

Dual trigger protocol is an effective in vitro fertilization strategy in both normal and high responders without compromising pregnancy outcomes in fresh cycles

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Objective: To study the birth rates of normal vs. high responders after dual trigger of final oocyte maturation with gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin in fresh in vitro fertilization (IVF) cycles in which ovarian stimulation was achieved by a flexible GnRH antagonist protocol.

Design: Retrospective cohort study.

Setting: University hospital.

Patient(s): In women <35 years of age, 290 fresh IVF cycles using the dual trigger protocol with day 5 embryo transfers from January 2013 to July 2018 were included. Cycles excluded were those with preimplantation genetic testing, gestational carriers, donor oocytes, and fertility preservation.

Intervention(s): IVF with dual trigger.

Main Outcome Measure(s): Clinical pregnancy rate, live birth rate.

Result(s): Comparing normal responders, defined as <30 oocytes retrieved, and high responders, defined as ≥30 oocytes retrieved, the clinical pregnancy rates (67.0% vs. 69.3%, respectively) and live birth rates (60.5% vs. 60.0%, respectively) were not significantly different. No cases of ovarian hyperstimulation syndrome were reported in either group.

Conclusion(s): Ovarian stimulation by a flexible GnRH antagonist protocol followed by dual trigger yields comparable outcomes between normal and high responders in fresh IVF cycles. (Fertil Steril Rep[®] 2021;2:314–9. ©2021 by American Society for Reproductive Medicine.)

Key Words: Dual trigger, fresh embryo transfer, in vitro fertilization, OHSS, pregnancy outcome

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Controlled ovarian stimulation (COS) during in vitro fertilization (IVF) is designed to synchronously stimulate multiple ovarian follicles before oocyte retrieval. In general, this is achieved with the use of exogenous follicle-stimulating

hormone and/or human menopausal gonadotropin. However, COS is associated with risks, including ovarian hyperstimulation syndrome (OHSS) and reduced endometrial receptivity leading to poor implantation (1–3), affecting the live birth rate (LBR).

The use of a gonadotropin-releasing hormone (GnRH) agonist as an alternative to the conventional human chorionic gonadotropin (hCG) trigger has been a strategy to mitigate the risk of OHSS. Both hCG and endogenous luteinizing hormone, which is stimulated by the GnRH agonist, trigger ovulation by binding to the same receptor, but the GnRH agonist may only be used in cycles in which a GnRH antagonist was used for pituitary desensitization. Although the use of a hCG trigger is associated with a higher LBR after a fresh embryo transfer (ET) when compared with the LBR with the use

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of a GnRH agonist, it is in addition associated with a higher rate of OHSS (4–6). Inversely, although the use of a GnRH agonist trigger alone is associated with a lower LBR, it decreases the risk of OHSS, especially in patients at increased risk, such as those with polycystic ovary syndrome (7–9). These differences are likely because of hCG's longer half-life compared with that of luteinizing hormone, which provides more sustained support for corpora lutea (8–9).

An additional strategy to decrease OHSS is cryopreserving all eligible embryos for planned use in a future cryopreserved cycle, also known as the freeze-all strategy (10). The freeze-all strategy has been useful for high responders, defined as women with a high number of oocytes retrieved, who not only are at risk for OHSS but may additionally have impaired endometrial receptivity because of high estrogen and progesterone levels in the fresh cycle (11, 12). Although regarded as a promising treatment strategy, the freeze-all strategy in IVF cycles delays the transfer of embryos, increasing the time to pregnancy and adding the potential cost of additional frozen cycles required to conceive.

To allow for a fresh transfer with improved pregnancy rates and reduced risk of OHSS, the combined use of both hCG in a lower dose and a GnRH agonist, called “dual trigger”, has been used to trigger final oocyte maturation. This combination has the advantage of minimizing the OHSS risk, because the GnRH agonist serves as the main ovulation trigger with a shorter half-life than that of hCG, whereas the inclusion of a low dose of hCG provides additional luteal support. Dual trigger has been shown to improve clinical pregnancy rates (CPRs) compared with those with the use of GnRH agonist alone (13) and has been found to be especially useful in high responders who have a greater risk of OHSS (14, 15). Although dual trigger is notably useful in high responders, there is limited data on the use of this protocol in normal responders and whether this protocol should be expanded to all responders. Because there is always a risk of OHSS in all patients who undergo COS, we sought to compare IVF outcomes of this protocol in normal and high responders. We hypothesized that high responders would have lower CPRs and LBRs in their fresh cycle compared with those of normal responders when using a dual trigger protocol. Our rationale was on the basis of previously noted concerns of a supraphysiologic hormone environment and diminished endometrial receptivity that is suggested in high responders.

