Published in final edited form as:

Fertil Steril. 2015 January ; 103(1): 264–269. doi:10.1016/j.fertnstert.2014.09.042.

Use of gonadotropin-releasing hormone agonist (GnRHa) trigger during IVF is associated with similar endocrine profiles and oocyte measures in women with and without PCOS

Kathleen E. O'Neill, M.D., Suneeta Senapati, M.D., M.S.C.E., and Anuja Dokras, M.D., Ph.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Pennsylvania, PA

Abstract

Objective—To compare endocrine profiles and IVF outcomes after using gonadotropin-releasing hormone agonists (GnRHa) to trigger final oocyte maturation in women with PCOS to other hyper responders.

Design—Retrospective cohort study

Setting—Academic center

Patients—40 women with PCOS and 74 hyper responders without PCOS

Interventions—GnRHa trigger

Main Outcome Measure—Number of oocytes

Results—Serum estradiol, luteinizing hormone, and progesterone levels on the day of GnRHa trigger and the day after trigger did not differ significantly between groups. There were no significant differences in total number of oocytes or percent mature oocytes obtained between groups after controlling for age, antral follicle count and total days of stimulation. The overall rate of no retrieval of oocytes after trigger was low (2.6%). Fertilization rate, implantation rate, clinical pregnancy and live birth rates were similar in the two groups. No patients developed OHSS.

Conclusions—The similar post-GnRHa trigger hormonal profiles and mature oocyte yield supports the routine use of GnRHa trigger to prevent OHSS in women with PCOS.

Keywords

GnRHa trigger; PCOS; IVF outcomes; OHSS

Introduction

Gonadotropin-releasing hormone agonists (GnRHa) were first introduced in the early 1990s as an alternative to human chorionic gonadotropin (hCG) for the induction of oocyte maturation during in vitro fertilization (IVF) (1, 2). The ability of GnRHa to trigger the final

step in oocyte maturation in an antagonist cycle relies on its ability to displace the GnRH antagonist in the pituitary, activate the GnRH receptor, and increase serum levels of endogenous luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which requires an intact hypothalamic-pituitary-ovary axis (2). The FSH surge that accompanies the GnRHa trigger promotes nuclear maturation and secures corpus luteum function (3–5). Administration of GnRHa results in a surge of both LH and FSH in contrast to hCG, which results in an increase in LH-like activity alone (2, 6). Additionally, hCG has a greater carbohydrate content than GnRHa, resulting in a longer circulating half-life and sustained LH receptor activity (7). The lack of this sustained activity after GnRHa trigger, results in a significant reduction in the risk of ovarian hyperstimulation syndrome (OHSS) (8–13).

A number of studies in heterogeneous populations of hyper responders have demonstrated that the GnRHa trigger is effective in increasing serum levels of endogenous LH and FSH, inducing oocyte maturation and that the number of total and mature oocytes retrieved, as well as embryo development and pregnancy rates are similar to those obtained after hCG trigger (2, 9, 14, 15). However, some studies have reported compromised pregnancy rates after GnRHa trigger (15–18), most likely related to inadequate luteal phase support provided by the short-acting effects of GnRHa (9, 13, 14, 19–22). Despite implementation of various strategies to exogenously support the luteal phase and achieve comparable pregnancy rates, some concerns remain regarding the effectiveness of GnRHa to induce optimal oocyte yield and maturity (23, 24).

Polycystic ovary syndrome (PCOS) is a common endocrine condition characterized by ovulatory dysfunction, hyperandrogenism and polycystic appearing ovaries. Women with PCOS exhibit neuroendocrine abnormalities including increased GnRH pulse frequency, which results in LH predominance over FSH (25). A few studies have shown that the magnitude of the LH increase and absolute post-GnRHa trigger value of LH may be used as independent predictors of the total number of oocytes and mature oocytes retrieved (26–28). It is not clear if the increased LH pulsatility and androgenic microenvironment observed in women with PCOS affects oocyte yield and maturity compared to women without PCOS. Women with PCOS are at an increased risk for OHSS and GnRHa protocols are commonly used in this population during IVF. However, there are no studies that have specifically examined the response to GnRHa trigger in women with PCOS compared to other high responders undergoing IVF.

