The effects of low-dose human chorionic gonadotropin for luteal phase support on pregnancy outcomes in poor ovarian responders: a randomized clinical trial

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Research Article

Keywords: luteal phase support, poor ovarian response, live birth rate, assisted reproductive technology

Posted Date: March 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-328212/v1

Abstract

Purpose: The question that remains is, does changing the type of luteal phase support (LPS) improve the pregnancy outcomes in patients with poor ovarian response (POR) diagnosis?. Therefore, this study was designed to investigate and compare the efficiency of different methods of luteal phase support (progesterone alone or hCG alone and the combination of progesterone with hCG) in these patients.

Methods: This randomized clinical trial evaluated three hundred seventy five patients who were diagnosed as POR on the basis of Bologna criteria undergoing intracytoplasmic sperm injection- embryo transfer (ICSI-ET) cycles at Royan institute from November 2015 to June 2019. The patients were allocated randomly into three different LPS groups on the day of oocyte pickup. In first group, 1500 IU of hCG IM on the ET day, as well as 4 days after that were administrated. In the second group, the patients received 1500 IU of hCG IM on the ET day, as well as 3 and 6 days after the ET along with vaginal suppositories 400 mg twice daily. For the third group, only vaginal suppositories twice daily was administrated from the day of oocyte pick up until the pregnancy test day.The clinical pregnancy, miscarriage and live birth rates were the main outcomes.

Results: The data analysis showed that the three groups were comparable. In the following, there is no significant difference in terms of implantation, clinical pregnancy, and miscarriage and live birth rates among groups. The twin pregnancy rate in the hCG-only group was higher than those of in the other two groups, although this difference was not statistically significant (P=0.06).

Conclusion: The type of LPS does not improve the pregnancy and live birth rates in POR patients. A multi-center clinical trial is warranted to confirm or refute these findings.

Trial registration: The study was registered in the clinicaltrial.gov site on 14 June 2015. (NCT02798653 at www. clinicaltrials.gov, registered prospectively).

Introduction

The requirement of luteal phase support (LPS) in assisted reproduction cycles is well established, but the issues that remain controversial are the ideal drug, the appropriate route of administration, the timing and duration of support [1]. The progesterone production in luteal phase is a key component that is necessary for the successful implantation of the developing embryo. Different route of progesterone administration was used including oral, intramuscular, subcutaneous and vaginal. Recently, different types of vaginal progesterone (suppositories, gels and tablets) are common choice for LPS; however, those may be associated with different side effects and discomfort of patients [2]. The need for simplified treatment approaches which will lessen the treatment burden of IVF is self-evident; therefore, clinical physicians in ART medicine usually recommend drug therapy with lower doses and repeated use. For example, the use of only two dose of human chorionic gonadotropin hormone (hCG) injection for luteal phase support is more comfortable and tolerable than administration of progesterone daily, either vaginally or by injection for patients.

A number of clinical trials have been compared the effect of hCG and progesterone for luteal phase support; the results of a recent *meta-analysis showed that there were no statistically significant difference among different luteal phase support methods* in terms of clinical pregnancy, miscarriage and ongoing pregnancy rates; therefore, it seems that progesterone alone is the best strategy due to lower risk of OHSS [3]. Recently, use of micro-dose of hCG without exogenous progesterone for luteal phase support has been considered and it is hypothesized that corpus luteum produces other hormones than estrogen and progesterone, which are essential for endometrial preparation and optimization of the environment for embryo implantation and development [4].

Due to the fact that in patients with poor ovarian response (POR) diagnosis, there is no risk of OHSS and on the basis of the novel concept that suggested two boluses of 1500 IU hCG with no additional luteal support revert the luteolysis after a GnRHa trigger in the normo-responder patient [5], designing a clinical trial study to evaluate this simple and patients friendly method for luteal phase support in POR patients is gaining interest. Therefore, this clinical trial was designed to investigate and compare the efficiency of different methods of luteal phase support (progesterone alone or hCG alone and the combination of progesterone with hCG) in these patients. It is hoped that the results of this study would be useful in improving the clinical pregnancy rate and in making decision for the best method of luteal phase support in these women.

