GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis

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Triggering final oocyte maturation with GnRH agonist during ovarian stimulation is feasible when inhibition of premature LH surge is performed with GnRH antagonists, and we aimed to systematically collate evidence on the clinical efficacy of GnRH agonist triggering in patients undergoing assisted reproduction in GnRH antagonist protocols. Twenty-three publications were identified by a comprehensive literature search that included PubMed, Embase and the Cochrane Library. Three publications out of 23 fulfilled the inclusion criteria for meta-analysis, which were (i) prospective, randomized controlled study design; (ii) stimulation with gonadotropins for induction of multifollicular development; (iii) suppression of endogenous LH by a GnRH antagonist; (iv) triggering of final oocyte maturation with GnRH agonist; (v) control group randomized to receive HCG for final oocyte maturation and (vi) any means of luteal phase support other than HCG. The participants were normoovulatory women undergoing IVF. The outcomes assessed were clinical pregnancy per randomized patient; number of oocytes retrieved; proportion of metaphase II oocytes; fertilization rate; embryo quality score; first trimester abortion rate; ovarian hyperstimulation syndrome (OHSS) incidence. Results are presented as combined standardized differences of the mean and combined odds ratios, as appropriate, with 95% confidence intervals. No significant difference was found for the number of oocytes retrieved (–0.94, –0.33–0.14), proportion of metaphase II oocytes (–0.03, –0.58–0.52), fertilization rate (0.15, –0.09–0.38) or embryo quality score (0.05, –0.18–0.29). No OHSS occurred in two of the studies, whereas in one study OHSS incidence was not reported. Thus from the available data, no conclusion can be drawn as regards OHSS incidence after GnRH agonist triggering. In comparison to HCG, GnRH agonist administration is associated with a significantly reduced likelihood of achieving a clinical pregnancy (0.21, 0.05–0.84; \( P = 0.03 \)). The odds of first trimester pregnancy loss is increased after GnRH agonist triggering; however, the confidence interval crosses unity (11.51, 0.95–138.98; \( P = 0.05 \)). In conclusion, the use of GnRH agonist to trigger final oocyte maturation in IVF, where inhibition of premature LH surge is achieved with GnRH antagonists, yields a number of oocytes capable to undergo fertilization and subsequent embryonic cleavage, which is comparable to that achieved with HCG. However, the likelihood of an ongoing clinical pregnancy after GnRH agonist triggering is significantly lower as compared to standard HCG treatment.

Key words: GnRH agonist/GnRH antagonist/meta-analysis/oocyte maturation

Introduction

Administration of a bolus of GnRH agonist induces release of LH from the pituitary gland similarly to a spontaneous mid-cycle LH surge, and thus provides an alternative to the administration of HCG in ovarian stimulation protocols. GnRH agonists have been used to trigger final oocyte maturation after controlled ovarian hyperstimulation (COH) for IVF as well as in non-IVF ovarian stimulation cycles (Bentick et al., 1990; Gonen et al., 1990; Imoedemhe et al., 1991; Segal and Casper, 1992; Lanzone et al., 1994; Buckett et al., 1998). In particular, GnRH agonist triggering has been suggested as a measure to prevent ovarian hyperstimulation syndrome (OHSS) (Emperaire and Ruffie, 1991; Itskovitz et al., 1991; Balasch et al., 1994; Kol et al., 1996; Lewit et al., 1996).

However, GnRH agonist triggering is only applicable in COH treatment regimen in which no desensitization of the pituitary by GnRH agonist has already been conducted. Because pituitary desensitizing GnRH agonist protocols have become the most widely used standard in COH (Deutsches IVF Register, 1996–2004; Fivnat, 2002), GnRH agonist usage for triggering final oocyte
maturation in IVF patients has attained little clinical interest until the market approval of the GnRH antagonists.