The primary aim of this study was to compare the effects of GnRHa trigger on endocrine parameters and oocyte number and maturity in women with PCOS compared to other hyper responders. We hypothesized that underlying abnormalities in hypothalamic–pituitary function in women with PCOS may result in altered ovarian response to a GnRHa trigger compared to other high responders. Our secondary aims were to assess fertilization, pregnancy and live birth rates.

Materials and Methods

Study Design and Participants

All women who underwent fresh autologous and oocyte donation cycles where GnRHa was used for the induction of oocyte maturation at Penn Fertility Care between January 1, 2008 and January 1, 2013 were included for analysis. The antagonist GnRHa protocol was selected if the patient was considered a high responder based on prior treatment cycles, age, ovarian reserve testing and infertility diagnosis. During this time period all IVF cycles were managed by one author (AD) including protocol selection, dose adjustments and timing and type of oocyte maturation trigger, providing consistency. We excluded cycles in which both GnRHa and hCG were co-administered (dual trigger). Patient clinical characteristics and details of the IVF cycle were obtained from the Penn Fertility Care IVF database. Baseline and post-GnRHa trigger hormone values as well as pregnancy data were obtained from the patients' medical records. The study protocol was approved by the Institutional Review Board at the University of Pennsylvania.

Ovarian Stimulation Protocols

All patients underwent ovarian hyperstimulation using a GnRH antagonist protocol. Determination of starting gonadotropin doses were made based on patient age, body mass index, infertility diagnosis, ovarian reserve testing. Ovarian stimulation using recombinant FSH (Follistim; Merck & Co., Inc., Whitehouse Station, NJ, USA or Gonal-F; EMD Serono, Inc., Rockland, MA, USA) was initiated by cycle day 2 after menses. Ganirelix acetate (Ganirelix acetate injection; Merck & Co., Inc., Whitehouse Station, NJ, USA) or Cetrotide (cetrotirelix acetate injection; EMD Serono, Rockland, MA, USA) was administered when serum E2 levels reached >300 pg/mL or when there was a 13–14 mm follicle and highly purified human menopausal gonadotropin (hMG; Menopur; Ferring Pharmaceuticals, Parsippany, NJ, USA) supplementation was added. Follicular growth was monitored by serial transvaginal ultrasonography and serum E2 levels which were used to titrate gonadotropin dosages. Leuprolide acetate (Lupron; TAP Pharmaceuticals, Lake Forest, IL, USA) 80U (4.0 mg) was administered when at least two ovarian follicles were ≥ 18 mm in mean diameter. Serum E2 and LH levels were measured on the morning of GnRHa administration and repeated 10–12 hours after GnRHa administration along with progesterone measurements. Transvaginal ultrasound-guided oocyte retrieval was performed 35 hours after GnRHa administration. Criteria for ICSI included the use of non-ejaculated sperm, total motile count <2.5 million and morphology <15% by WHO IV criteria. Embryo transfer was performed on the third or fifth day post-retrieval. Luteal phase support started on the day after oocyte retrieval with daily intramuscular injection of 50 mg progesterone and three 0.1 mg transdermal patches of estradiol (Vivelle-Dot; Noven Pharmaceuticals Inc., Miami, FL, USA) changed every other day. We also measured serum estradiol and progesterone levels weekly until the pregnancy test or up to 8 weeks gestation and maintained the E2 >200 pg/ml and the progesterone levels >20 ng/ml. Serum hCG was measured 10–14 days following embryo transfer and a value above 5 IU/mL was considered to be a positive test.