Methods

This randomized clinical trial was carried out to investigate the efficacy of different luteal phase support methods in patients with poor ovarian response (POR) undergoing intracytoplasmic sperm injection (ICSI) cycles in Royan institute from November 2015 to June 2019. The study protocol is approved by the Institutional Review Board and Ethics Committee of Royan institute. The study is conducted according to the Declaration of Helsinki for medical research. All participants provided informed consent after receiving explaining the purpose of the study. The trial protocol was registered prospectively in Clinicaltrials.gov site (NCT02798653).

All the patients who diagnose as poor ovarian responders (POR) based on the Bologna criteria were eligible for participation in this study. In order to define the poor response in IVF, at least two of the following three features must be present: (i) advanced maternal age (over 40 years); (ii) a previous POR (total retrieved oocytes less than three oocytes using conventional protocols) and (iii) an abnormal ovarian reserve test (ORT) (antral follicle count of less than 5 on menstrual cycle day 2–3; and basal serum follicle stimulating hormone (FSH) concentration between 10 and 19 IU/l or serum anti-Müllerian hormone level less than 1 ng/ml). Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT. The advanced maternal age over 45 years old, cigarette, alcohol and drug *addiction,* diagnosis of ovarian failure including basal FSH above 20 IU/l or no antral follicle by ultrasound examination, severe male factor (azoospermia) diagnosis, severe endometriosis and the presence of hydrosalpinges, uterine factor (polyps, myoma and previous myomectomy,…), the patients with cardiovascular disease and/or

uncontrolled systemic or endocrine diseases and repeated implantation failures and repeated miscarriages cases were excluded from study.

The ovarian stimulation is performed with GnRH agonist stop or antagonist protocols for the eligible patients as explained in details previously. In both protocols, controlled ovarian stimulation is started on day 2 of menstrual cycle with 225 IU recombinant FSH (Gonal-F®; Serono Laboratories Ltd., Geneva, Switzerland) and 75 IU hMG (Menopur®; Ferring). The doses of gonadotropins were adjusted as ovarian response in the ultrasound monitoring and final oocyte triggering will be done with 10000 IU of hCG (Choriomon®; IBSA). If there were or more dominant follicles, oocytes retrieval will be done under transvaginal ultrasound guidance 32-34 hours after hCG administration.

On the day of oocyte pickup, patients are allocated randomly (by the blocked randomization method) into three groups to receive three different luteal support protocols. Permuted block randomization was prepared by the methodological advisor according to a computer-generated list. The patients' enrolment and assignment to different groups were carried out by a researcher midwife in the clinic. Each patient was participated in the study only once and if she had written consent. The researcher who followed the results of patients' treatment and the researcher who analyzed the data were kept masked to the type of LPS regimen.

In first group, 1500 IU of hCG IM on the embryos transfer (ET) day, as well as 4 days after that were administrated for luteal phase support. In the second group, the patients received 1500 IU of hCG IM on the ET day, as well as 3 and 6 days after the ET along with vaginal suppositories (Cyclogest ®, Actavis, *UK*) 400 mg twice daily. For the third group, only vaginal suppositories (Cyclogest ®, Actavis, *UK*) 400 mg twice daily was given for luteal support from the day of oocyte pick up until the pregnancy test day. Intracytoplasmic sperm injection was performed for all metaphase II oocytes. Embryos were cultured in a commercially available culture medium until the day of transfer. The obtained embryos at cleavage stage were replaced by an embryo transfer catheter (Guardia™, Access ET Catheter, Cook Medical), 2 or 3 days after oocytes retrieval. The serum ß-hCG level was checked 2 weeks after ET to confirm positive pregnancy test. The vaginal progesterone was administrated in all patients who become pregnant in all three groups until the 10th week of pregnancy. The pregnancy outcomes are compared among three study groups.

Outcome measures

The primary outcome was implantation (the number of embryos transferred for each patient), chemical pregnancy (only positive ß-hCG test) and clinical pregnancy (the presence of a gestational sac with fetal heart beat on vaginal ultrasound) rates. The secondary outcomes included early miscarriage (the spontaneous loss of a clinical pregnancy under 12 weeks of gestation) and late miscarriage (the spontaneous loss of a clinical pregnancy between 12 and 20 weeks of gestation) and live birth (the delivery of a living child irrespective of the duration of pregnancy) rates.

