Measurement of Luteinizing Hormone Level After Gonadotropin-Releasing Hormone Agonist Trigger Is Not Useful for Predicting Oocyte Maturity


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Abstract

Objective: To study whether the measurement of LH after GnRH agonist trigger is correlated with the proportion of mature oocytes.

Methods: We performed a retrospective cohort study at a private, university-affiliated fertility centre in Vancouver, BC. Patients who underwent IVF/ICSI cycles and used a GnRH agonist trigger were included. Serum LH levels were measured on the day of trigger and one day later. The main study outcome measure was the proportion of mature oocytes.

Results: Including all 97 cycles in the cohort, the average post-trigger LH level was 69.3 IU/L (10.5–133.3 IU/L) and the average rise was 66.8 IU/L (10.0–129.4 IU/L). The mean number of oocytes collected was 17 and, on average, 82% were mature. We did not find any association between post-trigger LH levels (r = 0.004, *P* = 0.968) or rise in LH level (r = 0.01, *P* = 0.92) and the proportion of mature oocytes collected. The percentage rise in LH level was also not predictive of the proportion of mature oocytes in the estradiol and oral contraceptive pill groups separately (estradiol r = 0.118, OCP r = 0.07; *P* > 0.05) or together (r = 0.1, *P* = 0.34).

Conclusion: Neither the absolute post-trigger LH level nor the rise in LH level is predictive of the proportion of mature oocytes collected. Taken together with the excellent response to GnRH agonist trigger evidenced by the average oocyte maturity, we do not believe it is necessary to measure post-trigger LH levels.

Résumé

Objectif : Déterminer s'il y a une corrélation entre le taux de LH mesuré après l'administration d'agonistes de la GnRH et la proportion d'ovocytes matures.

Méthodologie : Nous avons mené une étude de cohorte rétrospective dans un centre de fertilité universitaire privé de Vancouver (Colombie-Britannique). Les femmes ayant subi des cycles de FIV ou d'IICS et ayant fait l'objet d'un déclenchement par agonistes de la GnRH ont été incluses. Le taux sérique de LH a été mesuré le jour du déclenchement et le lendemain. L'indicateur de résultat principal à l'étude était la proportion d'ovocytes matures.

Résultats : Les femmes de la cohorte représentaient 97 cycles. Le taux moyen de LH postdéclenchement était de 69,3 UI/l (10,5 UI/l–133,3 UI/l), et l'augmentation moyenne, de 66,8 UI/l (10,0 UI/l–129,4 UI/l). En moyenne, 17 ovocytes étaient prélevés et 82 % d'entre eux étaient matures. Aucun lien n'a pu être établi entre le taux de LH postdéclenchement (r = 0,004; *P* = 0,968) ou la hausse du taux de LH (r = 0,01; *P* = 0,92) et la proportion d'ovocytes mature prélevée. La hausse en pourcentage du taux de LH ne permettait pas de prédire la proportion d'ovocytes matures prélevée chez les groupes œstradiol et contraceptifs oraux (CO) séparément (œstradiol : r = 0,118; CO : r = 0,07; *P* > 0,05) ou ensemble (r = 0,1; *P* = 0,34).

Conclusion : Ni le taux absolu de LH postdéclenchement ni la hausse du taux de LH ne permettent de prédire la proportion d'ovocytes matures prélevée. Compte tenu de cette constatation et de l'excellente réponse au déclenchement par agonistes de la GnRH, dont témoigne la moyenne du nombre d'ovocytes matures, nous croyons qu'il n'est pas nécessaire de mesurer le taux de LH postdéclenchement.

Key Words: GnRH agonist trigger, luteinizing hormone, oocyte maturity, controlled ovarian stimulation

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INTRODUCTION

The GnRH antagonist protocol for controlled ovarian stimulation offers several advantages over the traditional long GnRH agonist protocol. GnRH antagonist cycles involve a shorter duration of stimulation, are more patient-friendly, and, perhaps most importantly, are associated with

a greater than 50% decrease in ovarian hyperstimulation syndrome.[1] Although initial research studies questioned their efficacy, a 2011 Cochrane meta-analysis demonstrated equivalent live birth rates with GnRH antagonists, providing an appealing alternative to the traditional long GnRH agonist protocol.[2]