Outcome Variables

The primary outcome analyzed was total number of oocytes retrieved. Other outcomes included post-trigger changes in hormone levels, percentage of mature oocytes, fertilization rate, implantation rate, clinical pregnancy rate, spontaneous abortion rate, and live birth rate. Percentage change in E2 and LH were calculated by subtracting the hormonal level on the day of trigger from the level the day following trigger and dividing the difference by the level on the day of trigger. The overall fertilization rate was calculated by dividing the number of 2 pronuclear stage embryos by the number of total oocytes obtained. For individuals in whom ICSI was used the fertilization rate was calculated by dividing the number of 2 pronuclear stage embryos by the number of total mature oocytes. For all pregnancy related outcomes, individuals using donor oocytes were excluded from the analyses performed. The implantation rate was calculated as the number of gestational sacs visualized on transvaginal ultrasound divided by the number of embryos transferred. A clinical pregnancy rate was calculated as the presence of fetal cardiac activity confirmed by transvaginal ultrasonography per embryo transfer (ET). Spontaneous abortion rate was defined as pregnancy loss after sonographic visualization of an intrauterine gestational sac per ET. Live birth rate was calculated as delivery of a viable infant after 24 weeks gestation per ET. OHSS was assessed for using the criteria proposed by Golan (29).

Statistical analysis

Associations of demographic and clinical characteristics of the patients by diagnostic group (PCOS vs. non-PCOS) were evaluated by Mann–Whitney U-test for continuous variables, and chi-square test for categorical variables. Univariate analysis was performed to identify significant associations between covariates and the clinical outcomes. Multivariable linear and logistic regression models were employed to evaluate the associations between diagnostic group and the outcome of interest (oocyte yield, percent immaturity, fertilization rate, implantation rate, clinical pregnancy rate, and spontaneous abortion rate) while adjusting for potential confounders (30). Data analysis was conducted using STATA version 11 (StataCorp, College Station, TX, USA). Statistical significance was interpreted as P value <0.05.

Results

Baseline Characteristics

Of the 114 women included in the analysis, 40 had PCOS as defined by Rotterdam criteria (31). Sixteen of the seventy-four women (22%) in the group without PCOS were women undergoing stimulation for egg donation. There were no egg donors in the PCOS group. Baseline demographics of the groups are shown in Table 1. Antral follicle counts (AFC) were significantly higher in the PCOS group.

Cycle Characteristics and Hormonal Profiles

The IVF cycle characteristics and endocrine changes are shown in Table 2. The LH levels at the start of the gonadotropin stimulation did not differ between women with and without PCOS (median value 3.3 (1.2–5.1) IU/L vs. 2.35 (0.65–4.5) IU/L, $p=0.18$). The starting

gonadotropin dose was slightly higher in the non-PCOS group ($p<0.01$, Table 2). There was no difference in total dose of gonadotropins used between groups after controlling for age, AFC, and BMI ($p=0.99$). There was no difference in the endometrial thickness between the groups on the day of GnRHa trigger ($p=0.58$). Serum E2, LH, and P4 levels on the day of trigger and post-trigger did not differ between the groups. The percentage E2 change and the proportion of women with a 10% increase in E2 level post-trigger exhibited a trend towards being higher in the PCOS group as compared to the non-PCOS group (29% vs. 17%, $p=0.05$ and 80% vs. 58%, $p=0.05$ respectively).

