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Does HCG Luteal Support Improve Pregnancy Rates in GnRH Antagonist IVF Cycles and GnRH Agonist Trigger? A Randomized Controlled Trial.

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ABSTRACT

Background: Ovarian hyperstimulation syndrome (OHSS) remains one of the most serious complications in IVF cycles. hCG the gold standard for ovulation trigger carries the risk of initiating the cascade of events leading to OHSS, especially in patients with high ovarian response. In patients undergoing IVF using the GnRH antagonist protocol with GnRH agonist trigger instead of hCG there is a lower risk of OHSS but on the expense of a lower pregnancy rate than patients receiving the traditional hCG trigger.
Aim of work: To evaluate whether a single dose of hCG 1500 units given to patients using the GnRH agonist trigger would improve pregnancy rates, without increasing the risk of OHSS.
Patient and Methods: This is a randomized controlled trial, set in Adam International IVF Hospital from December 2014 till June 2015. 154 patients undergoing IVF using the GnRH antagonist protocol and triggered with GnRH agonist. Administering a single dose of hCG 1500 units immediately after ovum pick-up, compared to no hCG. Main outcome measure is chemical pregnancy rate. Other outcome measures include clinical pregnancy rate and incidence of OHSS.
Results: There was a significant difference in chemical and clinical pregnancy rates (58.8% vs 35.9%, P 0.0485, 51.6% vs 20.0%, P 0.0001) in favour of intervention. No cases of severe OHSS were recorded in either groups.
Conclusion: Giving a single dose of hCG 1500 units immediately after ovum pick-up significantly improves pregnancy rates without increasing the incidence of severe OHSS. The trial was registered with Pan African Clinical Study Registry (www.pactr.org), no. PACTR201512000952372.

Keywords: *agonist trigger; antagonist protocol; HCG 1500 units, pregnancy rate*

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) remains one of the most serious complications in IVF cycles [1]. Primary prevention is the mainstay for avoiding such a complication [2]. HCG has been the gold standard for ovulation trigger as a surrogate for the mid-cycle LH surge for several decades, but it carries the risk of initiating the cascade of events leading to OHSS [1].

GnRH antagonist has been widely used in IVF protocols, and, if combined with GnRH agonist trigger, could largely reduce the incidence of early OHSS, if not entirely eliminate it [3,4]. In the early nineties, the final maturation of oocytes with a GnRH agonist was described.[5]. Aiming at reducing or preventing clinically significant OHSS. This is mainly due to the rapid and irreversible luteolysis. This unfortunately significantly reduced the pregnancy rates [6].

In 2006, Humaidan et al introduced the concept of adding a single "mini dose" of hCG for those patients as an additional measure for luteal support together with Progesterone [7]. This protocol has been incriminated to potentially increase the incidence of OHSS. To our knowledge, no controlled randomized trials (comparing giving and not giving hCG) have been published until now to study whether this protocol could really improve pregnancy rates and if so whether it would compromise the safety of patients.

PATIENT AND METHODS

This study is a prospective controlled randomized clinical trial. It was conducted between December 2014 and June 2015 at Adam International Hospital in Giza, Egypt, which is a private hospital performing about 3000 IVF cycles yearly. The trial was registered with the Pan African Clinical Study Registry (www.pactr.org), no. PACTR201512000952372.

Inclusion criteria:

We included patients between 18 and 40 years of age, who received GnRH antagonist for down-regulation and GnRH agonist as a trigger injection, and from whom < 25 cumulus-oocyte masses were retrieved.

Exclusion criteria:

Presence of significant symptoms and / or signs of OHSS on day of ovum pick-up (OPU), e.g. significant nausea, vomiting, shortness of breath, abdominal pain, fluid in pouch of Douglas (PoD) or abdominal distension.

- BMI > 19 kg/m2
- Past history of OHSS

Power calculation:

With an established pregnancy rate of 33% at our center in the group of patients who received the standard GnRH antagonist down-regulation, Triptoreline trigger, and only Progesterone for luteal support; and assuming an improvement of pregnancy rate to reach 50% on adding a “mini dose” of hCG for luteal support, with a power of 80% (1–β=0·80) and significance (α, two-tailed) of 5%, power calculation showed that each arm should include 64 patients.

Randomization:

This was done by means of sealed opaque envelopes randomizing the patients into either “Give hCG” or “Do Not Give hCG.”

Ethical approval:

This study was approved by the local ethics committee of Adam International Hospital and fulfilled the ethical considerations in accordance with the declaration of Helsinki for medical research involving human subjects. An informed consent was taken from all women who were enrolled in the study.