GnRH antagonists have emerged as an alternative to GnRH agonists in preventing premature LH surges in COH (Diedrich et al., 1994; Oliviaennes et al., 1995). Due to the specific mode of action of the antagonist, the pituitary remains responsive to GnRH agonist under GnRH antagonist treatment in standard doses (Felberbaum et al., 1995). Several studies have demonstrated the feasibility of inducing an endogenous LH surge by administering a bolus dose of GnRH agonist in a GnRH antagonist protocol (Olivaennes et al., 1996; Fauser et al., 2002; Beckers et al., 2003). As this manipulation has been suggested to prevent ovarian hyperstimulation syndrome, its use has been proposed as a safer and at the same time efficacious way to perform IVF (Kol and Itskovitz-Eldor, 2000; Kol 2003, 2004; Orvieto, 2005).

The present systematic review aims at calling the available evidence and thus answering the following question: Is GnRH agonist for triggering of final oocyte maturation in IVF patients undergoing ovarian hypertimulation in a GnRH antagonist protocol as efficacious as triggering final oocyte maturation with HCG?

Materials and methods

Search strategy for identification of studies

In March 2005, the bibliographic database Medline, Embase and Cochrane were searched using combinations of the following keywords: GnRH antagonist; GnRH agonist; IVF. Abstract books from the annual meetings of the American Society of Reproductive Medicine and the European Society of Human Reproduction and Embryology were hand searched from 2004 back to 1999, when the first GnRH antagonist became commercially available. The reference lists of review articles and the located studies were checked to identify further studies.

Types of studies considered for this review

Trials comparing clinical efficacy of GnRH agonist triggering with HCG triggering in a GnRH antagonist protocol were considered eligible for analysis. Criteria for inclusion/exclusion were established prior to the initiation of the literature search. The following criteria were necessary for inclusion: (i) prospective, randomized controlled study design; (ii) stimulation with gonadotropins for induction of multifollicular development in patients with an indication for assisted reproduction; (iii) suppression of endogenous LH by a GnRH antagonist concomitant to ovarian stimulation; (iv) triggering of final oocyte maturation with GnRH agonist; (v) control group randomized to receive HCG for final oocyte maturation (vi) any means of luteal phase support other than HCG.

Description of studies

Table I summarizes publications of clinical trials on GnRH agonist triggering in GnRH antagonist protocols. Twenty-three publications were retrieved from the literature, three of which fulfilled the inclusion criteria. Abstract publications could not be assessed for methodological quality, and important information for data synthesis was missing. Thus, abstract publications had to be excluded.

The three eligible trials (Fauser et al., 2002; Humaidan et al., 2005; Kolibianakis et al., 2005) were similar in study design as summarized in Table II. Participants were women with an indication for assisted reproduction (e.g. IVF with or without ICSI) undergoing COH using a GnRH antagonist protocol. Included studies were truly randomized, except Kolibianakis et al. (2005), in which treatment allocation was not concealed (computer-generated list). None of the authors declared financial support.

Definition of outcome measures

Outcomes assessed in the present meta-analysis were clinical pregnancy per randomized patient; number of oocytes retrieved; proportion of metaphase II oocytes; fertilization rate; embryo quality score; first trimester abortion rate; OHSS incidence.

These outcomes were defined in the individual studies included in the analysis as follows: (ongoing) clinical pregnancy was defined as an intrauterine gestational sac with a heartbeat 3 weeks after a positive HCG test (Humaidan et al., 2005), a pregnancy progressing beyond the 12th week of gestation (Kolibianakis et al., 2005), or a pregnancy confirmed by detection of positive heartbeat on ultrasound between 12 and 16 weeks of gestation (Fauser et al., 2002). Clinical pregnancy rate was calculated based on the number of patients randomized in all studies.

The mean number of oocytes retrieved was calculated based on the number of patients at oocyte retrieval in all studies. The proportion of metaphase oocytes was calculated for ICSI patients only. For fertilization rate, the numerator was the number of two pronuclear oocytes in all studies, with the number of cumulus-oocyte-complexes retrieved as the denominator in one study (Kolibianakis et al., 2005), whereas in the other two studies no further information on the denominator was provided. Embryo development and quality were assessed by (i) the mean number of good quality embryos (Grade 1 and 2) per patient (Fauser et al., 2002); (ii) the mean cleavage rate (Humaidan et al., 2005); (iii) an embryo score as described by Staessen et al. 1992 (Kolibianakis et al., 2005; centre 1) and a cumulative embryo score in a modified version as described by Ludwig et al. (2000) (Kolibianakis et al., 2005; centre 2). Early pregnancy loss was defined as miscarriage within the first 12 weeks after embryo transfer (Fauser et al., 2002; Kolibianakis et al., 2005), or as biochemical pregnancy with no further development (Humaidan et al., 2005). No specific definition of OHSS was provided in any study.