MATERIALS AND METHODS

This was a retrospective cohort study in women <35 years of age that included fresh IVF cycles using the dual trigger protocol with day 5 ETs from January 2013 to July 2018 at the University of Iowa Center for Advanced Reproductive Care. After excluding cycles that used preimplantation genetic testing, a gestational carrier, donated oocytes, and fertility preservation, a total of 290 fresh IVF cycles using the dual trigger protocol were identified. Our dual trigger protocol used injection of both leuprolide (40 mg) as the GnRH agonist and hCG (1500 IU) as the trigger for final oocyte maturation. Other additional strategies to mitigate the risk of OHSS,

including “coasting”, or the administration of cabergoline or baby aspirin, were not used at our institution. Luteal support with intramuscular progesterone (50 mg daily) was started on the day of retrieval through the 10th week of pregnancy or negative hCG. Two separate cohorts were assigned: “normal responders”, defined as those with <30 oocytes retrieved, and “high responders”, defined as those with ≥ 30 oocytes retrieved. Additionally, we analyzed the characteristics of the entire cohort of women who were able to achieve clinical pregnancies and live births.

The demographic variables collected comprised maternal age, body mass index, gravidity, parity, and baseline antral follicle count (AFC). The IVF cycle parameters included the total number of metaphase 1 and metaphase 2 oocytes retrieved, endometrial thickness on the day of ovulation trigger, and total numbers of embryos transferred and frozen. The outcome parameters measured were the CPR and LBR. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with fetal pole and heartbeat confirmed by ultrasound. Live birth was defined as the delivery of a neonate after >20 weeks gestation. Institutional review board approval from the University of Iowa Hospitals and Clinics was granted for the creation of the research database from which this study obtained data. This study was determined to be exempt by the institutional review board, because it used de-identified data from this database.

Statistical Analysis

We expected a 20% difference in CPR between the normal and high responders on the basis of the literature (13, 15–17). Sample size calculations were completed using G*power to determine the sample size needed to achieve 80% power for a two-sided X^2 test with an alpha of 0.05. Given the 58.9% pregnancy rate and 50.7% LBR among women <35 years old in our center (18) and a sample distribution of 3:1 normal to high responders, a sample size of 249 was required to detect a 20% difference in LBR, which would additionally be sufficient to detect a 20% difference in the CPR.

Statistical analyses were conducted with SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA). Because of the non-normal distribution of the data, descriptive analyses included median and interquartile ranges for all continuous demographic variables. Medians were then compared between groups with the Mann-Whitney U test, and the X^2 test was used for categorical variables.

RESULTS

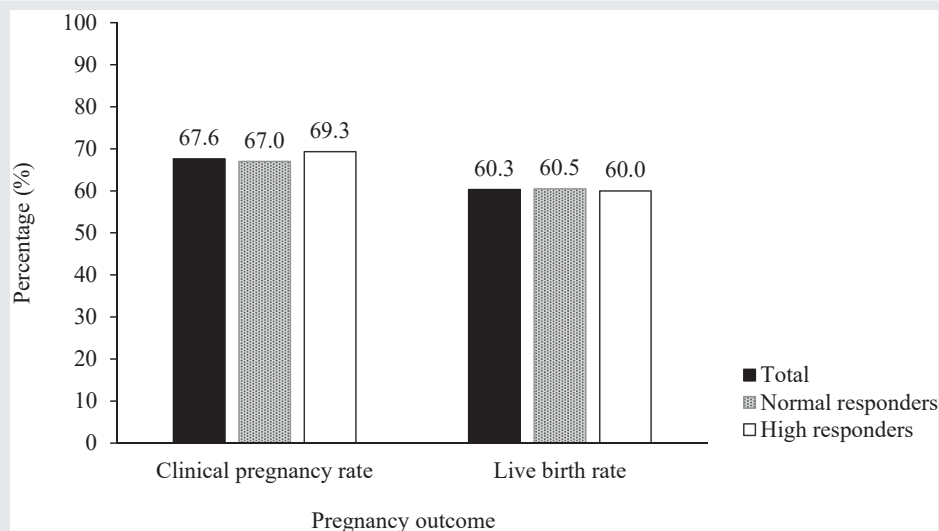
Of the 290 fresh cycles included, 215 (74.1%) cycles were identified as normal and 75 (25.9%) cycles were identified as high response. The demographic and clinical characteristics of these two groups are shown in Table 1. Overall, no significant differences were detected between the normal and high responders for age, body mass index, gravidity, parity, endometrial thickness, and the number of embryos transferred. As expected, high responders had significantly higher baseline AFC and total oocyte count, as well as the number of embryos cryopreserved.

