 1500 IU of hCG was administered two days after oocyte retrieval. No further support was given. In the control group, LPS was started on the day of embryo transfer with a vaginal progesterone preparation (Crinone 90 mg, progesterone 8% vaginal gel, Merck, Darmstadt, Germany). The primary outcome of the study was live birth. Secondary outcome was ongoing pregnancy.

Hormonal measurement and pregnancy follow-up

Serum β-hCG, P and E_2 levels were measured 14 days postoocyte retrieval to document pregnancy.

β-hCG measurement was repeated within the first 7 days after the first one, to rule out biochemical pregnancy. Viable pregnancy was ascertained by vaginal sonography 1-month postoocyte retrieval, and the number of embryos with normal fetal heart activity was recorded. Pregnancy outcome was recorded from the Rambam Health Care Campus database or by a phone call if the patient delivered in another hospital.

Statistical analysis

The association of LPS variants (1500 IU hCG, progesterone) and outcome (live birth, ongoing pregnancy, miscarriage) was examined using Pearson chi-square. The comparisons between groups and other continuous data were done using independent samples t-test, and the comparisons of groups and other categorical data were done using Pearson chi-square and Fisher's exact tests.

Significance was set at $p < .05$ for all tests.

Statistical analysis was done using SPSS software package (Release 20.0.0.0, SPSS Inc, Chicago, IL, 2011).

This study was approved by the Rambam Health Care Campus IRB.

Results

We included 44 IVF or ICSI cycles in the study group and 44 cycles in the control group.

Baseline characteristics, such as age, etiology of infertility, fertilization procedure, protocol, number of oocytes retrieved, number of embryos obtained and transferred, are depicted in Table 1.

Live birth rate was comparable between the two groups with 59.1% and 75% in the study and control groups, respectively (Table 2, p values = 0.15). Miscarriage rate was similar between the two groups: 4.5% and 6.8% in the study and control groups, respectively. These miscarriage rates are comparable to those described previously [9,10].

Mean progesterone levels (14 days postoocyte retrieval) in the study (no progesterone supplementation) and control (progesterone supplemented) groups were 197 nmol/l and 173 nmol/l, respectively (NS).

Mean E_2 levels (14 days post oocyte retrieval) in the study group was 6937 pmol/l, significantly higher ($p < .001$) than in the control group (3276 pmol/l).

None of the 88 patients included in the study developed OHSS.

Table 1. Baseline characteristics in the study and control groups.

	Study ($n = 44$)	Control ($n = 44$)	p value
Age (years)	28.2 ± 5.0	31.6 ± 5.8	.002
Etiology of infertility (%)			.85
Male factor	40.9	31.8	
Female factor	9.1	22.7	
Unexplained	43.2	27.3	
Combined	6.8	18.2	
Fertilization procedure (%)			.25
ICSI	72.7	61.4	
IVF	27.3	38.6	
Protocol (%)			<.001
Long	0	34.1	
Short	100	65.9	
Number of oocytes retrieved	12.07 ± 5.5	9.23 ± 4.1	.008
Number of oocytes fertilized	8.57 ± 4.6	6.66 ± 3.4	.031
Number of embryos obtained	4.0 ± 2.5	3.09 ± 2.0	.060
Number of embryos transferred	1.8 ± 0.4	2.0 ± 0.6	.050

(± = SD).

Discussion

To the best of our knowledge, this is the first study to introduce the concept of post-GnRHa trigger LPS based on 1500 IU hCG given two days postoocyte retrieval, without any further luteal support. Our results suggest that under these circumstances, exogenous progesterone is redundant. Therefore, the discomfort and burden associated with prolonged vaginal or intramuscular progesterone administration can be avoided.

Previous description of differed hCG administration (1500 IUI three days after oocyte retrieval in 'high' responders) included intense luteal support with exogenous progesterone [11].

The main purpose of any LPS is to provide high progesterone environment during the implantation window. If this is achieved, endogenous hCG secretion by the newly formed placenta may take over, and secure adequate corpora lutea function further on, if luteolysis did not occur before this time frame.