Method of review

The quality of selected studies were assessed and evaluated for methodology and appropriateness for inclusion by two independent reviewers (G.G and E.K).

Dichotomous results for each unit of analysis were expressed as an odds ratio (OR) with 95% confidence interval (CI). Continuous variables were expressed as standardized differences of the mean (Hedges adjusted effect size defined as the difference between two groups expressed in standard deviation units) with 95% CIs. The results were combined for meta-analysis with the computer software program Comprehensive Meta Analysis, version 1.0.25, using random effects model for all calculations and Mantel-Haenszel statistics where appropriate.

Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points and the overlap in their CIs. Formally, a statistical test for heterogeneity was employed.

One study included (Kolibianakis et al., 2005) was a two-centre study in which stratification of data by centre was conducted and
Table I. Trials identified by literature search, which were excluded from data synthesis, sorted chronologically by publication year and alphabetically by publication type

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial type</th>
<th>Publication type</th>
<th>Number of patients (GnRH agonist + HCG)</th>
<th>Main patient characteristics</th>
<th>GnRH agonist</th>
<th>HCG (IU)</th>
<th>Treatment type</th>
<th>LPS dosage/day</th>
<th>Main reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivennes et al. (1996)</td>
<td>Observational, uncontrolled</td>
<td>Full paper</td>
<td>5 + 0</td>
<td>Idiopathic infertility</td>
<td>0.1 mg triptorelin</td>
<td>NA</td>
<td>IUI</td>
<td>600 mg vag P</td>
<td>Non-IVF study, uncontrolled</td>
</tr>
<tr>
<td>Kol et al. (2000)</td>
<td>Observational, uncontrolled</td>
<td>Abstract</td>
<td>8 + 0</td>
<td>OHSS risk</td>
<td>0.2 mg triptorelin</td>
<td>NA</td>
<td>IVF</td>
<td>Not stated</td>
<td>Uncontrolled, overlap with Itskovitz-Eldor et al. (2000)</td>
</tr>
<tr>
<td>Itskovitz-Eldor et al. (2000)</td>
<td>Observational, uncontrolled</td>
<td>Full paper</td>
<td>8 + 0</td>
<td>OHSS risk</td>
<td>0.2 mg triptorelin</td>
<td>NA</td>
<td>IVF</td>
<td>50 mg i.m. P</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Bracero et al. (2001)</td>
<td>Retrospective, cohort</td>
<td>Abstract</td>
<td>8 + 11</td>
<td>Not stated</td>
<td>0.1 mg leuprorelin (×2 within 12 h)</td>
<td>10.000</td>
<td>IVF</td>
<td>200 mg vag. P</td>
<td>Non-randomized</td>
</tr>
<tr>
<td>Olivennes et al. (2001)</td>
<td>Observational, uncontrolled</td>
<td>Abstract</td>
<td>17 + 15 + 15</td>
<td>Regular cycle</td>
<td>0.2 mg triptorelin + 0.5 mg leuprorelin</td>
<td>10.000</td>
<td>IVF</td>
<td>50 mg i.m. P</td>
<td>Overlap with Fauser et al. (2002)</td>
</tr>
<tr>
<td>De Jong et al. (2001)</td>
<td>Case report</td>
<td>Full paper</td>
<td>1 + 0</td>
<td>Normo-ovulatory</td>
<td>0.5 mg leuprorelin</td>
<td>NA</td>
<td>IVF</td>
<td>50 mg i.m. P</td>
<td>Uncontrolled, overlap with Fauser et al. (2002)</td>
</tr>
<tr>
<td>Meltzer et al. (2002)</td>
<td>Observational, uncontrolled</td>
<td>Abstract</td>
<td>35 + 0</td>
