Life Science Journal

Websites:
http://www.lifesciencesite.com
http://www.sciencepub.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

# Safety and Efficacy of Dual Trigger of Oocyte Maturation Compared with Conventional Agents for High Responders

Mohammed El-Husseiny Radwan[1], Mustafa Taha Sharafel Din[1] and Seham Mahmoud Eldeeb[2]

[1]Obstetrics and Gynecology Department, Faculty of Medicine - Zagazig University, Egypt
[2]Public Health and Community Department, Biostatistics Unit, Faculty of Medicine - Zagazig University, Egypt
hussenyradwan@gmail.com

**Abstract:** This study was conducted to evaluate safety and efficacy of dual trigger of oocyte maturation in comparison with conventional agents for high responders. 122 women distributed into two groups (61 women in both two group) to compare number of oocytes retrieved and OHHS risk in dual trigger group in comparison with HCG trigger group. Women in the study group were significantly younger ($p \leq 0.003$), no significant differences in BMI ($p \geq 0.6$), etiology or duration of infertility ($p \geq 0.2$), basic sex hormone levels (LH: $p \geq 0.1$, FSH: $p \geq 0.1$, E2: $p \geq 0.4$). no significant difference were recorded regarding the number of follicles measuring ≥10 mm in diameter. On the other hand, high quality embryos ($p \leq 0.004$) and number usable embryos ($p \leq 0.001$) and number of transferred embryo (<0.001) were significantly higher in dual trigger group. Our results suggested that administration of dual trigger consisting of GnRH-a and low dose HCG is probably safe and effective method of triggering final oocyte maturation in cases of high responders in comparison with conventional triggering with standard dose HCG.
[Mohammed El-Husseiny Radwan, Mustafa Taha Sharafel Dinand Seham Mahmoud Eldee. **Safety and Efficacy of Dual Trigger of Oocyte Maturation Compared with Conventional Agents for High Responders.** *Life Sci J* 2019;16(10):45-50]. ISSN: 1097-8135 (Print) / ISSN: 2372-613X (Online). http://www.lifesciencesite.com. 5. doi:10.7537/marslsj161019.05.

**Keywords:** Dual trigger, OHSS, oocytes retrieval, high responders.

## 1. Introduction

GnRH-a trigger has been shown to be as effective as HCG trigger with respect to oocyte yield and maturity in both autologous and donor cycles **(Humaidan et al., 2009).** It is observed that the resultant surge after single bolus of GnRHa trigger consists of LH and follicle-stimulating hormone (FSH) which are the same hormones released during mid-cycle naturally and typically seen shortly before ovulation **(Nakano et al., 1973)**

Despite contradictory human data, FSH function in human may be related to oocyte maturation and resumption of meiosis **(Andersen; 2002, Zelinski et al.,1995),** function of oocyte-cumulus complex and facilitation of its detachment from the follicle wall **(Eppig et al., 1979**), and generation of LH receptors on granulosa cells (**Richards et al., 1987)**

In contrast to natural ovulatory surge having three phases: abrupt onset (14 hours), LH peak/plateau (14 hours), and gradual descent to baseline (20 hours), lasting a mean duration of 48 hours **(Hoff et al.,1983).** The surge after GnRHa happens in two stages: rapid ascent and moderate descent, remaining 24-36 hours (**Itskovitz et al., 1991**).

Although some studies suggest that GnRHa trigger may result in more mature oocytes other receptors of failed oocyte maturation after GnRHa trigger (empty follicle syndrome EFS) **(Meyer et al., 2015)**.

Despite rapid luteolysis occurs after GnRHa trigger, granulosa/luteal cells maintain similar functionality and viability within the first two days after trigger when compared with GnRHa trigger **(Engmann et al., 2011).**

The idea of a utilization of GnRH-a in addition to a low-dose HCG in assisting final oocyte maturation named as dual trigger **(Shapiro et al.,2008)** this protocol was initially innovated for the avoidance of OHSS particularly in high ovarian responders.