TABLE 1**Clinical characteristics of normal and high responders using dual trigger.**

	Normal responders (N = 215) Median (IQR)	High responders (N = 75) Median (IQR)	P-value
M1 and M2 oocytes retrieved	17.0 (14.0–20.0)	30.0 (26.0–33.0)	—
M1 oocytes	8.0 (5.0–11.0)	14.0 (12.0–18.0)	
M2 oocytes	9.0 (6.0–11.0)	15.0 (12.0–18.0)	
Age (years)	30.0 (28.0–33.0)	31.0 (28.0–33.0)	.339
BMI (kg/m ²)	25.9 (22.8–32.3)	26.0 (22.4–30.6)	.712
Gravida	0.0 (0.0–1.0)	0.0 (0.0–1.0)	.053
Para	0.0 (0.0–0.0)	0.0 (0.0–1.0)	.119
Antral follicle count	35.0 (28.0–40.0)	40.0 (36.0–42.0)	<.001
Total oocyte count	21.0 (17.0–24.0)	35.0 (32.0–41.0)	<.001
Endometrial thickness (mm)	10.5 (9.4–12.2)	10.6 (9.6–12.3)	.702
Embryos transferred	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.309
Embryos cryopreserved	3.0 (1.0–6.0)	8.0 (4.0–11.0)	<.001

Note: BMI = body mass index; IQR = interquartile range; M1 = metaphase 1; M2 = metaphase 2.

Chung. Dual trigger in high IVF responders. *Fertil Steril Rep* 2021.

FIGURE 1

Pregnancy outcomes for the normal and high responders using the dual trigger protocol.

Chung. Dual trigger in high IVF responders. *Fertil Steril Rep* 2021.

In total, 196 cycles (67.6%) resulted in clinical pregnancy and 175 cycles (60.3%) resulted in live birth. When stratified between normal and high responders, neither the LBR nor the CPR was significantly different between the two study groups (Fig. 1). No cases of moderate or severe OHSS were detected in either group. The characteristics of the women who achieved a live birth are displayed in Table 2. Those who achieved a live birth had a higher number of embryos cryopreserved; otherwise, all other characteristics were comparable. Of those who achieved a clinical pregnancy, 175 cycles (89.3%) resulted in a live birth and 21 cycles (10.7%) resulted in a miscarriage.

DISCUSSION

Our study sought to determine if the degree of patient response to COS impacted the IVF outcome in the fresh cycle when dual trigger was used. Although high responders had higher AFC, number of oocytes retrieved, and embryos frozen as anticipated (19–22), the CPR and LBR were similar between normal and high responders. For both cohorts, the median number of embryos transferred in the fresh cycle was one.

To our knowledge, our study is the first to analyze fresh IVF outcomes in cycles managed by dual trigger stratified by the degree of response to COS. Previous studies investigating the dual trigger strategy compared outcomes with

TABLE 2

Clinical characteristics of cycles that did and did not achieve a live birth.

	Live birth (N = 175) Median (IQR)	No live birth (N = 115) Median IQR	P-value
Age (years)	30.0 (28.0–33.0)	31.0 (29.0–33.0)	.063
BMI (kg/m ²)	26.0 (22.6–32.3)	25.9 (22.7–31.4)	.638
Gravida	0.0 (0.0–1.0)	0.0 (0.0–1.0)	.417
Para	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.499
Antral follicle count	36.0 (29.0–41.0)	37.0 (29.0–41.0)	.959
Total egg count	24.0 (19.0–30.0)	23.0 (18.0–30.0)	.414
M1 and M2 retrieved	20.0 (16.0–24.0)	18.0 (14.0–24.0)	.136
M1 oocytes	10.0 (7.0–13.0)	8.0 (5.0–13.0)	
M2 oocytes	10.0 (7.0–14.0)	10.0 (7.0–13.0)	
Endometrial thickness (mm)	10.7 (9.5–12.4)	10.4 (9.2–12.3)	.266
Fresh embryos transferred	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.233
Embryos cryopreserved	5.0 (2.0–8.0)	3.0 (1.0–7.0)	.009
Oocyte response			.944
High responders, No. (%)	45 (25.7)	30 (26.1)	
Normal responders, No. (%)	130 (74.3)	85 (73.9)	

Note: BMI = body mass index; IQR = interquartile range; M1 = metaphase 1; M2 = metaphase 2.