<td>PCOS/risk of OHSS</td>
<td>0.25 mg triptorelin</td>
<td>NA</td>
<td>IVF</td>
<td>Not stated</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Cunha-Filho et al. (2002)</td>
<td>RCT</td>
<td>Abstract</td>
<td>8 + 12</td>
<td>Normo-gonadotropic</td>
<td>1 mg leuprolide acetate</td>
<td>5000</td>
<td>IVF</td>
<td>Not stated</td>
<td>Incomplete data</td>
</tr>
<tr>
<td>Beckers et al. (2002)</td>
<td>RCT</td>
<td>Abstract</td>
<td>40 (total)</td>
<td>Regular cycle</td>
<td>NA</td>
<td>Not stated</td>
<td>IVF</td>
<td>None</td>
<td>No LPS performed, overlap with Beckers et al. (2003)</td>
</tr>
<tr>
<td>Egbase et al. (2002)</td>
<td>RCT</td>
<td>Abstract</td>
<td>46 + 53</td>
<td>PCOS</td>
<td>0.2 mg NA</td>
<td>5000</td>
<td>IUI</td>
<td>Not stated</td>
<td>Non-IVF study</td>
</tr>
<tr>
<td>Diaz et al. (2003)</td>
<td>RCT</td>
<td>Abstract</td>
<td>25 (total)</td>
<td>Not stated</td>
<td>0.2 mg triptorelin</td>
<td>5000</td>
<td>IUI</td>
<td>Not stated</td>
<td>Non-IVF study</td>
</tr>
<tr>
<td>Goto et al. (2003)</td>
<td>Non-randomized comparative cohort</td>
<td>Abstract</td>
<td>40 + 42</td>
<td>Repeated IVF failure</td>
<td>0.6 mg buserelin (nasal)</td>
<td>10.000</td>
<td>IVF</td>
<td>Not stated</td>
<td>Non-randomized</td>
</tr>
<tr>
<td>Nevo et al. (2003)</td>
<td>RCT</td>
<td>Full paper</td>
<td>8 + 8</td>
<td>Normo-ovulatory</td>
<td>0.2 mg triptorelin</td>
<td>10.000</td>
<td>IVF</td>
<td>50 mg i.m. P</td>
<td>Overlap with Fauser et al. (2002)</td>
</tr>
<tr>
<td>Lok et al. (2003)</td>
<td>Case report</td>
<td>Full paper</td>
<td>1 + 0</td>
<td>Not stated</td>
<td>0.2 mg buserelin</td>
<td>NA</td>
<td>IVF</td>
<td>250 μg rHCG</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Beckers et al. (2003)</td>
<td>RCT</td>
<td>Full paper</td>
<td>15 + 11</td>
<td>Regular cycle</td>
<td>0.2 mg triptorelin</td>
<td>250 μg rHCG</td>
<td>IVF</td>
<td>90 mg vag. P</td>
<td>Overlap with Humaidan et al. (2005)</td>
</tr>
<tr>
<td>Westergaard et al. (2004)</td>
<td>RCT</td>
<td>Abstract</td>
<td>48 + 48</td>
<td>Normo-gonadotropic</td>
<td>0.5 mg buserelin</td>
<td>10.000</td>
<td>IVF</td>
<td>90 mg vag. P</td>
<td>Overlap with Humaidan et al. (2005)</td>
</tr>
<tr>
<td>Ossina et al. (2004)</td>
<td>RCT</td>
<td>Abstract</td>
<td>101 (total)</td>
<td>Not stated</td>
<td>0.1 mg triptorelin</td>
<td>10.000</td>
<td>IVF</td>
<td>Not stated</td>
<td>Incomplete data</td>
</tr>
<tr>
<td>Bankowski et al. (2004)</td>
<td>Observational, non-randomized</td>
<td>Abstract</td>
<td>97 + 317</td>
<td>Not stated</td>
<td>1 mg leuprorelin</td>
<td>10.000</td>
<td>IVF</td>
<td>Not stated</td>
<td>Non-randomised</td>
</tr>
<tr>
<td>Carone et al. (2005)</td>
<td>Observational, uncontrolled</td>
<td>Abstract</td>
<td>10 + 0</td>
<td>PCOS/risk of OHSS</td>
<td>0.2 mg triptorelin</td>
<td>NA</td>
<td>IVF</td>
<td>Not stated</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Kol and Muchtar (2005)</td>
<td>Observational, uncontrolled</td>
<td>Full paper</td>
<td>6 + 0</td>
<td>Risk of OHSS</td>
<td>0.2 mg triptorelin</td>
<td>NA</td>
<td>IVF</td>
<td>3 × 200 mg vag. P + 4 mg oral E2</td>
<td>Uncontrolled</td>
</tr>
</tbody>
</table>