Addition of a standard or low-dose hCG to GnRHa trigger in a (dual trigger) protocol demonstrated an improvement in the number and proportion of mature oocyte **(Griffin et a**l., **2014),** and has been adopted for wide use in some clinics to reduce the chance of EFS with GnRHa trigger **(Meyer** et al., **2015).** However adjuvant hCG with GnRHa trigger should be used with caution in cases with high risk of OHSS development.

It is theorized that the endogenous LH and FSH emitted by the GnRH-a and low-dose of HCG, may result in much mature oocytes, expansion of live birth rates in high ovarian responders when compared with the classic dose (10000IU) HCG trigger alone **(Griftin**

**et al., 2012, Castillo et al., 2013, and Griffin et al., 2014)。**

The low-dose HCG trigger has a preferableimpactin avoidance the high risk of OHSS than the classic dose of HCG trigger in cases of high ovarian responders. So the use of dual trigger of oocyte maturation with GnRH-a and low-dose HCG (2,000 IU) was examined in high ovarian responders of GnRH-a protocols.

This retrospective study was conducted aiming for evaluating the number of retrieved total and mature oocytes, embryo quality rate, clinical pregnancy rate, fertilization rate, and compare the OHSS risk both after dual trigger GnRH-a and low dose HCG trigger (study group) versus HCG trigger with slandered dose (10000 IU) alone (control group).

## 2. Materials and methods:

### Study design:

A retrospective cohort study was conducted from September 2017 to March 2019 with total of 122patientsfulfilling inclusion criteria and so included for final examination divided into two groups: dual trigger group (study group n=61) and HCG alone group (control group n=61).

The study was conducting aiming to investigate the relationship between agents used to trigger final oocyte maturation with GnRH antagonist protocol.

Inclusion criteria include age from 18:40 years, BMI above 18 and below 30 and typically high ovarian responder (level of estradiol was higher than 4000 pg/ml on the same day of trigger administration or number of retrieved oocyte ≥20) completed fresh ICSI cycles with ET.

### Exclusion criteria:

The exclusion criteria included weak or normal ovarian responders characterized by serum estradiol level ≤500 pg/mL on trigger day or ≤3 retrieved oocytes for the former and serum estradiol level ≤500: ≥4000 pg/mL on trigger day or ≤3: ≥21 retrieved oocytes cases with a day-2-3follicle-stimulating hormone (FSH) concentration higher than 10 IU/L, women with recurrent ICSI failure (≥ 3 times), cases with uterine or endometrial abnormalities and any history or confirmed diagnosis of endocrinal abnormalities.

This study was conducted in Zagazig university Hospitals, Obstetrics and Gynecology Department. The approval of study protocol was achieved by the Zagazig University IRB. All procedures conducted in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. Being a retrospective study consent is not required.

### Stimulation protocol:

Determination of starting dosage of gonadotropin depends on various parameters as antral follicle count (AFC), body mass index, age, POR and serum FSH on day 2-3. Then, subsequent dosage was estimated depending on serum E2 and serially followed by transvaginal ultrasound. starting administration of 0.25 mg/day either cetrorelix or ganirelix in the presence of one of these parameters, the availability of at least one follicle measuring 14 mm, a serum estradiol level of ≥600 pg/mL a serum, (LH) level of ≥10 IU/L. continuation of this antagonist till the day of trigger administration.

In the event of reaching two follicles 18 mm or three follicles became17 mm in diameter at least, the choice of either conventional HCG trigger (control group) or dual trigger consisting of GnRH-a (0.2 mg triptorelin acetate SC) and 2.000 IUHCGIM (study group) was done, VOR was done 36 hours subsequent to trigger administration. All ETs were done 72 hours subsequent to VOR with culture of the rest of embryos with subsequent cryopreservation by verification at the blastocyst stage.

Intensive luteal support started on day of oocyte retrieval, value of β-HCG was evaluated fourteen days following ET and positive result is guaranteed if exceeding 5 IU/ml. continuous luteal support regimen was administers until the 8$^{th}$ week of pregnancy. The primary outcome was total number of oocyte retrieved, number of metaphase II (MII) oocytes and occurrence of OHSS. OHSS was evaluated utilizing the criteria suggested by Golan et al. [33] then it was compared between groups treated with trigger.

