ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Reproductive outcomes after a single dose of gonadotropin-releasing hormone agonist compared with human chorionic gonadotropin for the induction of final oocyte maturation in hyper-responder women aged 35–40 years

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Objective: To investigate the reproductive outcomes after the use of GnRH agonist (GnRHa) compared with hCG for the induction of final oocyte maturation in GnRH antagonist cycles performed in hyper-responder women aged 35–40 years.
Design: Retrospective study.
Setting: Academic fertility center.
Patient(s): Two hundred seventy-two hyper-responder women aged 35–40 years who underwent controlled ovarian stimulation under GnRH antagonist suppression were included. Final oocyte maturation was performed with GnRHa (n = 168) or hCG (n = 104). Embryos were cryopreserved at the blastocyst stage and transferred in subsequent warming cycles (n = 542). Subjects were included in the analysis until live birth was achieved, after which they were excluded from further analysis.
Intervention(s): None.
Main Outcome Measure(s): Cumulative live birth rate.
Result(s): Subjects in the GnRHa group achieved a higher number of oocytes (22 vs. 21) and a higher number of mature oocytes (16 vs. 14). The number of cryopreserved blastocysts (median of five blastocysts in both groups) was similar. Women in the hCG group needed a lower number of warming cycles to achieve live birth (1.32 vs. 2.12), had higher embryo implantation rates (48% vs. 39%), and the proportion of embryos transferred until live birth was lower (33% vs. 57%). The cumulative live birth rate was similar between the groups (48.15% vs. 48%).
Conclusion(s): Although the cumulative live birth rate is similar, a single dose of GnRHa possibly results in suboptimal oocyte and embryo competence, as manifested by decreased embryo implantation rates and increased time needed to achieve live birth. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Final oocyte maturation, GnRH agonist, hCG, live birth rate, ovulation trigger

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A single bolus of GnRH agonist (GnRHa) can stimulate the release of LH and FSH from the pituitary gland (1, 2). This gonadotropin release mimics the natural mid-cycle LH surge required for final oocyte maturation. The use of GnRHa to trigger final oocyte maturation became possible in IVF cycles with the introduction of GnRH antagonist into clinical use two decades ago (3). Unlike the GnRHa that achieves pituitary desensitization by GnRH receptor down-regulation, the GnRH antagonist blocks the GnRH receptor competitively and can be displaced by an exogenous bolus of GnRH agonist. Although the gonadotropin surge following GnRHa is considered more "physiologic" because it results in the release of endogenous LH and FSH, there are significant differences between the GnRHa-induced gonadotropin surge and the gonadotropin surge that occurs in the natural cycle. The LH surge in the natural cycle is characterized by three phases, with a total duration of 48 hours (4). However, the GnRH agonist–induced LH surge has a shorter duration and a lower secretion amplitude and consists of two phases lasting 24–36 hours (1). This results in a reduced amount of gonadotropins being released from the pituitary gland and limited and shorter exposure of the ovarian follicles to LH after GnRHa compared with the natural cycle. This short, self-limited gonadotropin surge following the agonist trigger and the lack of a stimulatory effect that extends into the luteal phase results in rapid luteolysis and consequently a reduced risk of developing ovarian hyperstimulation syndrome (OHSS) (5). This is compared with the traditional hCG trigger, which has a prolonged stimulatory effect on the ovarian follicles and later on the corpora lutea due to its longer half-life (6). Early experience with the GnRHa trigger was disappointing and was associated with an increased risk of miscarriage and reduced live birth rates compared with the hCG trigger (7, 8). This has shifted the research toward trying to optimize the luteal phase, either by supplementing it with high doses of E_2 and P (9) or by adding a low dose of hCG acting as an LH analogue (10). Little attention has been paid to the effect of a GnRHa-induced gonadotropin surge on oocyte or embryo competence. Recently several studies have shown that there are differences in genetic expression (11), postreceptor signaling in the cumulus–oocyte complex (12), and the morphokinetics (13) of embryo development when comparing GnRHa with the hCG trigger. Whether these differences in the mechanisms of action during the final stages of oocyte maturation improve or impair oocyte competence is still unknown. However, studies that have shown a trend toward a higher yield of mature oocytes after GnRHa did not result in a higher number of embryos available for transfer or in better reproductive outcomes (10, 14).

Considering the different effects both triggers have on the cumulus–oocyte complex, it is still unclear whether the limited exposure of the stimulated ovarian follicles to LH after GnRHa has negative effects on oocyte and/or embryo development. Assessing the reproductive outcomes in subsequent vitrified warming cycles can provide an optimal comparison, because this skips any luteal phase deficiency associated with fresh cycles. Earlier studies that compared GnRHa with the hCG trigger and freeze-all embryos included mainly young donors, who do not represent the general IVF population. The aim of the present study was to compare the reproductive outcomes following the use of GnRHa compared with the use of hCG in hyper-responder women aged 35–40 years who had segmented IVF cycles and freeze-all embryos because of an increased risk of OHSS.

MATERIALS AND METHODS

Study Design

The study was conducted at a single academic fertility center. All the antagonist IVF cycles performed in women aged 35–40 years between January 2012 and December 2014 were reviewed for possible inclusion. Our clinic guideline is to perform cycle segmentation when an increased risk of developing OHSS is suspected by freezing all embryos. Embryo transfer was performed in subsequent warming cycles. When an increased risk of OHSS was suspected, final oocyte maturation was performed either by hCG or GnRHa. In part of these cycles (particularly when the hCG trigger was used), the risk of OHSS was recognized on the day of oocyte retrieval (owing to a high number of retrieved oocytes), and the decision was made to freeze all embryos. Inclusion criteria included the following: controlled ovarian stimulation cycles performed under GnRH antagonist pituitary suppression, triggering final oocyte maturation either by urinary/recombinant hCG or GnRHa, and freeze-all embryos due to an increased risk of OHSS. Exclusion criteria included the following: ovarian stimulation cycles in which GnRH agonist was used for pituitary suppression, cycles with freeze-all embryos performed for reasons other than an increased risk of OHSS, cycles in which the embryo culture was not extended to the blastocyst stage, cycles in which subsequent warming cycles were not performed, and cycles in which surgically retrieved sperm was used owing to severe male factor infertility. All the subsequent frozen cycles performed in each subject until live birth was achieved were reviewed, after which the subjects were excluded from further analysis. The outcomes of the consecutive warming cycles were analyzed until December 2015. The study was performed according to the guidelines and was approved by the local ethics committee.

Ovarian Stimulation and Oocyte retrieval

Ovarian stimulation was performed using the GnRH antagonist protocol in combination with recombinant FSH and LH. The gonadotropin was started on day 2 to 3 of the menstrual cycle. The GnRH antagonist was started on day 6 of gonadotropin stimulation (fixed antagonist protocol). Final oocyte maturation was achieved by administering either hCG (urinary hCG: hCG PPC, Ferring, 5,000 IU or 10,000 IU; or recombinant hCG: 250 μg Ovidrel, EMD Serono) or a single bolus of GnRHa (buserelin acetate 1 mg, Suprefact, Sanofi) when at least two follicles were $\geq$17 mm. Oocyte retrieval was performed 36–38 hours after triggering. The decision regarding the trigger type depended on the treating physician. In our practice there are no specific guidelines about when to trigger final oocyte maturation with the GnRh agonist to prevent OHSS. However, a history of previous OHSS, peak E_2 >12,000 pmol/L, and the presence of 15 or more follicles