Statistical Analysis

Sample size was calculated on the basis of previous related studies by using the Power Analysis and *Sample Size* (*PASS*) software Version 11. A sample size of 125 patients was required in each group at a significance level of 0.05 and a power of 80%. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0. The continuous variables were compared among groups by the one-way analysis of variance (*ANOVA*) and were presented as mean ± standard deviation (SD). The chi-square test was applied for comparing the categorical variables among groups and the results were reported as numbers/percentages. The statistical significant level was considered at p value <0.05.

Results

A total of 524 women were evaluated to participate in the study. 38 patients did not consent to participate and 111 patients did not reach to ET stage; finally, 375 patients allocated into three groups randomly. 125 patients were received only two boluses of 1500 IU hCG (intervention group1), 125 patients were received three boluses of I500 IU hCG plus vaginal progesterone daily (intervention group 2), and 125 patients were received only vaginal progesterone daily (control group) (Fig. 1).

The analysis of data showed that the three groups were comparable and there was no significant difference in terms of age, BMI, duration of infertility, and other basic characteristics of patients among three groups (Table 1).

The ovarian stimulation outcomes are presented in Table 2. No difference existed among the three groups with respect to the type of COH protocol, total dose of gonadotropins and the duration of the ovarian stimulation, the number of retrieved oocytes, fertilization rate, number of good quality embryos transferred, and endometrial thickness on the day of ovum pickup. Coincidentally the ratio of 2 and 3-day cleavage stage embryos in the hCG-only group had a statistically significant difference in compared to other groups (P =0.007).

Table 3 shows the pregnancy outcomes in three groups. The analysis demonstrated that the implantation, clinical pregnancy, miscarriage and live birth rates were similar between groups.

The twin pregnancy rate in the hCG-only group was higher than those of in the other two groups, although this difference was not statistically significant (P=0.06).

Discussion

The present study was conducted to response the question of whether changing the type of luteal phase support (LPS) in patients with POR diagnosis improves the rates of clinical pregnancy and live birth. The results of the study showed that the type of luteal phase support did not affect the clinical pregnancy and live birth rates in POR patients, just the rate of twin pregnancy in the hCG -alone group was a little more than progesterone- alone group.

Fundamentally, LPS has been demonstrated as a vital part in IVF cycles because ovarian stimulation disrupts the particular function of corpus luteum (CL) by different mechanisms. The formation of several mature ovarian follicles, E_2 levels reach to supraphysiological ranges specifically during the follicular phase; moreover, progesterone levels increase in early days of luteal phase due to numerous CLs affected by triggering doses of hCG. Thus LH secretion decompressed during luteal phase afterwards, CL support by pituitary LH will not precede [6, 7]. Notwithstanding the foregoing, it is important to realize that the CL does not require supraphysiologic levels of LH/hCG to secrete high values of progesterone [8]. During the natural menstrual cycle, the LH level in the luteal phase rarely rises over 5–10 IU/L and most commonly is capable to elicit P levels up to 25–35 nmol/L. When ten CLs are exist, each will secrete P in amounts similar to the natural menstrual cycle when exposed to physiologic concentrations of LH/hCG [8]. Collectively, this results in high concentration of P. However, this condition occurs when the ovarian response is normal or excessive, and therefore in POR patients due to limited AFC and growing follicles and the lack of existence of suitable CL, the possibility of hormonal defects in the LPS is higher.

Several protocols have been developed to correct this hormonal inadequacy in IVF cycles, based on the substances used or the route of administration. The development of new regimens for LPS based on “low-dose” or “microdose” hCG supplementation was considered recently. In preliminary studies, four injections of 1500 to 2500 IU of hCG were administrated after final oocyte triggering with 10000 IU of hCG [9]; since then, several studies have examined different methods of luteal phase support using hCG alone or with progesterone in normal patients or donor patients[10-13]. With these regimes, the LH/ hCG concentration in the luteal phase often reaches more than five to ten times that observed in the normal menstrual cycle which make powerful luteal phase support; however, significantly increase the risk of OHSS[4]. In a recent Cochrane review study reported that the administration of hCG alone or in combination with progesterone to support the luteal phase should be avoided due to increase the risk of OHSS[3].