IUI, intruterine insemination; LPS, luteal phase support; NA, not applicable; OHSS, ovarian hyperstimulation syndrome; oral E2, orally administered estradiol; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; rHCG, recombinant HCG; vag P, vaginal progesterone.
Table II. Characteristics of the trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fauser et al. (2002)</td>
<td>RCT; six centres (multi-national); open label; parallel design, 1:1:1 randomization ratio; randomization by telephone line on day of reaching ovulation induction criteria; number of subjects at randomization, 47 (GnRH agonist 32/hCG 15); number of subjects at oocyte retrieval, 47 (GnRH agonist 32/hCG 15); number of subjects at ET, 46 (GnRH agonist 32/hCG 14); no intention-to-treat analysis; no power calculation; analysis not adjusted for centre; inclusion criteria: ICSI patients only; female age, 18–39 years; regular menstrual cycle (24–35 day); BMI 18–29 kg/m² demographics: demographic characteristics not reported stratified for study groups</td>
<td>150 or 225 IU rFSH starting on cycle day 2 or 3; dose adjustment allowed after 5 stimulation days; ganirelix 0.25 mg from stimulation day 6 onwards; HCG 10.000 IU/keprolgin 0.5 mg/triprolein 0.2 mg (15/15/17 subjects) when at least 3 follicles ≥ 17 mm; ICSI only; ET on day 2–5; LPS, 50 mg i.m. progesterone/day for at least 2 weeks from day of ET</td>
<td>FSH consumption (IU); duration of FSH treatment (days); duration of ganirelix treatment (days); number of follicles on day of HCG or GnRH agonist; serum hormone (HCG, LH, E₂, P) profiles in luteal phase; number of oocytes; proportion of MII oocytes; fertilization rate; embryo quality; implantation rate; ongoing clinical pregnancy rate at 12 weeks after ET; first trimester miscarriage</td>
<td>Trial initially planned for 200 participants. Herein, outcome of the first 57 recruited subjects is reported</td>
<td></td>
</tr>
<tr>
<td>Humaidan et al. (2005)</td>
<td>RCT; two centres (Danish national); open label; parallel design; two armed, 1:1 randomization ratio; randomization by study nurse using computer-generated random numbers in sealed envelopes on day of reaching ovulation induction criteria; number of subjects at randomization: 122 (GnRH agonist 55/HCG 67); number of subjects at oocyte retrieval, 122 (GnRH agonist 55/HCG 67); number of subjects at ET, 105 (GnRH agonist 48/HCG 57); no intention-to-treat analysis; power calculation performed; analysis not adjusted for centre; inclusion criteria: female age &gt;25/&lt;40 years; baseline FSH and LH &lt; 12 mIU/ml; menstrual cycle 25–34 days; both ovaries present; absence of uterine abnormalities demographics age (years) HCG, 32.3 ± 3.8 GnRH agonist, 33.4 ± 3.9 BMI (kg/m²) GnRH agonist, 23.6 ± 3.1 HCG, 23.5 ± 3.0 FSH (basal, IU/L) GnRH agonist, 6.8 ± 2.4 HCG, 6.7 ± 2.0</td>
<td>150 or 200 IU rFSH starting on cycle day 2; no dose adjustment allowed; ganirelix 0.25 mg as soon as leading follicle was 15 mm; HCG s.c. 10.000 IU or buserelin s.c. 0.5 mg (67/55 subjects) when at least 3 follicles ≥ 17 mm; IVF or ICSI; ET on day 2 or 3; LPS, 90 mg vaginal progesterone + 4 mg estradiol p.o./d for 12 days from ET; no LPS in early pregnancy</td>
<td>FSH consumption (IU); duration of FSH treatment (days); dose of ganirelix (mg); day of first ganirelix injection; mean size of largest follicle on day of HCG or GnRH agonist; serum hormone (FSH, LH, E₂, P) profiles in follicular and luteal phase; number of oocytes; proportion of MII oocytes in ICSI cases; fertilization rate; cleavage rate; transfer rate; biochemical pregnancy rate; implantation rate; clinical pregnancy (intrauterine sac with heartbeat at ET +3 weeks) rate; early pregnancy loss</td>
<td>Trial prematurely discontinued due to differences in pregnancy rate observed</td>
<td></td>
</tr>
</tbody>
</table>
Table II. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolibianakis et al. (2005)</td>
<td>RCT, two centres (Belgium, Germany); open label; parallel design; two armed, 1:1 randomization ratio; randomization by computer-generated list at start of stimulation; allocation sequence not concealed; number of subjects at intention-to-treat; 106, number of subjects at randomization, 106 (GnRH agonist 52/HCG 54); number of subjects at oocyte retrieval, 104 (GnRH agonist 50/HCG 54); number of subjects at ET, 92 (GnRH agonist 44/HCG 48); power calculation performed; analysis adjusted for centre</td>
<td>Inclusion criteria: Female age ≤39 years; normal basal FSH; ≤3 previous ART attempts; normal BMI; regular menstrual cycle; no PCOS; both ovaries present; no previous poor response; fresh ejaculated sperm; no PGD-AS</td>
<td>200 IU rFSH starting on cycle day 2; no dose adjustment allowed; ganirelix 0.25 mg from stimulation day 6 onwards; HCG 10,000 IU or triptorelin 0.2 mg (54/50 subjects) as soon as 3 follicles ≥17 mm; IVF or ICSI; ET on day 2-5; LPS: 600 mg vaginal progesterone +4 mg estradiol p.o./day from day one after oocyte retrieval; LPS continued in case of pregnancy until 7 weeks of gestation</td>
<td>FSH consumption (IU); duration of FSH treatment (days); number of follicles ≥11 mm on day of HCG or GnRH agonist; serum hormone (FSH, LH, E2, P) values on day of HCG or GnRH agonist; number of oocytes; proportion of MII oocytes in ICSI cases; number of 2 PN oocytes; fertilization rate; embryo score; biochemical pregnancy rate; implantation rate; clinical pregnancy (ongoing at 12 weeks of gestation) rate; early pregnancy loss</td>
<td>Trial discontinued according to stopping rules of continuous safety monitoring</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>GnRH agonist, 32.4 ± 0.6</th>
<th>HCG, 32.3 ± 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>GnRH agonist, 22.9 ± 0.5</td>
<td>HCG, 23.4 ± 0.5</td>
</tr>
<tr>
<td>FSH (basal, IU/L)</td>
<td>GnRH agonist, 8.24 ± 0.37</td>
<td>HCG, 8.15 ± 0.39</td>
</tr>
</tbody>
</table>