IVF Laboratory and Pregnancy Outcomes

The IVF cycle outcomes are shown in Table 3. There were no differences in total number of oocytes or percent mature oocytes obtained between groups after controlling for age, AFC and total days of stimulation ($p=0.92$ and $p=0.55$ respectively). Of note three patients with PCOS did not have any oocytes retrieved after administration of GnRHa trigger. In two subjects, the post-trigger LH level was >15 IU/mL and the post-trigger P4 level was >3.5 ng/mL. In one subject the post-trigger LH level was >15 IU/mL but the post-trigger P4 level was 3.2 ng/mL. In one patient, the post-trigger E2 dropped $>10\%$. One woman had undergone a previous IVF cycle in which GnRHa trigger had also been used and the oocyte yield was appropriate. There were no differences in the overall fertilization rates between groups. There were no differences between the non-PCOS women (excluding donor oocyte recipients) and PCOS women with respect to implantation rate (median 50% IQR [30%–100%] vs 50% [IQR 50%–100%] $p=0.76$), clinical pregnancy (33% vs 40%, $p=0.50$) and live birth rates (30% vs 33%, $p=0.78$) in unadjusted analyses and after adjusting for age, BMI, and parity ($p=0.37$, 0.92, and 0.83 respectively). No patients in either group that had received GnRHa trigger developed early or late OHSS. One of the patients that had no oocytes retrieved was subsequently given 10,000 IU of hCG to trigger oocyte maturation and developed severe OHSS requiring hospitalization.

Discussion

In this cohort study we found that women with PCOS had similar post-GnRHa trigger hormonal profiles, oocytes numbers and maturity compared to women without PCOS. A rise in LH and P4 after GnRHa trigger indicates that an endogenous flare has occurred and oocyte maturation has been initiated. In our study we noted a similar response to GnRHa as indicated by the rise in LH and P4 levels in both groups. It has previously been shown that post-trigger LH and P4 levels correlate with oocyte yield after GnRH trigger (26). In fact Humaidan et al, showed in a randomized controlled trial that more MII oocytes were obtained after GnRHa trigger compared to hCG trigger and attributed this finding to the action of elevated FSH levels in response to GnRHa (33). Although women with PCOS usually have a high oocyte yield after IVF, it has been suggested that the quality of the oocytes may be compromised due to the androgenic environment (32). We detected higher percentage change in E2 levels post-GnRHa trigger in women with PCOS. These findings are similar to our previous report where women with PCOS had a higher rise in E2 after hCG trigger compared to women without PCOS (34). It has previously been shown that granulosa cells obtained from women with PCOS secrete significantly higher levels of E2 in

response to FSH compared to controls (35). PCOS is associated with persistent rapid frequency GnRH release resulting in increased LH pulse amplitude and frequency (36). In addition there is altered hypothalamic sensitivity to feedback inhibition by sex steroids. In our current study both endocrine parameters after GnRHa trigger and oocyte numbers and maturity did not differ between the two groups, suggesting that GnRH agonists can be successfully used in women with PCOS.

In our cohort no oocytes were retrieved after GnRHa trigger in three women with PCOS. Previous studies have shown no difference in rates of no retrieval of oocytes after GnRHa and hCG triggers (24). The rate of this event in two large studies using GnRHa trigger were reported to be 1.4% and 3.5% which is similar to our overall rate of 2.6% (24, 26). One of the subjects in our cohort had a previous IVF cycle with adequate oocyte yield after using the GnRHa trigger. In all of our cases post-trigger LH and P4 levels did not predict no retrieval of oocytes (26). The post-trigger LH values were <15IU/ml in 1.3% of the non PCOS women and 2.5% of the women with PCOS. The post-trigger P4 values were <3.5ng/ml in 5% of the women without PCOS (mean number of oocytes 14.5) and 15% of the women with PCOS (mean number of oocytes 15.8). As previously suggested by Kummer et al, these post-trigger LH and P4 cutoffs did not predict oocyte yield or no oocyte retrieval in our population.

Using the large SART registry we have previously shown that IVF success rates are comparable, if not higher, in women with PCOS compared to women with tubal factor infertility (37). However, women with PCOS are at a significantly higher risk for OHSS when stimulated with gonadotropins (38, 39). It is therefore imperative that we choose protocols that will minimize or completely prevent the risk of OHSS. Use of GnRH antagonist protocols allows the use of GnRHa to trigger final oocyte maturation. In a meta-analysis it has been shown that use of GnRH antagonist protocols in women with PCOS have comparable pregnancy outcomes to longer suppression protocols (40). Although use of GnRHa trigger has been described in hyper responders, we are not aware of any study that has compared outcomes in women with PCOS to other hyper responders. Our results indicate that GnRHa trigger used in conjunction with GnRH antagonist provides adequate endocrine response, oocyte numbers and maturity in women with PCOS.