Moreover, a number of studies have suggested that in cases where GnRH agonist is used for the final oocyte triggering, very low doses of hCG of 100 to 150 IU per day could be appropriate option for the LPS [14, 15]. Progesterone levels in the middle of the luteal phase in this procedure were similar to the use of progesterone with 6500 IU of hCG to induce ovulation[8]. The limitation of this strategy that prevents from being applied to routine procedures is that the difficulty HCG dilution over time with normal saline to achieve a dose of 100 to 150 units and daily injection for the patient[4].

Considering that there is no risk of OHSS in POR patients, it seems that the study of this new LPS regime with low-dose hCG for improving pregnancy rate is valuable. Furthermore, women appear to prefer low-dose hCG administration to exogenous P administration, especially by the vaginal route.

In present study, when twin pregnancy rate was compared among groups, it was higher in the hCG–only group than that of in the P-only and hCG + P groups; however, it was close to significant level. In this regard, Var et al. reported that multiple pregnancies rate were significantly higher in the hCG+ P group than in the P-only and E_2 + P groups [11]. Similar to their findings, Ludwig et al. also found that multiple

pregnancy rate were higher in the hCG +P group than in the P-only group [10]. However, Ghanem and colleagues reported no statistical difference among the groups in terms of multiple pregnancies; they determined a higher tendency in the E_2 + P and hCG + P groups compared with the P-only group [16]. It is likely that the use of hCG for LPS are involved in increasing the rate of multiple pregnancies and more studies are necessary in this regard.

The main limitation of the study is that we did not consider the good quality euploid blastocysts and unique COH protocol as inclusion criteria. Although, in data analysis the number and quality of transferred embryos and the proportions of two COH protocols were similar among groups, it is recommended that these points be considered in future studies to eliminate these confounding factors.

In conclusion the present study is the first clinical trial to compare the effect of low-dose hCG with routine protocol for LPS in patients with POR diagnosis on the basis of the *Bologna* criteria. We found the same pregnancy and live birth rates in different regimes for LPS. Interestingly, the use of two bolus of low- dose hCG 1500 was associated a slight increase in multiple pregnancies. We recommend a multi-center clinical trial with a larger sample size in this field to confirm or refute our findings.

Abbreviations

POR: Poor ovarian response; LPS: luteal phase support; ICSI-ET: intracytoplasmic sperm injection- embryo transfer; rFSH: recombinant follicle stimulating hormone; ORT: abnormal ovarian reserve test; CL: corpus luteum; E_2: estradiol; HMG*:* human menopausal gonadotrophins; hCG: human chorionic gonadotropin; SD: standard deviation.

Declarations

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Competing interests

All authors have nothing to disclose.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Royan Institute and the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Ethics approval number: IR.ACECR.ROYAN.REC.1394.121).

Consent to participate

The eligible patients signed written informed consent prior to participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Authors' contributions

TM and FR designed the research. AA, FR and SHKH contributed in patient's selection, data collection, interpretation of data and manuscript writing/editing. AA and TM wrote the manuscript. ZZ helped in the analysis of the data. All authors read and approved the final manuscript.

Acknowledgments

We extend thanks to our colleagues in Royan Institute and all the women participated in this study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

Table 1: Comparison of demographic and basic characteristics of studied women in three groups

P value	Group C (Cyclogest) (n = 125)	Group B (three doses of hCG 1500 IU + cyclogest) (n = 125)	Group A (only two doses of hCG 1500 IU) (n = 125)	Variable
0.396	36.21 ± 4.846	35.72 ± 4.76	35.8 ± 4.712	Age (year)
0.503	26.12 ± 3.460	25.61 ± 3.596	25.79 ± 3.163	BMI (Kg/m^2)
0.288	5.172 ± 2.979	5.220 ± 3.068	4.994 ± 2.660	Basal serum LH level (IU/L)
0.735	8.172 ± 3,956	8.298 ± 3,969	7.807 ± 3.365	Basal serum FSH level (IU/L)
0.729	0.908 ± 0.687	0.962 ± 0.672	1,019 ± 1,024	serum AMH level (ng/mL)
0.253	7.436 ± 4.625	7.512 ± 5.263	6.44 ± 4.363	Duration of infertility
0.746	94 (75.2%)	89 (71.2%)	95 (76%)	No. of couple with primary infertility n (%)
0.334				Cause of infertility n (%)
	72 (57.6%)	71 (57.2%	75 (60%)	Ovulatory factor
	6	2	5	Unexplained factor
	12 (9.6%)	22 (17.7%)	13 (10.4%)	Ovulatory factor +Tubal factor
	35 (28%)	29 (23.3%)	32 (25.6%)	Ovulatory factor +Male factor
0.715				Subgroups of POR according to Bologna criteria
	7 (5.73%)	10 (8.47%)	11 (9.32%)	Subgroup I, n (%)
	51 (41.8%)	46 (38.9%)	55 (46.6%)	Subgroup group II, n (%)
	6 (4.91%)	2 (1.69%)	3 (2.54%)	Subgroup III, n (%)