Statistical analysis:

This was a superiority study undertaken to test the hypothesis that compared to Triptoreline triggering given to women, luteal support with a single dose of hCG 1500 units may increase the rate of chemical and clinical pregnancy. The primary outcome measure was the rate of chemical pregnancy.

The primary and secondary outcomes of clinical and chemical pregnancy respectively are dichotomous variables that were analyzed statistically using Z test for difference in proportions using ITT analysis .

Baseline characteristics for women were summarized and analyzed. Chi-square test was used to compare differences in binary variables; t-test was used to compare differences in continuous variables as appropriate. All analyses were carried out with SPSS version 15.

Intervention:

Protocols for ovulation induction are initiated by a Consultant or Senior Specialist at our center. According to the clinical, hormonal and ultrasonographic criteria of each patient, and when deemed appropriate, patients were put on the standard GnRH antagonist protocol. We used Follitropin alpha (Gonal-F pen, Merck Serono) for ovulation induction, starting on day 2 of the menstrual cycle, with a dose tailored for each individual patient. For this study, we used Cetrorelix (Cetrotide, Merck Serono) 0.25 mg starting on day 5 of ovulation induction, and taken daily until the time of triggering. The patients were followed up by trans-vaginal ultrasonography and serum Estradiol regularly until 3 or more follicles reached a diameter of 18 mm. Again, when deemed appropriate, and for the sake of preventing OHSS, some patients with a higher risk were given the GnRH agonist Triptoreline (Decapeptyl, Ferring) 0.2 mg as a single subcutaneous injection as a trigger injection.

Ovum pick-up (OPU) was scheduled 35-36 hours after the trigger injection. On the morning of OPU, each patient was assessed by a Senior Specialist. If it was confirmed that she fulfilled the inclusion criteria and that none of the exclusion criteria was present, the patient was counseled for possible participation in the study, and informed consent was obtained at least 2 hours prior to the scheduled procedure. The final decision for enrolment was only taken after OPU, when it was confirmed that no more than 25 cumulus-oocyte complexes were obtained, and that there was no or minimal free fluid in the pouch of Douglas seen on ultrasonography during the procedure. Only then would the patient be randomized.

For the intervention group, 1500 units of hCG (Choriomon, IBSA) were given as a single intramuscular injection within 2 hours from the culmination of OPU. A vial of hCG 5000 units was reconstituted in 3 mL of normal saline, 2.1 mL were discarded and each patient received 0.9 mL of the solution .

Control group patients received no injections.

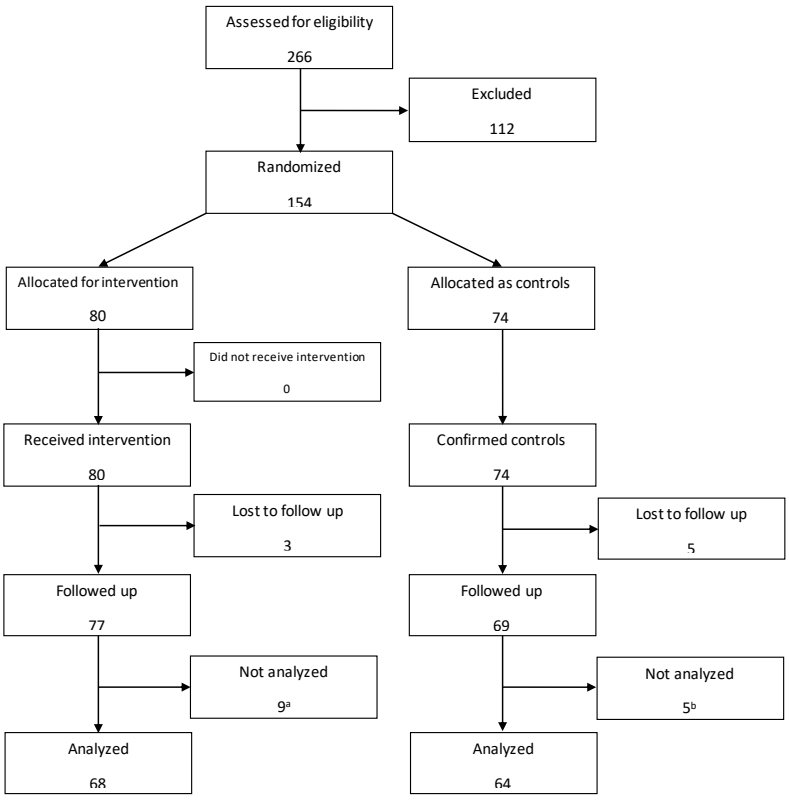
All patients received Progesterone (Cyclogest, Actavis) 400 mg intra-vaginally twice daily as luteal phase support.

