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ARTICLE

GnRH agonist triggering followed by 1500 IU of HCG 48 h after oocyte retrieval for luteal phase support

BIOGRAPHY

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KEY MESSAGE

After gonadotrophin releasing hormone (GnRH) agonist trigger in GnRH antagonist cycles for IVF, a bolus of 1500 IU HCG 2 days after oocyte retrieval provides adequate luteal support with no further need for progesterone. This approach to luteal phase support after GnRH agonist trigger is simple, patient friendly and effective.

ABSTRACT

Research question: Gonadotrophin releasing hormone (GnRH) agonist trigger after GnRH antagonist-based ovarian stimulation protocol for IVF is gaining popularity, because it prevents ovarian hyperstimulation syndrome and allows for near physiological LH and FSH surges. A 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 after GnRH agonist trigger. In the present study, the possibility that a bolus of 1500 IU HCG, given 2 days after oocyte retrieval, may be sufficient to sustain adequate luteal support without additional progesterone treatment was questioned.

Design: A non-interventional retrospective cohort study between conducted between April 2017 and August 2018. A total of 154 consecutive patients treated with GnRH agonist trigger followed by day-2 HCG (1500 IU) support only (study group) were included. Data were compared with 155 consecutive patients who were treated with HCG (6500 IU) trigger followed by conventional progesterone luteal support (control group).

Results: Pregnancy, miscarriage and live birth rates were comparable between the study and control groups. In patients who became pregnant, mean oestradiol level 14 days after oocyte retrieval was 4719 pmol/l and 2672 pmol/l in the study and control group, respectively ($P < 0.001$), reflecting robust luteal activity in the study group.

Conclusions: A bolus of 1500 IU HCG, administered 2 days after retrieval, can provide excellent luteal support, without the need for further progesterone supplementation.

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Declaration: The study was supported by Merck KGaA.

KEYWORDS
GnRH agonist trigger
GnRH antagonist
HCG
IVF
luteal support

INTRODUCTION

Given the endocrine disruption induced by ovarian stimulation for IVF, luteal phase support (LPS) with progesterone or HCG is needed to secure embryo implantation and early pregnancy development (*Yanushpolsky, 2015*). In the natural ovulatory cycle, serum progesterone increases from ovulation to a peak in the mid-luteal phase (day 6–8 after ovulation). If an embryo implants, the newly formed placenta secretes HCG, which supports progesterone secretion from the corpus luteum (*Stewart et al., 1993*). It is reasonable to assume that the desired LPS after IVF should follow this endocrine paradigm.

The use of gonadotrophin releasing hormone (GnRH) agonist to trigger final oocyte maturation is gaining popularity. A survey from 2013 found that 36% of IVF cycles are triggered with GnRH agonist (*IVF Worldwide, 2013*). Currently, this percentage is probably higher. The main reason for the widespread use of GnRH agonist trigger is its ability to prevent ovarian hyperstimulation syndrome (OHSS) (*Kol, 2004*; *Devroey et al., 2011*), thereby promoting patient safety. In addition, GnRH agonist trigger elicits LH and FSH surges, closely mimicking the natural mid-cycle surge. The best way to handle the luteal phase post-GnRH agonist trigger, if a fresh embryo transfer is carried out, is still under debate.

Several approaches have been suggested: intensive daily oestradiol and progesterone (administered intramuscularly) (*Engmann et al., 2008*); a single bolus of 1500 IU of HCG on the day of oocyte retrieval followed by daily standard dose of oral oestradiol and vaginal progesterone (*Humaidan et al., 2010*); six doses of 300 IU recombinant LH (given on alternate days) with daily standard dose of oral oestradiol and vaginal progesterone (*Papanikolaou et al., 2011*); daily dose of 125 IU HCG until pregnancy test (*Andersen et al., 2015*); nasal buserelin three times a day (*Bar-Hava et al., 2016*); triptorelin (Decapeptyl) 0.1 mg every other day and daily vaginal progesterone (*Wiser at al., 2019*); a single bolus of HCG 1500 IU 3 days after oocyte retrieval and daily intensive oestradiol and progesterone (*Haas et al., 2014*).

To simplify luteal support for patient convenience, and maintain maximal support efficacy, we have suggested that a single bolus of 1500 IU HCG given 48 h after oocyte retrieval is all that is needed. The rationale for this approach has been described in detail previously (*Kol, 2019*). Briefly, it is based on two important time points that fortunately coincide: luteolysis after GnRH agonist trigger starts 48 h after oocyte retrieval (*Tannus et al., 2017*); and maximal progesterone after HCG is achieved 5 days after its administration (*Goldrat et al., 2015*; *Young et al., 2020*).