ART, assisted reproductive treatment; BMI, body mass index; E₂, estradiol; ET, embryo transfer; LPS, luteal phase support; MII, metaphase II; PCOS, polycystic ovary syndrome; PGD-AS, preimplantation genetic diagnosis aneuploidy screening; RCT, randomized, controlled trial; rFSH, recombinant FSH.
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results were presented as combined estimates. The other two included studies (Fauser et al., 2002; Humaidan et al., 2005) did not consider the multi-centric approach and presented outcomes from pooled data. One of the studies (Fauser et al., 2002) was a three-armed study, with two study arms in which a GnRH agonist was employed, and a single study arm with the HCG treatment as a control. For the meta-analysis the unit of centre and the unit of trial group were maintained, where appropriate or where necessary, for synthesizing data.

Results

The included studies enrolled in total 275 randomized subjects. One hundred and thirty-nine subjects were randomized to receive GnRH agonist, and 136 subjects were randomized to receive HCG.

Main demographic parameters [age, body mass index (BMI), basal FSH, infertility diagnosis and cycle rank] were compared in two studies (Humaidan et al., 2005; Kolibianakis et al., 2005), and no statistically significant difference was found. In the third study (Fauser et al., 2002), it was stated that treatment groups were similar with respect to age, height, weight and BMI. Treatment groups were similar in all trials as regards FSH consumption, duration of FSH treatment, and folliculometry on the day of triggering final oocyte maturation. Figures 1 and 2 summarize outcome of data synthesis.