Our study had some limitations. Although it is a retrospective chart review it provides clinicians with information to counsel women with PCOS on routine use of GnRHa trigger protocols. Our study included relatively young non-obese women and our results may not be applicable to obese women with PCOS. It has been previously noted that BMI negatively correlates with oocyte yield and maturity in hyper responders using GnRHa trigger (26). We acknowledge that the heterogeneity of the group without PCOS may affect some of the secondary outcomes. Although we adjusted the secondary analysis for known confounders, the numbers were likely too small to detect significant differences in pregnancy outcomes. Additionally, the inclusion of individuals undergoing stimulation for egg donation limits our ability to draw conclusions regarding pregnancy outcomes.

Severe ovarian hyperstimulation syndrome is one of the most serious complications of gonadotropin administration and affects ~0.5–2% of all ovarian stimulation cycles (41).

PCOS constitutes a high risk for the development of OHSS, and ~15% risk of developing severe OHSS (35, 39). A number of strategies have been used for preventing or decreasing the risk of OHSS including embryo cryopreservation with no transfer, IV albumin administration, GnRH antagonist protocol, dopamine agonists, low-dose aspirin, coasting and treatment with metformin (42–49). The most effective strategy to date is the use of GnRHa to trigger oocyte maturation, which virtually eliminates the occurrence of this potentially life threatening condition (33, 50). Despite this advance, concerns remain regarding oocyte yield and maturity as well as impaired implantation and pregnancy outcomes. There is adequate data to support the use of GnRHa for oocyte maturation with diligent monitoring of post-trigger endocrine parameters. Our study adds to the literature supporting the use of GnRHa trigger in women with PCOS who are inherently at high risk for OHSS. A number of studies recommend the use of dual trigger (GnRHa and low dose hCG) to improve pregnancy rates by potentially improving the luteal phase. However, reports of OHSS after using the dual trigger protocol have been described (22, 51). It may therefore be prudent to use GnRHa alone and freeze all embryos if there is concern regarding the luteal phase or an inappropriate rise in LH/P4 levels post trigger. This strategy used in hyper responders with polycystic appearing ovaries has been associated with high cumulative pregnancy rates (17, 49). Implementation of antagonist protocols with GnRHa trigger is integral to our efforts to embrace patient friendly and safe IVF in women with PCOS.

Acknowledgments

Financial disclosures/support: T32 PD10032525 (KEO), 5K12HD001265-14 (SS)

References

1. Itskovitz J, Boldes R, Levron J, Erlik Y, Kahana L, Brandes JM. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. *Fertil Steril*. 1991; 56:213–220. [PubMed: 1906406]
2. Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. *J Clin Endocrinol Metab*. 1990; 71:918–922. [PubMed: 2119392]
3. Yding Andersen C. Effect of FSH and its different isoforms on maturation of oocytes from preovulatory follicles. *Repro Biomed Online*. 2002; 5:232–239.
4. Zelinski-Wooten MB, Hutchison JS, Hess DL, Wolf DP, Stouffer RL. Follicle stimulating hormone alone supports follicle growth and oocyte development in gonadotrophin-releasing hormone antagonist-treated monkeys. *Hum Reprod*. 1995; 10:1658–1666. [PubMed: 8582957]
5. Eppig JJ. FSH stimulates hyaluronic acid synthesis by oocyte-cumulus cell complexes from mouse preovulatory follicles. *Nature*. 1979; 281:483–484. [PubMed: 492307]
6. Hoff JD, Quigley ME, Yen SS. Hormonal dynamics at midcycle: a reevaluation. *J Clin Endocrinol Metab J*. 1983; 57:792–796.
7. Moyle WR, Bahl OP, Marz L. Role of carbohydrate of human chorionic gonadotropin in the mechanism of hormone action. *J Biol Chem*. 1975; 250:9163–9169. [PubMed: 172504]
8. Kol S. Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome. *Fertil Steril*. 2004; 81:1–5. [PubMed: 14711532]
9. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian

- hyperstimulation syndrome: a prospective randomized controlled study. *Fertil Steril*. 2008; 89:84–91. [PubMed: 17462639]
10. DiLuigi AJ, Engmann L, Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting. *Fertil Steril*. 2010; 94:1111–1114. [PubMed: 20074722]
 11. Engmann L, Benadiva C. GnRH agonist (buserelin) or HCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. *Hum Reprod*. 2005; 20:3258–3260. author reply 60. [PubMed: 16246862]
 12. Lewit N, Kol S, Manor D, Itskovitz-Eldor J. Comparison of gonadotrophin-releasing hormone analogues and human chorionic gonadotrophin for the induction of ovulation and prevention of ovarian hyperstimulation syndrome: a case-control study. *Hum Reprod*. 1996; 11:1399–1402. [PubMed: 8671474]
 13. Humaidan P, Papanikolaou EG, Kyrou D, Alsbjerg B, Polyzos NP, Devroey P, et al. The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. *Repro Biomed Online*. 2012; 24:134–141.
 14. Fauser BC, de Jong D, Olivennes F, Wramsby H, Tay C, Itskovitz-Eldor J, et al. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. *J Clin Endocrinol Metab*. 2002; 87:709–715. [PubMed: 11836309]
 15. Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, Diedrich K, et al. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. *Hum Reprod*. 2005; 20:2887–2892. [PubMed: 15979994]
 16. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grondahl ML, Westergaard L, et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. *Hum Reprod*. 2005; 20:1213–1220. [PubMed: 15760966]
 17. Griesinger G, Schultz L, Bauer T, Broessner A, Frambach T, Kissler S. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a "freeze-all" strategy: a prospective multicentric study. *Fertil Steril*. 2011; 95:2029–2033. 33 e1. [PubMed: 21371705]
 18. Youssef MA, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. *The Cochrane database of systematic reviews*. 2011 CD008046.
 19. Nevo O, Eldar-Geva T, Kol S, Itskovitz-Eldor J. Lower levels of inhibin A and pro-alphaC during the luteal phase after triggering oocyte maturation with a gonadotropin-releasing hormone agonist versus human chorionic gonadotropin. *Fertil Steril*. 2003; 79:1123–1128. [PubMed: 12738506]
 20. Engmann L, DiLuigi A, Schmidt D, Benadiva C, Maier D, Nulsen J. The effect of luteal phase vaginal estradiol supplementation on the success of in vitro fertilization treatment: a prospective randomized study. *Fertil Steril*. 2008; 89:554–561. [PubMed: 17678651]
 21. Iliodromiti S, Blockeel C, Tremellen KP, Fleming R, Tournaye H, Humaidan P, et al. Consistent high clinical pregnancy rates and low ovarian hyperstimulation syndrome rates in high-risk patients after GnRH agonist triggering and modified luteal support: a retrospective multicentre study. *Hum Reprod*. 2013; 28:2529–2536. [PubMed: 23873146]
 22. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. *Fertil Steril*. 2011; 95:2715–2717. [PubMed: 21550042]
 23. Honnma H, Hashiba Y, Asada Y, Endo T. Failure of triggering oocyte maturation with a GnRH agonist in polycystic ovary syndrome: two case reports. *Eur J Obstet Gyn R B*. 2011; 157:239–240.
 24. Castillo JC, Garcia-Velasco J, Humaidan P. Empty follicle syndrome after GnRH α triggering versus hCG triggering in COS. *J Assist Reprod Genet*. 2012; 29:249–253. [PubMed: 22237554]