Therefore, it was reasoned that to obtain increasing progesterone levels from oocyte retrieval to mid-luteal phase, a single bolus of 1500 IU HCG timed exactly when luteolysis begins could be sufficient. If pregnancy is achieved, endogenous HCG will take over the role of corpora lutea stimulation, hence additional oestradiol and progesterone support is redundant.

In a previous proof of concept publication (*Vanetik et al., 2018*), 44 pregnancies achieved were compared with GnRH agonist trigger followed by day-2 HCG (1500 IU) support only, with 44 pregnancies obtained with HCG (6500 IU) trigger followed by conventional progesterone luteal support (control group). It was concluded that a bolus of 1500 IU HCG, administered 2 days after retrieval, can provide excellent support without the need to further supplement with progesterone.

In the present study, this approach was further evaluated by comparing the outcomes of cycles in patients triggered with GnRH agonist supported with a single bolus of 1500 IU HCG 48 h after oocyte retrieval, with patients triggered with HCG and supported by daily vaginal progesterone.

MATERIALS AND METHODS

This is a non-interventional retrospective cohort study involving a single IVF unit. From April 2017 to August 2018, data of consecutive patients who fulfilled the study criteria were collected. The aim was to obtain data from 150 patients in each arm, a goal that was reached during the above-mentioned period.

Inclusion criteria were as follows: all patients treated with a GnRH antagonist ovarian stimulation protocol for IVF and intracytoplasmic sperm injection (ICSI); number of oocytes retrieved ranged from six to 15; and patients aged younger than 40 years.

Exclusion criteria were as follows: endometriosis; repeated implantation failure; endometrial lining less than 7 mm (on the day of the triggering); long agonist protocol; current endocrine disorder (pituitary disease, thyroid disease or adrenal disease); and cancer.

Progesterone measurement had an upper quantitation limit of 190 nmol/l. All results above 190 nmol/l were given as '>190 nmol/l'. For statistical analysis all these cases were recorded as $P = 191$ nmol/l.

Oestradiol measurements were all below the upper quantitation limit of the assay, and all values were exact. Therefore, oestradiol results reflect endogenous luteal phase activity for both groups.

A single physician (SK) followed most patients in the study group; other physicians working with the IVF unit followed the control group.

Study protocol

A GnRH antagonist 'short' protocol as used for ovarian stimulation. Cycles were monitored according to the policy of the clinic, or by treating physicians. Triptorelin (Decapeptyl 0.2 mg) (Ferring, Saint-Prex, Switzerland) was used for final oocyte maturation trigger in the study group and choriogonadotropin alfa (Ovitrelle 250 µg) (Merck, Kenilworth, NJ, USA), mostly in a pre-filled syringe device, was used in the control group. The final oocyte maturation trigger was administered as soon as three leading follicles reached 17 mm in diameter or wider; oocyte retrieval was carried out 34–36-h later. Oocytes were fertilized with conventional IVF or ICSI, according to individual patient criteria.

The study group included 154 patients triggered with GnRH agonist and supported with a single bolus of 1500 IU HCG (Ovitrelle, equivalent to 62 µg) administered 48 h after oocyte retrieval.

The control group included 155 patients triggered with HCG 6500 IU (Ovitrelle 250 µg) and supported by daily vaginal progesterone preparations.

TABLE 1 MAIN CHARACTERISTICS OF THE STUDY AND CONTROL GROUPS

	Study (*n* = 154)	Control (*n* = 155)	*P*-value
Age, years	31.1 ± 4.1	32.9 ± 4.1	<0.001
Fertilization procedure, %			0.39
ICSI	83.8	80.0	
IVF	16.2	20.0	
Oocytes retrieved, *n*	10.1 ± 3.4	8.2 ± 3.8	<0.001
Fertilizations, *n*	5.9 ± 3.1	4.8 ± 3.0	0.002
Embryos obtained, *n*	4.4 ± 2.5	3.4 ± 2.2	<0.001
Embryos transferred, *n*	1.9 ± 0.7	2.0 ± 0.7	0.041
Embryos cryopreserved, *n*	2.6 ± 2.6	1.5 ± 2.2	<0.001

Data presented as mean ± SD unless otherwise stated.

For each patient, primary clinical outcomes were obtained, including beta-HCG, oestradiol and progesterone as measured 14 days after oocyte retrieval, and gestational sacs with fetal heart beats about 1 month after oocyte retrieval. Secondary clinical outcomes included number of oocytes retrieved, number of normally fertilized oocytes, number of embryos obtained, number of embryos transferred, number of embryos frozen and 'take home' baby rate (live birth rate). Data on the number of follicles wider than 11 mm on the day of trigger and incidence of OHSS were not collected.