Follow-up of all patients was performed as follows: All patients were advised to call or come to the hospital if they feel unwell or if they develop any significant symptoms of OHSS. Also, on the day of embryo transfer (ET) all patients were assessed clinically and by abdominal and vaginal ultrasonography by a Senior Specialist for any evidence of OHSS.

Serum β-hCG was assessed 14 days after ET, and if positive trans-vaginal ultrasonography was performed 14 days thereafter.

RESULTS

A total of 154 patients were recruited for this study, and all of them consented to take part, and were therefore randomized between the 2 groups. For group 1 (intervention group) 80 patients were allocated, and 74 patients were allocated for group 2 (control group). All 80 patients allocated for group 1 received the proposed intervention. In this group, 3 patients were lost for follow up, and 5 patients in group 2 were also lost for follow up. On assessment of the patients on the day of embryo transfer (ET), 9 patients from group one and 5 from group 2 did not have ET. The main reason (for 7 from group 1 and all 5 in group 2) was to prevent OHSS. Those patients had some symptoms and signs of early mild OHSS, so it was decided not to transfer embryos to prevent any further risk of escalation of the condition. One patient in group 1 had a thin endometrium (6 mm), and another from the same group had fever (flu). Therefore, results were analyzed for 68 patients in group 1 and 64 patients in group 2 (Figure 1).



[a] Cancelled ET: 7 with picture of early mild OHSS, 1 with thin endometrium, 1 with fever (flu)

[b] Cancelled ET: 5 with picture of early mild OHSS

Fig. 1: Flow char of patiants recruited.

Both groups were similar regarding age, basal FSH, AMH and number of previous IVF trials. There was also no difference in the levels of E2 and endometrial thickness on day of triggering. The two groups had a similar number of Metaphase II (M II) oocytes obtained and were similar as regards the embryos transferred (number and grade of embryos, and day of ET) (Table 1).

Variable		Study group	Control group	p value
Age (years)		28.7 (5.0)	28.5 (4.8)	0.47
Day 2 FSH (mIU/mL)		7.0 (1.5)	6.8 (1.4)	0.30
AMH (ng/mL)		3.9 (2.6)	4.2 (2.6)	0.78
No. of previous trials		0.4 (0.8)	0.3 (0.7)	0.53
E2 on day of triggering (pg/mL)		5459.7 (2424.2)	4793.2 (2206.8)	0.07
Endometrial thickness on day of triggering (mm)		10.6 (1.9)	10.6 (2.0)	0.63
No. of M II oocytes obtained		14.9 (5.5)	16.0 (5.1)	0.62
Day of embryo transfer		4.4 (1.0)	4.0 (1.0)	0.58
No. of embryos transferred		2.5 (1.3)	2.7 (0.8)	0.45
Grade of embyos transferred	**Good embryos**	1.3 (1.1)	1.6 (1.2)	0.80
	Fair embryos	0.5 (0.8)	0.6 (0.9)	0.43
	Bad embyos	0.6 (1.1)	0.5 (0.9)	0.09

Table 1: Baseline characteristics of study and control groups (values are presented as Mean (SD)).

We summarized the outcome of this study in (Tabel 2). There was a significant difference in chemical pregnancy rate in favour of intervention (58.8% vs 35.9%, p = 0.0485). This superiority was much clearer when clinical pregnancy rates were compared (51.6% vs 20.0%, p = 0.0001).

Variable	Study group	Control group	p value
Chemical pregnancy (%)	40/68 (58.8%)	23/64 (35.9%)	0.0485*
Clinical pregnancy (%)	33a/64b (51.6%)	12c/60d (20.0%)	0.0001**
[a] Out of 40 patients: 1 patient with ectopic pregnancy, 2 patients with blighted ovum, 4 lost to further follow up			
[b] Out of 68 patients: 4 lost to further follow up			
[c] Out of 23 patients: 4 patients with ectopic pregnancies, 3 patients with blighted ovum, 4 lost to further follow up			
[d] Out of 64 patients: 4 lost to further follow up			
* Statistically significant			
** Highly statistically significant			

Table 2: Main results of study and control groups

Another striking finding that is worth mentioning was that ectopic pregnancies occurred more frequently in the control group (4/60; 6.7%) as compared to the intervention group (1/64; 1.6%).