The protocol to diagnose mild degree of this syndrome needed the existence of abdominal enlargement with or without nausea, diarrhea, vomiting, also, subsequent more intense degree indicated by the presence of ultrasound evidence of ascites constitute moderate OHSS. Criteria of the severe degree include occurrence of fluid in closed cavities namely abdomen and chest. hemoconcentration, disturbed coagulation profile, and/or altered kidney or liver functions with presence of moderate OHSS features.

Secondary outcomes included clinical pregnancy rate -defined as the existence of fetal pulsation diagnosed by vaginal ultrasound per embryo transfer (ET)-, fertilization rate, quality embryo rate and number of usable embryos.

### Statistical analysis:

Assuming that mean ± SD of number of oocytes retrieved in HCG trigger group versus in dual trigger group were 18.5 ± 4.4 versus 21.6 ± 7.4 (Li *et al.,* 2018), at confidence level 95% and power 80%, (total sample size was 122; 61 in every group). Sample size was calculated by Open Epi version 2.3.1 **(Dean *et al.*, 2013).**

The collected data was entered to and analyzed by computer using Statistical Package of Social Services, version 25 (SPSS) **(IBM, 2017).** Quantitative data was presented as mean and standard deviation. Qualitative data was presented as frequencies and proportions. Pearson Chi square test ($\chi^2$) and fisher's **exact** were used to analyze qualitative independent data. **Student's T test (t)** was used to analyze quantitative independent data. In all the tests, p value of ≤0.05 was taken as significant **(Petrie & Sabin, 2009).**

## 3. Results:

The two groups were compared regarding base line characteristics (Table 1) and ovarian stimulation parameters (Table 1).

Women in the study group were significantly younger (p≤0.003), no significant differences in BMI (p≥0.6), etiology or duration of infertility (p≥0.2), basic sex hormone levels (LH: p≥0.1, FSH: p≥0.1, E2: p≥ 0.4), initial or total dose or gonadotropins used for stimulation as shown in table (2); (p≥0.2, p≥0.4, p≥.04 respectively).

There was no significant difference regarding the number of follicles measuring ≥10 mm in diameter and mean E2 concentration on day of trigger administration, number of oocyte retrieval and number of MII oocytes was higher in study group in comparison with control group but this difference does not reach statistically significance (Table 2).

**Table (1): Baseline characteristics of the studied groups:**

| Variables | Dual trigger group (n=61) | HCG trigger group (n=61) | Test of sig. | p |
|---|---|---|---|---|
| **Age (years):** Mean ± SD | 28.4 ± 7.6 | 32.1 ± 6.2 | t 2.9 | **0.003*** |
| **BMI (kg/m$^2$):** Mean ± SD | 25.3 ± 5.2 | 24.9 ± 4.6 | t 0.4 | 0.6 |
| **Duration of infertility (years):** Mean ± SD | 5.7 ± 1.9 | 6.1 ± 2.2 | t 1.1 | 0.2 |
| **Basic LH level (IU/L):** Mean ± SD | 4.9 ± 1.3 | 4.5 ± 1.6 | t 1.5 | 0.1 |
| **Basic FSH level (IU/L):** Mean ± SD | 6.2 ± 2.0 | 6.7 ± 1.5 | t 1.6 | 0.1 |
| **Basic E2 level (pg/mL):** Mean ± SD | 42.6 ± 14.8 | 40.5 ± 17.1 | t 0.7 | 0.4 |
| **Causes of infertility, n (%):** Male infertility<br>Ovulatory dysfunction<br>Tubal factor<br>Combined factors<br>Unexplained | 11(18.0%)<br>26 (42.6%)<br>17 (27.9%)<br>6 (9.9%)<br>1 (1.6%) | 9 (14.8%)<br>24 (39.3%)<br>20 (32.8%)<br>6 (9.9%)<br>2 (3.2%) | $\chi^2$ 0.8 | 0.9 |

* Statistically significant.