Statistical analysis

To formulate the research groups, two groups with the same number of participants were formed. For this purpose, pre-evaluation of the repository was conducted, and it was decided to include at least 300 patients in the study.

The association of luteal support variants (1500 IU HCG, progesterone) and outcome (live birth, ectopic pregnancy, negative beta-HCG and miscarriage) was examined using Pearson's chi-squared test. Independent samples t-test was used to make comparisons between groups and other continuous data, and Pearson's chi-squared test was used for comparisons of groups and other categorical data.

The primary outcomes of the study were ongoing pregnancy and hormonal level assessments. The ongoing pregnancy rate analysed by the difference between two groups and its corresponding 80% confidence interval will be estimated with Pearson's chi-squared test.

Hormonal levels (oestradiol, progesterone and HCG) 14 days after triggering were compared between treatment groups by using independent samples t-test or Mann–Whitney U test, depending on the normality of the distribution of the results.

Secondary endpoints included the following clinical parameters: number of oocytes retrieved; fertilization rate; number of embryos (obtained, transferred and cryopreserved); gestational sack; fetal heartbeat at 6-weeks' gestation; and number of newborns. All were analysed as categorical variables presented with number and its corresponding SD and compared using Pearson's chi-squared test. In addition, the levels of oestradiol were compared 14 days after triggering between groups by using independent samples t-test. Finally, two adverse events were compared between the groups: miscarriages and ectopic pregnancy using Pearson's chi-squared test. Significance was set at $P < 0.05$ for all tests.

SPSS software package (Release 20.0.0.0, SPSS Inc., 2011) was used for statistical analysis. This study was approved by 'Meuhedet' health maintenance organization (HMO) IRB (number 02-29-05-19, 28 November 2019).

RESULTS

A total of 154 cycles were included in the study group and 155 cycles in the control group. Baseline characteristics, i.e. age, fertilization procedure, number of oocytes retrieved, number of embryos obtained and transferred, are presented in TABLE 1. Patients in the study group were younger compared with the control group (31.1 ± 4.1 versus 32.9 ± 4.1; $P < 0.001$). Patients in the study group had more oocytes retrieved (10.1 ± 3.4 versus 8.2 ± 3.8; $P < 0.001$), more fertilized oocytes (5.9 ± 3.1 versus 4.8 ± 3.0; $P = 0.002$), more embryos obtained (4.4 ± 2.5 versus 3.4 ± 2.2; $P < 0.001$) and more embryos cryopreserved (2.6 ± 2.6 versus 1.5 ± 2.2; $P < 0.001$) compared with the control group.

Mean progesterone levels (14 days after oocyte retrieval) in the study (no progesterone supplementation) and control (progesterone supplemented) groups (TABLE 2) were 161 nmol/l and 166 nmol/l, respectively ($P = 0.8$) in positive beta-HCG cycles. Mean oestradiol level (14 days after oocyte retrieval) in the study group was 4719 pmol/l (range 191–13,973), significantly higher (<0.001) than in the control group (2673 pmol/l; range 73–9107) in positive beta-HCG cycles.

Pregnancy and live birth rates were comparable between the two groups, with pregnancy rates of 46.8% and 45.2%, and live birth rates of 38.3% and 40% in the study and control groups, respectively (TABLE 3) ($P = 0.66$ for cycle outcome). Miscarriage rate was 7.1% and 3.9% in the study and control groups, respectively.

The progesterone level of miscarriage cases on the day of HCG trigger in the study group was further evaluated. In all of but one, progesterone (14 days after oocyte retrieval) was above upper measurement limit (>190 nmol/l) and mean oestradiol was 4083 pmol/l, confirming the fact that the miscarriages were not related to a lack of luteal support. In one case, low progesterone level (12 pmol/l) was found. It was assumed that this patient did not inject the Ovitrelle correctly.

DISCUSSION

The main purpose of luteal phase support is to secure favourable hormonal conditions for embryo implantation. Our cohort retrospective study confirms that, after GnRH agonist trigger, luteal phase support based on 1500 IU HCG given 2 days after oocyte retrieval is comparable to HCG trigger followed by daily vaginal progesterone in main clinical outcomes.

In a natural cycle, progesterone levels over 30 nmol/l may be sufficient to maintain pregnancy. *Yovich et al. (1985)* documented that, in IVF cycles, luteal phase progesterone levels were two to three times higher than that expected during spontaneous conception cycles.