Segal and Casper were among the first to show that final oocyte maturation in IVF can be achieved by provoking the release of endogenous LH with a GnRH-agonist instead of human chorionic gonadotropin.[3] It has since been shown that, in combination with a freeze-all strategy in antagonist cycles, this technique can reduce the risk of OHSS to almost zero.[4] Despite this advantage of safety, anxiety arises from concerns that agonist triggering may compromise the number of mature oocytes and/or result in empty follicle syndrome.[5] As a result, clinicians have sought to use endocrine markers in order to confirm a patient's response to the agonist trigger. One study described a small predictive association between peak estradiol, post-trigger LH, rise in LH, and post-trigger progesterone with the total number of oocytes and number of mature oocytes retrieved.[6] There has been no consensus, however, on what the minimal or optimal change in LH or estradiol is to ensure a good yield of mature oocytes.[6,7]

The objective of our study was to determine whether the measurement of LH after GnRH agonist trigger is correlated with the number of oocytes retrieved or with the proportion of those that are mature. We aimed to describe the endocrine profiles immediately before and after GnRH agonist trigger as they relate to IVF cycle outcomes.

METHODS

A retrospective review of 97 IVF/ICSI cycles that used a GnRH agonist trigger was performed. Subjects were treated between November 2013 and March 2015 at a private, university-affiliated IVF facility in Vancouver, BC. All charts within that time period were reviewed, and any cases that used an agonist trigger were included. The two instances of patients who received a dual trigger (hCG in any dose and GnRH agonist) were excluded.

ABBREVIATIONS

E2	estradiol
hCG	human chorionic gonadotropin
OCP	oral contraceptive pill
OHSS	ovarian hyperstimulation syndrome

The controlled ovarian stimulation protocol consisted of pre-treatment with 7 days of estradiol-prime or 14 to 21 days of the oral contraceptive pill. Gonadotropins were administered beginning on the fifth day of menses and followed a GnRH antagonist protocol. The antagonist (ganirelix 0.25 mg subcutaneously, daily) was initiated either when the lead follicle was ≥14 mm or on day 6 of gonadotropins. Triggering of final oocyte maturation was prescribed when three or more follicles were ≥17 mm. Agonist trigger was used to stimulate final oocyte maturation in patients believed to be at risk of OHSS. This decision was made at the physician's discretion, but in general, considered patients with: ≥ 15 follicles >12 mm seen on transvaginal ultrasound, serum estradiol ≥12 000 pmol/L, polycystic ovarian syndrome, prior history of OHSS, and oocyte donors. Buserelin (0.5 mg) subcutaneously was used. Serum LH levels were recorded on the day of trigger and one day later, and then egg retrieval took place 35 hours after buserelin administration.

For the statistical analysis, SPSS software was used (IBM SPSS Statistics for Macintosh, Version 24.0) and a P value <0.05 was considered significant. Cycles were first grouped by type of pre-treatment (E2-prime or OCP) and compared using two-sided Student's t tests for parametric data. Baseline cycle characteristics analysed were: age (years), peak estradiol (E2) (pmol/L), E2 on trigger day + 1, change in E2 (ΔE2), percent change in E2 (%E2), baseline LH (IU/L), LH on trigger day + 1, change in LH (ΔLH), and percent change in LH (%LH). For our primary outcome, linear regression was used to examine for an association between the proportion of mature oocytes collected and three different LH parameters: post-trigger LH level, rise in LH (ΔLH), and percentage rise in LH (% rise). Secondary outcomes included the total number of oocytes collected and cases of empty follicle syndrome.

The study was approved by the Research Ethics Board of the University of British Columbia (Vancouver, BC), and reporting of results adhered to the STROBE guideline.[8]

RESULTS

A total of 97 IVF/ICSI cycles using GnRH agonist trigger were included in this analysis. Sixty cycles used estrace priming with antagonist cycles, and 37 were OCP-antagonist cycles. The average age of the subjects was 34.5 years (range 24–44 years). The average post-trigger LH level was 69.3 IU/L (10.5–133.3 IU/L). The average rise in LH was 66.8 IU/L (10.0–129.4 IU/L) from a baseline of 2.5 IU/L (0.2–9.4 IU/L). The change in E2 level post-trigger from its peak was 4219.4 pmol/L (-8255.0 to 21,023.0 pmol/L; Table).