**Table (2): Cycle and embryological parameters of the studied groups:**

| Variables | Dual trigger group (n=61) | HCG trigger group (n=61) | Test of sig. | p |
|---|---|---|---|---|
| **Starting dose of gonadotropin (IU):** Mean ± SD | 245.7 ± 55.0 | 233.2 ± 62.1 | t 1.2 | 0.2 |
| **Total gonadotropin ampules (75 IU):** Mean ± SD | 30.7 ± 12.4 | 32.5 ± 14.8 | t 0.7 | 0.4 |
| **Duration of gonadotropin stimulation (days):** Mean ± SD | 9.6 ± 1.9 | 9.8 ± 1.2 | t 0.7 | 0.4 |
| **No. of follicles ≥10 mm:** Mean ± SD | 9.9 ± 3.2 | 10.1 ± 2.5 | t 0.3 | 0.7 |
| **E2on the day of HCG (pg/mL):** Mean ± SD | 6.2 ± 2.0 | 6.7 ± 1.5 | t 1.6 | 0.1 |
| **No. of oocytes retrieved:** Mean ± SD | 42.6 ± 14.8 | 40.5 ± 17.1 | t 0.7 | 0.4 |
| **No. of MII oocytes retrieved:** Mean ± SD | 6.1 ± 1.5 | 5.6 ± 1.9 | t 1.6 | 0.1 |
| **Fertilization rate, n (%):** | 37 (60.7%) | 35 (57.4%) | $\chi^2$ 0.1 | 0.7 |
| **No. of usable embryos:** Mean ± SD | 10.2 ± 2.1 | 9.0 ± 2.5 | t 2.9 | **0.004*** |
| **Quality embryo rate (%):** Mean ± SD | 60.3 ± 15.6 | 52.4 ± 11.7 | t 3.1 | **0.001*** |
| **No. of transferred embryo:** Mean ± SD | 2.8 ± 0.8 | 2.0 ± 0.6 | t 6.2 | **<0.001**** |

* Statistically significant. ** Highly statistical significant.

High quality embryos (p≤0.004) and number usable embryos (p≤0.001) and number of transferred embryo (<0.001) were significantly higher in dual trigger group.

The incidence of early OHSS was significantly less after dual trigger agent also majority of these patients were diagnosed with mild HSS lastly incidence rate of complications was significantly less in study group versus control group (table 3).

**Table (3): Outcome of the studied groups:**

| Variables | Dual trigger group (n=61) | HCG trigger group (n=61) | Test of sig. | p |
|---|---|---|---|---|
| **Clinical pregnancy rate, n (%):** | 35 (57.4%) | 31 (50.8%) | $\chi^2$ 0.5 | 0.4 |
| **Early spontaneous abortion rate, n (%):** | 6/35 (17.1%) | 5/31 (16.1%) | $\chi^2$ fisher | 0.9 |
| **OHSS, n (%):** | 4 (6.6%) | 12 (19.7%) | $\chi^2$ 4.6 | **0.03*** |
| **Severity of OHSS, n (%):**<br>Mild<br>Moderate<br>Severe | <br>3/4 (75.0%)<br>1/4 (25.0%)<br>0/4 (0.0%) | <br>2/12 (16.7%)<br>7/12 (58.3%)<br>3/12 (25.0%) | $\chi^2$ 4.0 | **0.04*** |
| **Length of stay in hospital (days):** Mean ± SD | 5.4 ± 1.6 | 10.0 ± 2.4 | t 3.4 | **0.004*** |
| **Paracentesis, n (%):** | 0 (0.0%) | 7 (58.3%) | $\chi^2$ fisher | **0.04*** |

* Statistically significant.

**4. Discussion:**

Dual trigger protocol demonstrated non-significant trend towards increase of both total and mature oocyte retrieved. Of greater importance, number of high quality and usable embryos was higher in study group. In accordance with our results **Griffin et. al. (2014)** found that combination of low dose hCG to GnRHa trigger in a "dual trigger" protocol demonstrated an improvement in both number and proportion of MII oocytes. Adoption of dual trigger protocol aiming at reduction of rates of empty follicle syndrome (EFS) with GnRH-a trigger alone recently had gained much interest **(Meyer et al., 2015).**

The improved quantity and quality of oocyte and embryos may be explained by fact that the use of GnRH-a results in an increase in both LH and FSH. This increase is similar but not identical with natural mid-ovulatory gonadotropin surge. There is multiple physiological roles played by FSH particularly in the last stage of oocyte maturation namely resumption of the first meiotic division and cumulus expansion **(Kol et al., 2010).** Also, addition of FSH at the time with conventional hCG trigger leads to significant improvement regarding the rate of VOR and 2PNembryos, and results in a higher level of FSH in follicular fluid in comparison with HCG alone as triggering agent **(Lamb et al., 2011).**

In contrast to our results, number of both usable and high quality embryos were similar in both groups as described by Lin et. al.