37 (30.3%)	30 (25.4%)	28 (23.7%)	Subgroup IV, n (%)
21 (17.2%)	30 (25.4%)	21 (17.7%)	Subgroup V, n (%)

Descriptive data were presented as Mean ± SD. P-value≤0.05 was considered statistically significant. No.: number, FSH: Follicle stimulating hormone, LH = Luteinizing hormone, TSH= Thyroid stimulating hormone, AMH: Anti-müllerian hormone, E_2= estradiol, P= Progesterone. Subgroup I: age> 40 + a history POR or risk factor Subgroup II: one history of POR + abnormal ovarian reserve tests; Subgroup III: age> 40 + abnormal ovarian reserve tests or risk factor; Subgroup IV: a history of POR + age >40+abnormal ovarian reserve tests; Subgroup V: Two previous history of POR

Table2: Comparison of ovarian stimulation cycle results among three groups				
P value	**Group C** (Cyclogest) (n = 125)	**Group B** (three doses of hCG 1500 IU + cyclogest) (n = 125)	**Group A** (only two doses s of hCG 1500 IU) (n = 125)	Variable
0.483				Type of COH protocol
	75 (60%)	73 (58.4%)	69 (55.6%)	Antagonist
	50 (40%)	52 (41.6%)	55 (44.3%)	Agonist
0.136	2781.6 ± 1116.7	2688.0 ± 980.49	2576.4 ± 880.49	Total dose of used gonadotropins (rFSH+ hMG) (IU)
0.737	9.71 ± 2.31	9.96 ± 2.24	9.88 ± 2.48	Duration of stimulation (day)
0.329	3.88 ± 2.06	4.05 ± 1.75	4.05 ± 1.75	The total number of retrieved oocytes
0.626	3.16 ± 1.50	3.44 ± 2.00	3.35 ± 1.60	No. of metaphase II oocytes
0.960	0.53 ± 0.20	0.55 ± 0.21	0.56 ± 0.25	Fertilization rate mean ± (SD)
0.635	1.31 ± 0.91	1.42 ± 0.99	1.35 ± 0.93	The total number of grade AB transferred embryos
0.007				Day of embryo transfer
	80 (64%)	79 (63.2%)	100 (80%)	Day 2 embryo
	45 (36%)	46 (36.8%)	25 (20%)	Day 3 embryo
0.559	1,912 ± 0.729	1,952 ± 0.791	1,912 ± 0.762	The total number of embryos transferred
0.709	9.16 ± 1.55	9.08 ± 1.31	8.96 ± 1.31	Endometrial thickness on ovum pick up day (mm)

Table 3: Comparison of IVF- ICSI/ ET cycle outcomes among three groups

P value	Group C (Cyclogest) (n = 125)	Group B (three doses of hCG 1500 IU + cyclogest) (n = 125)	Group A (only two doses s of hCG 1500 IU) (n = 125	Variables
0.960	0.53 ± 0.20	0.55 ± 0.21	0.56 ± 0.25	Fertilization rate, mean ± (SD)
0.499	0.69 ± 0.27	0.71 ± 0.27	0.72 ± 0.29	Implantation rate, mean ± (SD)
0.689	2 (1.6%)	3 (2.4%)	5 (4%)	Chemical pregnancy rate
0.962	19 (15.2%)	20 (16%)	22 (17.6%)	Clinical pregnancy rate
0.060	0 (0%)	2 (1.6%)	4 (3.2%)	Twin pregnancy rate
0.236	8 (6.4%)	2 (1.6%)	5 (4%)	Miscarriage rate
0.676	19 (65.5%)	20 (80%)	21 (70%)	Live birth rate /ET