Clinical pregnancy rate

Two of the studies (Humaidan et al., 2005; Kolibianakis et al., 2005) were prematurely stopped due to significant differences between study groups in clinical pregnancy rates. Combined point estimate calculation was performed on the number of patients randomized and was 0.21, 95% CI = 0.05–0.84, P = 0.03, in favour of HCG. Formally, test of heterogeneity was negative (P = 0.07). In one of the studies (Kolibianakis et al., 2005), randomization was performed at the initiation of gonadotropin stimulation, whereas in the other two studies (Fauser et al., 2002; Humaidan et al., 2005) randomization was performed on the day of HCG or GnRH agonist administration. Recalculating the odds of clinical pregnancy achievement by only considering patients reaching HCG or GnRH agonist administration leads to an OR of 0.22, 95% CI = 0.05–0.85, P = 0.03.

Early pregnancy loss

Early pregnancy loss was significantly increased after GnRH agonist triggering of final oocyte maturation only in the study by Humaidan et al. (2005). A strong trend for an increased risk of first trimester pregnancy loss was present in the study by Kolibianakis et al. (2005). No such trend was observed in the study by Fauser et al. (2002). Combined point estimate and 95% CI were 11.51, 0.95–138.98; P = 0.05. Individual study results were heterogenous at P = 0.013.

Number of oocytes

No statistically significant difference in the number of oocytes retrieved was observed in any of the individual studies. Accordingly, combined point estimate and 95% CI were –0.94, –0.33–0.14, P = 0.43. Test of heterogeneity was negative (P = 0.49). Results remained stable when only the triptorelin study group (–0.11, –0.37–0.14, P = 0.38) or only the leuprorelin study group (–0.14, –0.34–0.10, P = 0.25) from the study by Fauser et al. were included in the meta-analysis.

Proportion of metaphase II oocytes

Combined point estimate and 95% CI for the proportion of metaphase II oocytes was –0.03, –0.58–0.52, P = 0.90. Individual study results were heterogenous at P < 0.01. Results remained stable, when only the triptorelin study group (–0.03, –0.72–0.65, P = 0.92) or only the leuprorelin study group (0.14, –0.41–0.69, P = 0.63) from the study by Fauser et al. were included in the meta-analysis.

Fertilization rate

No statistically significant difference in fertilization rate was observed in any of the individual studies. Combined point estimate and 95% CI for fertilization rate was 0.15, –0.09–0.38, P = 0.21. Test of heterogeneity was negative (P = 0.93). Results remained stable when only the triptorelin study group (0.13, –0.11–0.38, P = 0.29) or only the leuprorelin study group (0.14, –0.11–0.39, P = 0.26) from the study by Fauser et al. were included in the meta-analysis.

Embryo quality score

No statistically significant difference in embryo quality score was observed in any of the individual studies. Combined point estimate and 95% CI for embryo quality score was 0.05, –0.18–0.29, P = 0.66. Test of heterogeneity was negative (P = 0.82). Results remained stable when only the triptorelin study group (0.06, –0.18–0.32, P = 0.61) or only the leuprorelin group (0.09, –0.15–0.35, P = 0.44) from the study by Fauser et al. were included in the meta-analysis.

OHSS incidence

No cases of OHSS occurred in two of the trials (Humaidan et al., 2005; Kolibianakis et al., 2005), irrespective of the type of drug employed for triggering final oocyte maturation. In the third trial, (Fauser et al., 2002) OHSS incidence was not reported. Thus, no estimate on OHSS incidence can be inferred from the literature.

Discussion

A systematic review of the literature shows that although a number of trials on GnRH agonist triggering of final oocyte maturation in GnRH antagonist ovarian stimulation protocols has been published, assessment of the clinical efficacy of this measure by means of a randomized controlled trial has as yet only been pursued in a few trials (Table I). Furthermore, only three trials have eventually been published in peer-reviewed journals by March 2005 allowing assessment of methodological quality and data retrieval for meta-analysis (Table II).