The concept of dual trigger with low-dose hCG and GnRHa is to supply a mini dose of hCG aiming at salvaging the corpora lutea by giving the necessary signal leading to correction of luteal phase defect. The added value of the dual trigger is to serve as a "back up" in the case of GnRHa trigger failure **(Meyer et al., 2015).** In the present study non-significant trend towards higher implantation rate but similar clinical pregnancy rate and early spontaneous apportion.

In accordance with our data **Shaprio et al., (2008)** recorded that a dual trigger protocol using variable an hCG doses from 1000 to 2500 IU depending on body weight results in 53.3% continuing pregnancy rate. Later publication also demonstrating a 57.7% continuing pregnancy rate with one case of clinically significant OHSS (Shapiro et al., 2011). Aiming at simplification and decreasing the risk of OHSS, **Griffin et al. (2012)** described a constant low hCG dose of 1000 IU administered with GnRHa trigger and intensive luteal steroid support. There is significant improvement in live birth rate of 30.96% to 52.9% with using dual trigger in comparison with GnRHa trigger alone in cases with serum E2 <4000 pg/mL and **Schachter et al. (2008)** demonstrated considerable improvement in implantation rates among cases receiving dual trigger (0.2 mg triptorelin in addition to 5000 IU hCG) than those receiving conventional HCG trigger.

The above findings may be partially explained by different affinities regarding the GnRH receptor as the agonist affinity is more than that for the antagonist, it could remove the antagonist from endometrial receptors, so enhancing convenient post-receptor events for implantation. Also, dual trigger administration can encourage luteal phase recruitment leading to better gestation outcomes.

In the current study, 4 patients develop OHSS but majority of them (n=3) were mild OHSS according to Golan classification.

So dual trigger group had significantly less risk of developing OHSS both in terms of incidence and severity in comparison with slandered dosage HCG.

The administration of dual trigger in normal/high responders has been investigated by many authors **(Shapiro et al., 2007, Shapiro et al., 2011 and Grifin et al., 2012).** Despite lake of sufficient power regarding examining the risk of OHSS, **Shapiro et al., (2011)** reported very low rates of OHSS (<1 %) with a dual trigger in women at a relatively high risk for OHSS (mean serum E2 on the day of trigger was >4700 pg/mL and 227 follicles on the day of trigger). Griffin et al., (2014) restricted the use of the dual trigger to cases with serum E2 less than 4000 pg/ml and recorded one case of early OHSS in 102 cycles suffering from mild degree of this syndrome.

In conclusion our results suggested that administration of dual trigger consisting of GnRH-a and low dose HCG is probably safe and effective method of triggering final oocyte maturation in cases of high responders in comparison with conventional triggering with standard dose HCG. It is associated with higher quality embryo rate and lower incidence and severity of early OHSS. However our study is limited by small sample size and being retrospective, so it is recommended that our results should be further confirmed on a larger sample size in a prospective randomized controlled method.

**References:**

1. Castillo JC, Morenoa J, Dolza M, Bonilla-Musoles F (2013). Successful pregnancy following dual triggering concept (rhCG + GnRH agonist) in a patient showing repetitive inmature oocytes and empty follicle syndrome: case report. J Med Cases: (4)221-226. https://doi.org/10.4021/ jmc1055w.
2. Dean, A., Sullivan, K., & Soe, M. (2013). OpenEpi: Open Source Epidemiologic Statistics for Public Health. Updated 2013/4/6. https://www.OpenEpi.com
3. Engmann L, Romak J and Nulsen J (2011). In vitro viability and secretory capacity of human