Table. Baseline cycle characteristics

Characteristic	Mean ± standard deviation [range]
Maternal age (years)	34.5 ± 4.7 [24.0–44.0]
E2 (pmol/L)	
Peak E2	17,636.2 ± 6155.4 [3403.0–45,325.0]
Post-trigger E2	21,855.6 ± 8173.8 [4873.0–48,675.0]
Change in E2	4219.4 ± 5454.3 [-8255.0 to 21,023.0]
% Change in E2	25.8 ± 31.6 [-35.1 to 141.6]
LH (IU/L)	
Baseline LH	2.5 ± 2.0 [0.2–9.4]
Post-trigger LH	69.3 ± 30.5 [10.5–133.3]
Change in LH	66.8 ± 30.1 [10.0–129.4]
% Change in LH	5733.9 ± 8097.8 [330.0–51,745.0]

The average percentage rise in LH differed between the E2-prime antagonist (3804%) and OCP antagonist (8730%) groups ($P = 0.003$). The baseline LH levels in the OCP group were lower compared with the E2-prime antagonist group (mean difference = 1.1 IU/L, $P = 0.007$, 95% CI 0.31–1.93 IU/L).

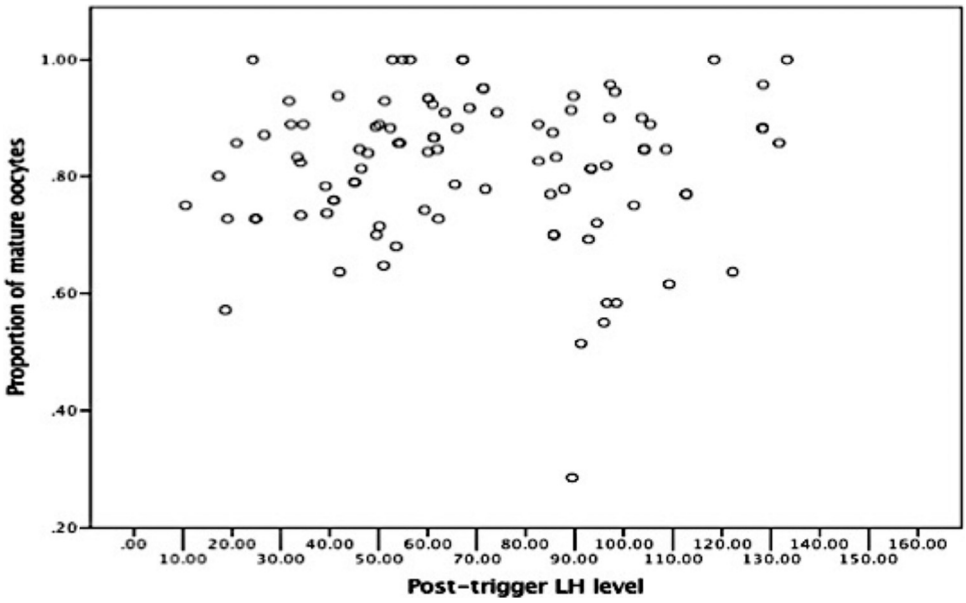
The mean number of oocytes collected was 17 (3–38 oocytes) and, on average, 82% (29–100%) were mature. We did not find any association between post-trigger LH levels and the proportion of mature oocytes (r = 0.004, $P = 0.968$; Figure). Similarly, the rise in LH level was not associated with the proportion of mature oocytes (r = 0.01, $P = 0.92$). The percentage rise in LH level was also not predictive of the proportion of mature oocytes in the E2-prime and OCP groups separately (E2-prime r = 0.118, OCP r = 0.07, $P > 0.05$), or together (r = 0.1, $P = 0.34$). In addition, there were no cases of empty follicle syndrome.