25. Burt Solorzano CM, Beller JP, Abshire MY, Collins JS, McCartney CR, Marshall JC. Neuroendocrine dysfunction in polycystic ovary syndrome. *Steroids*. 2012; 77:332–337. [PubMed: 22172593]
26. Kummer NE, Feinn RS, Griffin DW, Nulsen JC, Benadiva CA, Engmann LL. Predicting successful induction of oocyte maturation after gonadotropin-releasing hormone agonist (GnRHa) trigger. *Hum Reprod*. 2013; 28:152–159. [PubMed: 23077235]
27. Shapiro BS, Daneshmand ST, Restrepo H, Garner FC, Aguirre M, Hudson C. Efficacy of induced luteinizing hormone surge after "trigger" with gonadotropin-releasing hormone agonist. *Fertil Steril*. 2011; 95:826–828. [PubMed: 20961539]
28. Chen SL, Ye DS, Chen X, Yang XH, Zheng HY, Tang Y, et al. Circulating luteinizing hormone level after triggering oocyte maturation with GnRH agonist may predict oocyte yield in flexible GnRH antagonist protocol. *Hum Reprod*. 2012; 27:1351–1356. [PubMed: 22419746]
29. Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. *Obstet Gynecol Surv*. 1989; 44:430–440. [PubMed: 2660037]
30. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Hum Reprod*. 2011; 26:245–252. [PubMed: 21071489]
31. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004; 81:19–25.
32. Qiao J, Feng HL. Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. *Hum Reprod Update*. 2011; 17:17–33. [PubMed: 20639519]
33. Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? *Hum Reprod Update*. 2011; 17:510–524. [PubMed: 21450755]
34. Kondapalli LA, Molinaro TA, Sammel MD, Dokras A. A decrease in serum estradiol levels after human chorionic gonadotrophin administration predicts significantly lower clinical pregnancy and live birth rates in in vitro fertilization cycles. *Hum Reprod*. 2012; 27:2690–2697. [PubMed: 22752608]
35. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update*. 2008; 14:367–378. [PubMed: 18499708]
36. Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. *Hum Reprod Update*. 2006; 12:351–361. [PubMed: 16670102]
37. Kalra SK, Ratcliffe SJ, Dokras A. Is the fertile window extended in women with polycystic ovary syndrome? Utilizing the Society for Assisted Reproductive Technology registry to assess the impact of reproductive aging on live-birth rate. *Fertil Steril*. 2013; 100:208–213. [PubMed: 23557762]
38. MacDougall MJ, Tan SL, Balen A, Jacobs HS. A controlled study comparing patients with and without polycystic ovaries undergoing in-vitro fertilization. *Hum Reprod*. 1993; 8:233–237. [PubMed: 8473426]
39. Swanton A, Storey L, McVeigh E, Child T. IVF outcome in women with PCOS, PCO and normal ovarian morphology. *Eur J Obstet Gyn R B*. 2010; 149:68–71.
40. Lin H, Li Y, Li L, Wang W, Yang D, Zhang Q. Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs. *PloS one*. 2014; 9:e91796. [PubMed: 24642641]
41. Forman RG, Frydman R, Egan D, Ross C, Barlow DH. Severe ovarian hyperstimulation syndrome using agonists of gonadotropin-releasing hormone for in vitro fertilization: a European series and a proposal for prevention. *Fertil Steril*. 1990; 53:502–509. [PubMed: 2106456]
42. D'Angelo A, Amso N. Embryo freezing for preventing ovarian hyperstimulation syndrome. *The Cochrane database of systematic reviews*. 2007 CD002806.
43. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, et al. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). *Hum Reprod*. 2010; 25:683–689. [PubMed: 20008886]