luteinized granulosa cells after gonadotropin-releasing hormone agonist trigger of oocyte maturation. Fertil Steril, (961): 198-202.
4. Eppig JJ (1979). FSH stimulates hyaluronic acid synthesis by0ocyte-cumulus cell complexes from mouse preovulatory follicles. Nature; 281(5731): 483-494.
5. Griffin D, Feinn R, Engmann L, Nulsen J, Budinetz T, Benadiva C (2014). Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates. Fertil Steril. fertnstert.2014.04.028. 2014; 102:405-9. https://doi.org/10.1016j.
6. Grifin D, Benadiva C, Kummer N, Budinetz T, Nulsen J, Engmann L (2012). Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders. Fertil Steril.:97(6):1316-20. doi:10.1016/j.fertnstert.2012.03.015.
7. Hoff JD, Quigley ME, Yen SS (1983). Hormonal dynamics at midcycle: A reevaluation. J Clin Endocrinol Metab; 57(4): 792-6.
8. Humaidan P, Westergaard, LG, Mikkelsen AL Fukuda M, Yding Andersen C (2009). Levels of the EGF- like peptide amphiregulin are significantly reduced in follicular fluid after GnRHa triggering of final oocyte maturation. Hum Reprod; 24: 0-284.
9. IBM. (2017). IBM SPSS Statistics for Windows, Version 25. Armonk, NY: IBM Corp. http://www-01.ibm.com/support/docview.wss?uid=swg27049428
10. Itskovitz J, Boldes R, Levron J (1991). Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyper stimulation syndrome by gonadotropin-releasing hormone agonist. Fertil Steril;56(2): 213-220.
11. Kol S, Humaidan P. (2010). LH HCG and FSH surges for final oocyte maturation: Sometimes it takes two to tango Reprod Biomed Online. 21:590-592.
12. Lamb JD, Shen S, McCulloch C, Jalalian L, Cedars MI, Rosen MP (2011). Follicle-stimulating hormone administered at the time of human chorionic gonadotropin trigger improves oocyte developmental com petence in vitro fertilization cycles: A randomized, double-blind, placebo-controlled trial. Fertil Steril.95:1655-1660.
13. Li, S., Zhou, D., Yin, T., Xu, W., Xie, Q., Cheng, D., & Yang, J. (2018). Dual trigger of triptorelin and HCG optimizes clinical outcome for high ovarian responder in GnRH-antagonist protocols. Oncotarget, 9(4), 37- 53.
14. Meyer L, Murphy LA, Gumer A (2015). Risk factors for a suboptimal response to gonadotropin-releasing hormone agonist trigger during in vitro fertilization cycles. Fertil Steril; 104(3): 637-42.
15. Nakano R, Mizuno T, Kotsuji (1973) Triggering" of ovulation after infusion of synthetic luteinizing hormone releasing factor (LR). Acta Obstet Gynecol Scand; 52(3): 269-72.
16. Petrie, A., & Sabin, C. (2009). Medical Statistics at a Glance (3rd edition, Vol. 23). Wiley-Blackwell. https://doi.org/10.1017/CBO9781107415324.004
17. Richards JS, Jahnsen T, Hedin L (1987). Ovarian follicular development: From physiology to molecular biology. Recent Prog Horm Res; 43: 231-76.
18. Schachter M, Friedler S, Ron-El R, (2008). Can pregnancy rate be improved in gonadotropin-releasing hormone (GnRH) antagonist cycles by administering GnRH agonist before oocyte retrieval A pro spective, randomized study. Fertil Steril.;90:1087-1093.
19. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C (2011). Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. Fertil Steril.:95(8):2715-7. doi:10.1016/j.fertnstert.2011.03.109.
20. Shapiro BS, Daneshm and ST, Garner FC, Aguirre M, Thomas S (2008). Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of in vitro fertilization. Fertil Steril. 2008; 90:231-3. https://doi.org/10.1016/j.fertnstert.2007.06.030.
21. Yding Andersen C (2002). Effect of FSH and its different isoforms on maturation of oocytes iron pre-ovulatory follicles. Reprod Biomed Online; 5(3): 232-9.
22. Zelinski-Wooten MB, Hutchison JS, Hess DL (1995). Follicle stimulating hormone alone supports follicle growth and oocyte development in gonadotropin releasing hormone antagonist-treated monkeys. Hum Reprod; 10(7): 1658-66.

10/5/2019