DISCUSSION

Our study did not find a correlation between the absolute post-trigger LH level or the percentage change in LH level and the proportion of mature oocytes collected after GnRH agonist trigger. Physiologic LH surge levels for oocyte maturation vary widely from 20 IU/L to well over 100 IU/L. LH plays an important role in the complex interaction of factors that promote oocyte maturation. LH decreases cGMP which normally inhibits oocyte meiosis resumption.[9] Theca and mural granulosa cells respond to LH by releasing growth factors which stimulates inner cumulus granulosa cell expansion, subsequent oocyte maturation, and eventual ovulation in natural cycles.[10]

The hCG trigger uses its structural and biological similarity to LH to stimulate oocyte maturation whereby the cell re-enters meiosis from the arrested stage of prophase I to metaphase II. In contrast, GnRH agonist trigger induces an endogenous release of LH and FSH, which could be considered more physiologic compared with the hCG trigger. Measurement of LH level before and after administration of a GnRH agonist trigger has been used to ensure "adequate" release of endogenous gonadotropin in the hopes of avoiding pick-up of immature oocytes or empty follicle syndrome. However, there is no consensus on the minimal

Figure. Scatter plot of post-trigger LH level (IU/L) and proportion of mature oocyte shows no association (r = 0.004, *P* = 0.968).



or optimal change in LH level after GnRH agonist trigger that is sufficient to ensure oocyte maturity.

Different LH thresholds have been proposed. Shapiro et al.[11] previously suggested that a post-trigger LH below 12 IU/L is a threshold below which oocyte maturity declines. The authors reviewed 252 cycles and found that below 12 IU/L, 12 hours after GnRH agonist trigger, there was a 97% specificity in predicting both low oocyte yield and oocyte maturity. Above 52 IU/L, increasing LH levels did not correspond to further yield or maturity. In our study, all post-trigger LH values except one were above 12 IU/L, which could have been influenced by the later measurement of LH 12 to 20 hours post-trigger, vs. 12 hours.

A recent retrospective study by Meyer et al.[12] of 500 IVF cycles suggested that the rate of suboptimal response to agonist trigger could be reduced from 5.2% to 0.2% by excluding patients with an LH of ≤0.5 IU/L on the day of trigger. This study used a post-trigger LH level ≤15 IU/L to define their main outcome measure; however, this parameter has been associated with poorer oocyte yield but does not allow us to make any conclusions about what a minimum acceptable LH value would have been in our cohort when referring to the actual proportion of mature oocytes.

In contrast, Chang et al.[13] reviewed 1878 autologous IVF cycles and used both LH and progesterone levels post-trigger to assess adequate response to GnRH agonist trigger, and they did not find strict LH or progesterone cut offs. In their study, successful oocyte retrieval was observed with LH levels as low as 2 IU/L, and despite LH levels above 30 IU/L, there were cases where no oocytes were retrieved.[13] In our study, we were also unable to demonstrate a specific LH threshold level one day post-trigger that was correlated with poor oocyte maturity.

Post-GnRH agonist trigger, the level of LH follows a usual pattern. The peak level is seen around 4 hours followed by a rapid decline.[14] Baseline and post-trigger LH level varies among individuals. In the present study, the baseline LH level in the OCP anatagonist group was lower compared with the E2-prime antagonist group. This likely accounted for the difference in the average percentage rise in LH between the two groups. In addition to absolute LH levels, we examined the rise in LH level and percent change post-trigger from baseline. Both were not predictive of the proportion of oocyte maturity. LH is one factor among many gonadotropins, growth factors, sterols, and steroids that promote oocyte maturation.[10] In addition, multiple signaling pathways are involved; therefore, specifically looking at LH alone may not accurately predict oocyte maturity.[9]

In patients with hypothalamic hypopituitarism, GnRH agonist trigger should be avoided. It is important to recognize that there is a risk that these patients may be misclassified as having polycystic ovarian syndrome and inappropriately triggered with a GnRH agonist. However, unmedicated baseline LH levels and careful elucidation of their oligomenorrhea history is likely to eliminate the majority of this risk.

The response to GnRH agonist trigger was excellent in our study and comparable to findings reported in literature. The average proportion of mature oocytes in the present study was 82%, which is similar to the 84% found by Humaidan et al.[15] No cases of empty follicle syndrome was found. This may be due to the low incidence of empty follicle syndrome which has been estimated to be between 0.045% and 3.4%.[16]

CONCLUSION

Our study demonstrates that neither the absolute post-trigger LH level nor the rise in LH level is predictive of the proportion of mature oocytes collected. Taken together with the excellent response to GnRH agonist trigger evidenced by the average oocyte maturity, we do not believe it is necessary to measure post-trigger LH levels. However, this was a retrospective study at a single centre. Future prospective, multi-centre studies will help to further elucidate the presence or absence of relationship between post-trigger LH and oocyte maturity.

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