Figures

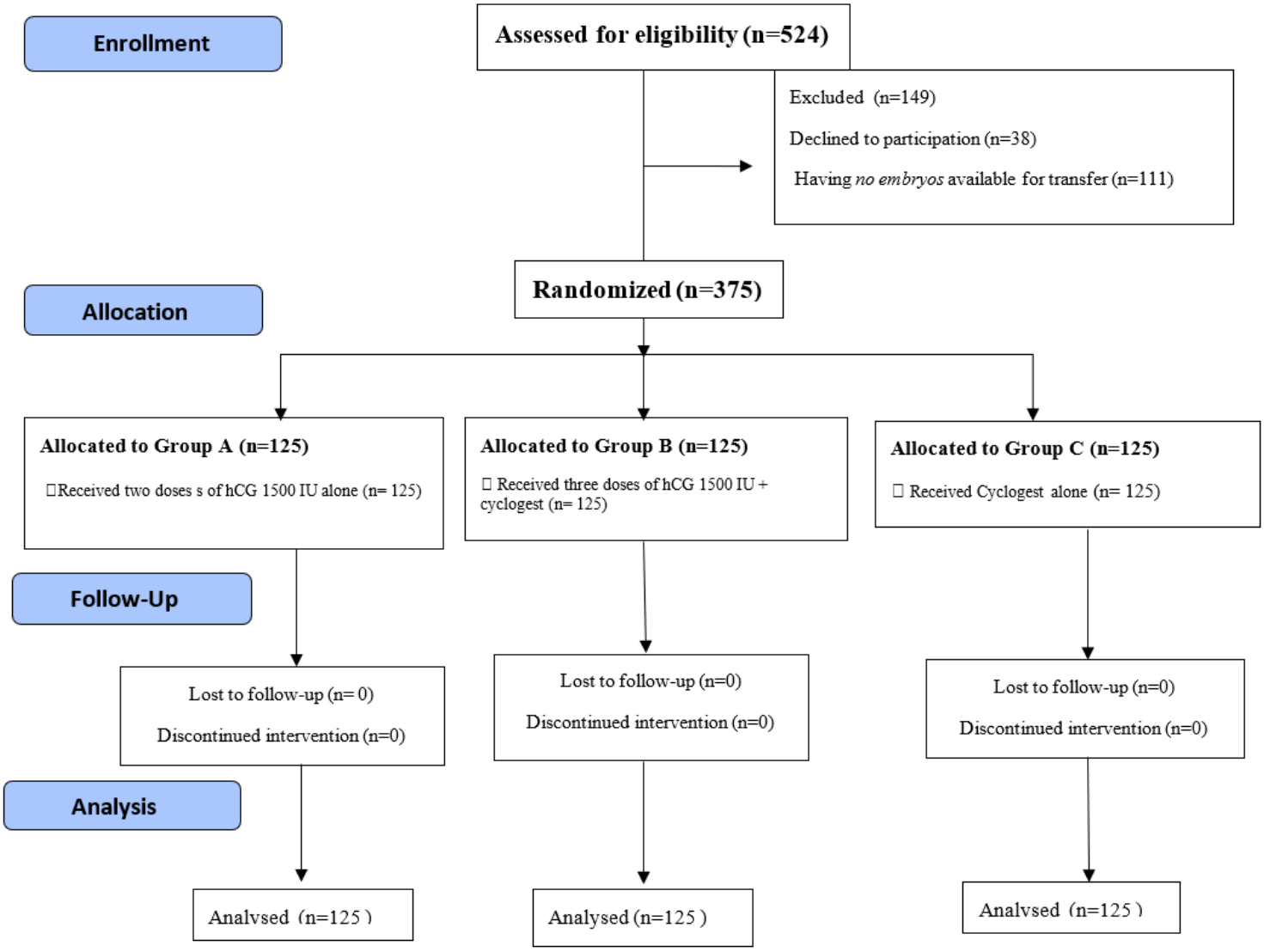

Figure 1

The study flowchart