There were two cases of mild/moderate OHSS in group 1, and 1 case in group 2. None of them needed tapping of ascetic fluid nor received albumin, and only one patient in group 1 was admitted to hospital for 24 hours for observation. No patients developed late OHSS.

DISCUSSION

OHSS remains to be one of the most serious and potentially fatal risks that face IVF programs [1]. Many strategies tried to reduce this risk, ranging from reducing hCG dose, cycle cancellation, coasting, and triggering with GnRH agonist in antagonist cycles. Unfortunately, all these strategies were on the expense of a markedly lowered pregnancy rate [2,8]. The concept of cycle segmentation was thought to be the way forward to eliminate this risk. Yet, this comes with the price of a prolonged time to achieve pregnancy, increased expenses due to freezing and endometrial preparation, and facing the yet unknown long-term effects on embryos that have been frozen [9-10].

In 2006, Humaidan and his colleagues first introduced the idea of giving a mini dose (1500 Units) of hCG to GnRH agonist triggered cycles after GnRH antagonist protocols [7]. This aims to act as a rescue to the corpus luteum that suffers from significant degeneration after GnRH agonist trigger [11-12]. Some studies claimed that this could be the cornerstone for OHSS-free cycles with good pregnancy rates [4]. Those studies were either pilot studies [7], observational [12] or retrospective studies [13]. No randomized controlled trials have yet answered the question whether such patients could have a better outcome if an hCG mini dose were given, and if OHSS could still be entirely eliminated. In the literature we have cited a study (RCT) by Humaidan et al. in 2010 that compared the suggested protocol of adding hCG mini dose after GnRH agonist trigger and conventional trigger using 10000 Units of hCG. It concluded that this protocol is not different from hCG 10000 Units triggering in term of pregnancy rates [14]. It still has not resolved the dilemma of whether to give or not to give the hCG rescue dose in those who have actually been triggered by GnRH agonist. In an editorial article by Bodri, none of the trials he included could clearly answer the question [15].

This randomized controlled trial aimed to compare pregnancy rates and incidence of moderate/severe OHSS in patients undergoing IVF cycles using the antagonist protocol and agonist trigger. Patients were randomly allocated to receiving or not receiving a mini dose of hCG 1500 Units immediately after ovum pick-up. In our exclusion criteria, we tried to avoid very high-risk patients for the sake of safety. The results vary significantly favoured giving hCG. Chemical pregnancy rates were 58.8% in the hCG group as compared to 35.9% only in the control group. This difference was more striking when we compared clinical pregnancy rates, that were more than 2.5-fold in the hCG group (51.6% vs 20%). Chemical and clinical pregnancy rates in GnRH agonist-triggered patients (without hCG) were consistently low in many studies, very similar to those of our control group [6]. Both groups in our trial were similar in all other known aspects that could affect pregnancy rates, including transferred embryo numbers and grades, day of transfer and endometrial thickness on day of triggering, and age. Hence, we believe that the only reason for this markedly improved pregnancy rates could be due to the single dose of hCG 1500 Units .

In a non-controlled retrospective study by Iliodromiti et al. in 2013, they concluded that clinical pregnancy rates reached 41.8% in high risk patients after a similar protocol. However, they reported 2 cases of severe OHSS and were therefore skeptical and recommended further studies to assess this risk [16]. In our trial, there were two cases of mild/moderate OHSS in the hCG group, and 1 case in the control group. None of them needed tapping of ascetic fluid nor received albumin, and only one patient in the hCG group was admitted to a regular ward in hospital for 24 hours for observation. No patients developed late OHSS. These results are generally better than those reported in other trials [16-17]. The reason behind this difference in our opinion is that we were relatively selective in the patients recruited for this study.

There was another striking finding that is worth mentioning in our study: ectopic pregnancies occurred more frequently in the control group (4/60; 6.7%) as compared to the intervention group (1/64; 1.6%). This could further prove the theory of a more receptive endometrium after hCG as compared to an "un-welcoming" endometrial after GnRH triggering and no hCG. This will need further exploration.

One of the drawbacks of our study is that we did not report on take-home baby rate. The reason behind that was that our cohort of patients come from far places in Egypt, and once have achieved a clinical pregnancy prefer to travel back to their hometowns for further ante-natal care. Very frequently we lose contact with them.

CONCLUSION

Giving a single dose of hCG 1500 units immediately after ovum pick-up in patients undergoing IVF using the GnRH antagonist protocol (Cetrorelix) and triggered with GnRH agonist (Triptoreline) significantly improves chemical and clinical pregnancy rates without compromising the safety of the patients regarding the incidence of severe OHSS.

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