In a natural cycle P levels of >30 nmol/l may be sufficient to maintain pregnancy [10]. Yovich et al [12] found that in IVF cycles, luteal phase data indicated that progesterone levels were two to three times higher than that expected during spontaneous conception cycles. Moreover, those pregnancies, which subsequently aborted, had significantly lower levels in the late luteal phase. Our data in the study group suggest that luteal progesterone secretion is more than enough in that regard. Moreover, progesterone levels in the study group were even higher (though not significantly so) than those recorded for the control, progesterone supplemented group.

In our study, estradiol levels can reliably reflect luteal activity in both groups, since both groups were not supplemented with exogenous estradiol. Since estradiol levels were significantly higher in the study group, we may conclude that our approach results in robust luteal phase, leaving any additional supplementation redundant.

Table 2. Hormonal levels as measured 14 days postoocyte retrieval and pregnancy outcome.

	Study ($n = 44$)	Control ($n = 44$)	p value
hCG levels on 14th day post-OPU (IU/l)	143.90 ± 81.90	183.22 ± 144.10	.135
Progesterone levels on 14th day post-OPU (nmol/l)	197.34 ± 92.90	173.89 ± 158.45	.428
E_2 levels on 14th day post-OPU (pmol/l)	6937.60 ± 4692.65	3276.59 ± 2137	<.001
Number of gestational sacs (%)			.58
1	79.5	84.1	
2	20.5	15.9	
Pregnancy outcome (%)[a]			.15
Live birth	59.1	75.0	
Miscarriage	4.5	6.8	
Ongoing pregnancy	36.4	18.2	
Number of newborn(s) (%)			.26
1	80.8	90.0	
2	19.2	9.1	

(± = SD).
[a]Data on pregnancy outcome on the day database was closed for writing the paper.

The conventional low-dose hCG rescue bolus is given on the day of oocyte retrieval, which is 6–7 days before embryo implantation. This low dose may not be sufficient to stimulate adequately the corpora lutea around the window of implantation; therefore, additional progesterone support is needed. Early hCG administration overstimulate the corpora lutea in the early luteal phase, which serves no purpose, other than increase OHSS risk. Importantly, such sharp early progesterone rise might shift the endometrial window of receptivity, resulting in a synchronization with the transferred embryo (s). By delaying hCG administration for 48 h, complete corpora lutea rescue is possible, securing more than enough progesterone in the implantation window and further on [13] with no need for further exogenous support. In addition, it may allow for more physiological early luteal progesterone rise, with better embryo-endometrial synchronization.

Progesterone supplementation is considered harmless; however, it is a source for complaints by patients, either because of continuous vaginal messy leakage due to vaginal formulations, or painful intramuscular injections. Patient comfort must be an important consideration in the field of ART. A great deal of research and development was invested to ease treatment burden during the follicular phase, the introduction of corifollitropin α being a bold example [14]. Unfortunately, such close attention and resources were never given to the much longer luteal phase (if pregnancy is achieved), where there is a clear interest to decrease treatment burden and cost. Previously, we showed that two hCG boluses (1500 IU each) can secure adequate luteal support post GnRHa trigger in 'low' responders (mean of 6.7 oocytes) without additional progesterone supplementation [15]. Our current study shows that in patients with more intense ovarian response (mean of 12 oocytes) one bolus, given two days postretrieval, is enough. Daily small hCG dose (125 IU) from the day of oocyte retrieval can also provide for adequate luteal support without exogenous progesterone, however, at a cost of 14 injections [16].

The obvious disadvantage of our study is its retrospective nature. However, from the endocrine point of view, we think it adequately delineates the concept of achieving enough endogenous progesterone production in the luteal phase, without resorting to additional support.

Conclusion

We maintain that following GnRHa trigger, delaying the administration of 1500 IU hCG luteal support to 48 h after oocyte retrieval adequately rescues the corpora luteal, without the need of any additional support.

Disclosure statement

The authors report no conflicts of interest while conducting this research.

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