44. Alvarez C, Marti-Bonmati L, Novella-Maestre E, Sanz R, Gomez R, Fernandez-Sanchez M, et al. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. *J Clin Endocrinol Metab.* 2007; 92:2931–2937. [PubMed: 17456571]
45. Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT, et al. Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study. *Repro Biomed Online.* 2008; 17:751–755.
46. Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. *Fertil Steril.* 2010; 93:2281–2284. [PubMed: 19261278]
47. Egbase PE, Al-Sharhan M, Grudzinskas JG. 'Early coasting' in patients with polycystic ovarian syndrome is consistent with good clinical outcome. *Hum Reprod.* 2002; 17:1212–1216. [PubMed: 11980740]
48. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Freitas V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *The Cochrane database of systematic reviews.* 2009 CD006105.
49. Manzanares MA, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonist in in vitro fertilization patients with polycystic ovaries does not cause ovarian hyperstimulation syndrome despite very high estradiol levels. *Fertil Steril.* 2010; 93:1215–1219. [PubMed: 19200978]
50. Kol S, Humaidan P. GnRH agonist triggering: recent developments. *Repro Biomed Online.* 2013; 26:226–230.
51. Humaidan P. Luteal phase rescue in high-risk OHSS patients by GnRH α triggering in combination with low-dose HCG: a pilot study. *Repro Biomed Online.* 2009; 18:630–634.

Table 1

Demographics and baseline characteristics by diagnostic group.

	Non-PCOS (n=74)	PCOS (n=40)
Age (years)	31.6 (26.9–35.0)	31.0 (29.0–34.1)
BMI (kg/m ²)	22 (20–26.5)	24 (21.5–26.9)
Caucasian	48 (65%)	26 (65%)
Nulliparous	51 (68.9%)	29 (72.5%)
Maximum day 3 FSH (mIU/mL)	6 (5–7.1)	5.5 (4–7) *
Antral follicle count	21 (16–28)	30.5 (20–40) **

Data are median (interquartile range).

*
p<0.05,**
p<0.01

Table 2

IVF cycle characteristics and endocrine changes after GnRHa trigger.

	Non-PCOS (n=74)	PCOS (n=40)
Total dose of gonadotropins used (IU)	1462.5 (975–1900)	1300 (1012.5–2037.5)
Days of stimulation	10 (9–11)	11 (10–12)
Maximum E2 (pg/mL)	3817 (2897–4979)	4019 (3143–4942.5)
E2 levels on day of trigger (pg/mL)	3367.5 (2624–4273)	3479.5 (2887–4525.5)
LH levels on day of trigger (mIU/mL)	0.5 (0.3–1.1)	0.65 (0.3–1.1)
E2 levels post-trigger (pg/mL)	3965.5 (3240–5447)	4832 (3808–5771.5)
LH levels post-trigger (mIU/mL)	55.6 (38.4–83)	44.5 (31.65–76.5)
P4 levels post-trigger (ng/mL)	6.6 (4.8–9.5)	5.5 (4–8.4) #
% E2 change after trigger	17 (3–35)	29 (13–50) *
E2 > 10% change after trigger	46 (62%)	32 (80%) *
% LH change after trigger	105 (67–199)	96 (39–170)

Data are median (interquartile range).

*
p<0.05,**
p<0.01#
One individual in the non-PCOS group and three in the PCOS group did not have post-retrieval progesterone values available for analysis.

Table 3

IVF oocyte and embryo yield and cycle outcomes.

	Non-PCOS (n=74)	PCOS (n=40)
Total number of follicles on day of GnRHa trigger	30 (25–35)	35.5 (28–43.5) **
Total oocyte number	16 (11–20)	16 (10–22.5)
Percent mature oocyte	74% (55%–88%)	80% (61%–87%)
% IVF cycles using ICSI	31 (42.5%)	8 (22.5%) *
Total fertilization rate (%)	50 (30–74)	50 (40–73)

Data are median (interquartile range).

*
p<0.05,**
p<0.01