TABLE 2 MEAN HORMONAL LEVELS MEASURED 14 DAYS AFTER OOCYTE RETRIEVAL IN POSITIVE BETA-HCG CYCLES

	Study (*n* = 72)	Control (*n* = 70)	*P*-value
HCG levels 14 days after oocyte retrieval, IU/l	176.3 ± 149.4	273.6 ± 344.0	0.03
Progesterone levels 14 days after oocyte retrieval, nmol/l	160.8 ± 73.3	166.5 ± 146.5	0.80
Oestradiol levels 14 days after oocyte retrieval, pmol/l	4719.3 ± 2708.6	2672.78 ± 2229.7	<0.001
Number of gestational sacs, *n* %			0.85
0	2 (2.8)	2 (2.9)	
1	55 (76.4)	56 (80.0)	
2	15 (20.8)	12 (17.1)	
Fetal heartbeat at 6-weeks' gestation, *n* %			0.45
0	7 (9.7)	3 (4.3)	
1	52 (72.2)	54 (77.1)	
2	13 (18.1)	12 (17.1)	

Data presented as mean ± SD unless otherwise stated.

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 was more than enough in that regard.

In the present study, oestradiol levels can reliably reflect luteal activity in both groups, as both groups were not supplemented with exogenous oestradiol. As oestradiol levels were significantly higher in the study group, we may conclude that our approach results in robust luteal phase stimulation, leaving any additional vaginal supplementation redundant. Therefore, the discomfort and burden associated with prolonged vaginal progesterone administration can be avoided. Mean oestradiol level in the study group was almost twice that measured for the control group, exactly as we reported in a previous publication (*Vanetik et al., 2018*).

The conventional low-dose HCG rescue bolus is given on the day of oocyte retrieval (*Humaidan, 2010*), which is 6–7 days before embryo implantation. As maximal progesterone is reached 5 days after HCG administration, mid-luteal progesterone might be too low. This low dose may not be sufficient to stimulate adequately the corpora lutea around the window of implantation; therefore, additional progesterone support is needed. Indeed, mid-luteal progesterone after 1500 IU HCG on day of oocyte retrieval was previously shown to be 74 nmol/l (*Humaidan et al., 2010*), reflecting a decrease from its peak 2–3 days before. To secure the best chance for embryo implantation, mid-luteal progesterone level should be over 150 nmol/l (*Thomsen et al., 2018*). By delaying HCG administration for 48 h, complete corpora lutea rescue is possible, securing more than enough progesterone in the implantation window 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 (*Baker et al., 2014*).

A miscarriage rate of about 10% cannot be avoided, even if the system provides ample progesterone. In women undergoing ovulation with GnRH agonist trigger, pregnancy loss converges to 10% if mid-luteal phase progesterone levels exceed 100 nmol/l (*Yding Andersen and Andersen, 2014*). Therefore, it seems that a sharp decline in miscarriage rate from about 80% to 10% occurs as the mid-luteal-phase progesterone concentration increases from about 40 nmol/l to about 80–100 nmol/l. In contrast, increasing the mid-luteal progesterone concentration beyond 100 nmol/l does not seem to reduce the miscarriage rate any further; it maintains it at a low rate of about 10%. In our series, almost all miscarriage cases developed despite progesterone levels being over 100 nmol/l. In one case, progesterone was lower, probably owing to mistaken application of the dose, before a pen device was available. Miscarriage rate must be further evaluated in a randomized controlled trial.

The present study confirms previous studies describing the advantage of GnRH agonist trigger over the conventional HCG trigger in number of retrieved oocytes, fertilization rate and available embryos (*Reddy et al., 2014*). The study group, however, was younger than the control group (31.1 versus 32.9 years), which can explain the difference in oocyte yield.

TABLE 3 CYCLE OUTCOME IN THE STUDY AND CONTROL GROUPS

	Study (*n* = 154)	Control (*n* = 155)	*P*-value
Cycle outcome, *n* %			0.66
Negative HCG	82 (53.2)	85 (54.8)	
Live birth	59 (38.3)	62 (40.0)	
Miscarriage	11 (7.1)	6 (3.9)	
Ectopic pregnancy	2 (1.3)	2 (1.3)	
Newborns, *n* (%)			0.89
1	47 (79.7)	50 (80.6)	
2	12 (20.3)	12 (19.4)	

The obvious disadvantage of our study is its retrospective nature. This fact may affect the results, and a possible bias cannot be ruled out, as the study group is a better prognosis group in all parameters except the number of embryos transferred. In addition, as we included patients with up to 15 retrieved oocytes, a fair assumption can be made that patients with higher oocyte yield could develop OHSS.

In conclusion, the need for a randomized controlled trial is reiterated. From an endocrine perspective, we think it adequately delineates the concept of achieving sufficient endogenous progesterone production in the luteal phase, without resorting to additional support.

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Received 28 April 2020; received in revised form 20 July 2020; accepted 24 July 2020.