Chung. Dual trigger in high IVF responders. *Fertil Steril Rep* 2021.

those of single trigger protocols and restricted their cohorts to either only normal responders (16), high responders (13, 15), or were completely unstratified (22). Lin et al. (16) found that in normal responders, dual trigger of final oocyte maturation improved the CPR and LBR compared with the results for hCG trigger alone. In addition, both Griffin et al. (14) and Shapiro et al. (15) found similar results in high responders. When other studies did compare both high and normal responders, they found that implantation rates were lower in high responders; however, these were completed in the setting of a single trigger for oocyte maturation either by hCG or a GnRH agonist (23–26). Our findings add to this literature by reviewing the impact of the responder type on the CPR and LBR with the use of dual trigger in fresh cycles, in which our study indicates no difference in CPR and LBR between normal and high responders.

The term “high responder” has historically been defined as patients who are either clinically at risk for having OHSS or whose retrieval resulted in a high number of oocytes. This oocyte threshold has varied significantly from >15 to >30 oocytes in previous studies (27–31). Our rationale for defining “high responders” as >30 oocytes retrieved in our cohort was to examine this upper limit, because we felt that this would be the highest risk group for OHSS; however, it is possible that we may have seen different results if some of the other oocyte cutoffs were used.

It is possible that the effect of very high sex steroid levels, as seen in the high responders, on endometrial receptivity may not be as critical as suggested or may be overcome by younger age. Concerns have arisen regarding impaired endometrial receptivity because of very high levels of progesterone and estrogen in cycles with robust ovarian response (24, 25). High responders not only have a high number of follicles but in addition typically have high progesterone and estrogen levels at the time of implantation and are reported to have a lower pregnancy rate in the fresh cycle (22, 25). In contrast, some studies, including a meta-

analysis, have found that elevated hormone levels of either progesterone or estrogen do not impact the CPR or LBR (32–34). More specifically, one study found that the elevated progesterone level in high responders did not compromise pregnancy rates when compared with those of normal responders (34). This is more in keeping with our findings, which revealed that high responders using dual trigger did not have impaired endometrial receptivity, because we found CPR and LBR comparable to those of normal responders. Additionally, no cases of OHSS were observed. These findings of no OHSS cases and no impairment in LBR in the high responders are overall reassuring and may indicate a GnRH agonist trigger alone is not necessary, even in high responders, and would still provide an opportunity for a fresh ET.

We do not routinely measure estradiol and progesterone levels during IVF cycles at the time of ovulation trigger; therefore, we cannot compare those between the study groups. Hormone levels may be a confounding factor that we did not investigate, because some studies have suggested that these levels affect IVF pregnancy outcomes in fresh cycles (35–37). Future studies should evaluate hormone serum levels in patients undergoing the dual trigger protocol to determine if estradiol or progesterone levels impact outcomes. Nevertheless, on the basis of our findings, dual trigger may be used liberally in antagonist IVF-ET cycles in all women under the age of 35 regardless of response type. Although our study is limited by its retrospective nature, data from a single institution allows uniformity in the clinical practices, including the dosing used for the dual trigger protocol.

In addition, it is important to note that both study groups exceeded expectations for both CPR and LBR compared with our center’s overall success rate in women <35 years old undergoing fresh autologous ET. This finding correlates with multiple research studies that showed that dual trigger improves IVF outcomes (38–43). Included in these studies was

a double-blind, randomized, controlled trial that showed that the use of dual trigger had a significantly higher number of M2 oocytes retrieved, CPR, and LBR compared with those of hCG only trigger (40). In addition, a systematic review and meta-analysis of four randomized-controlled trials revealed a higher CPR in the dual trigger group compared with that of hCG only (43). Additionally, it was found that dual trigger improved outcomes compared with those of GnRH agonist only trigger (15).

CONCLUSION

In conclusion, the use of dual trigger with low-dose hCG and a GnRH agonist for final oocyte maturation provided comparable IVF outcome in normal and high responders, allowing fresh ET while minimizing the OHSS risk. Excellent CPR and LBR can be achieved using dual trigger during fresh cycles, eliminating the need to delay embryo transfer because of endometrial receptivity concerns.

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