As regards the likelihood of achievement of an ongoing clinical pregnancy, the results from the present meta-analysis put in serious doubt the feasibility of using GnRH agonist to induce final oocyte maturation in assisted reproduction treatments (ART) in GnRH antagonist protocols. Of note, two of the trials (Humaidan et al., 2005; Kolibianakis et al., 2005) included in this systematic evaluation were prematurely discontinued because of the comparatively lower pregnancy rate observed after GnRH agonist treatment, although the primary objectives of the trials were to study implantation rate (Humaidan et al., 2005) and fertilization rate...
GnRH agonist for final oocyte maturations

Pregnancy rate per randomised patient

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Pregnancy loss

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Figure 1. Forest plots of odds ratios. Outcomes were heterogeneous at P = 0.01 for first trimester pregnancy loss.

(Kolibianakis et al., 2005). The study by Fauser et al. (2002), which reported comparable clinical outcome for GnRH agonist and HCG triggering aimed at comparing endocrine characteristics after GnRH agonist versus HCG and stated to present only preliminary clinical outcomes. Sample size in this latter study was small, and ongoing clinical pregnancy rates were comparatively low (18%, 20% in the GnRH agonist study groups and 13% in the HCG study group; Figure 1).

Both Humaidan et al. and Kolibianakis et al. extensively hypothesize about the potential causes of the observed lower pregnancy rate in the GnRH agonist treatment groups in their publications. In short, it was suggested that GnRH agonist triggering of final oocyte maturation might be associated with a defective luteal phase due to insufficient stimulation of corpora lutea formation and that the employed luteal phase support regimen might possibly not be sufficient to overcome this luteal phase defect. Alternatively, it was suggested that GnRH agonist triggering possibly impairs the developmental capacity of oocytes, although this appears unlikely in view of the comparable outcome for oocyte maturity, fertilization rate and embryo development. Another hypothetical cause is that the massive luteolysis (Kol, 2004) occurring after GnRH agonist administration is associated with some negative signalling (e.g. pro-inflammatory cytokines) that affects the procedure of implantation. This latter hypothesis is supported by the observation that in frozen-thawed embryo transfer cycles where no corpora lutea are present, luteal phase regimen as assessed by the studies analysed herein appear to suffice to support implantation.

For quantitative variables assessed herein (Figure 2), results from the manuscript by Fauser et al. are overweighted in the meta-analysis, because each GnRH agonist study arm was considered as an individual study. However, this appeared to introduce no bias to the analysis, as in sensitivity analysis exclusion of one or the other study arm did not significantly alter the combined estimates.

To test for heterogeneity between the results of individual studies, a statistical test was employed, although such a test has low sensitivity considering the small sample size. Formally, heterogeneity between study results exists for early pregnancy loss and proportion of MII oocytes. Heterogeneous outcomes in meta-analysis should normally be addressed by future studies. From a clinical perspective, this is futile for interim outcomes taking the reduction in pregnancy likelihood that can be expected after GnRH agonist triggering into account. As regards proportion of MII oocytes, the study of Humaidan et al. (2005), suggests a beneficial effect of the simultaneous and coordinated effect of the mid-cycle endogenous gonadotropin surge (LH and FSH) on oocyte maturity. Although this contrasts with the results by Kolibianakis et al. (2005), and Fauser et al. (2002), this finding warrants further investigation apart from the context of GnRH agonist triggering, as exogenous FSH can additionally be given concomitantly to triggering final oocyte maturation with HCG. As regards early pregnancy loss, it has to be noted that luteal phase support regimen varied between studies (Table II).

Only in the trial by Fauser et al. (2002), progesterone was supplemented by intra-muscular injection. As this has been suggested to be more effective than vaginal progesterone (Pritts and Atwood, 2002; Daya and Gunby, 2004), this possibly explains equivalence of study groups in the trial by Fauser et al. (Figure 1). Furthermore, the trial with the highest early pregnancy loss rate (Humaidan et al., 2005) stopped luteal phase support as soon as pregnancy test was positive. Taking this together suggests that the kind, duration and route of administration of the luteal phase-supporting agents possibly have a significant impact on the likelihood of pregnancy loss after GnRH agonist triggering of final oocyte maturation, and that this crucial issue thus warrants further investigation.

A number of authors suggested using GnRH agonist triggering of final oocyte maturation as a measure to prevent OHSS in patients at risk. The studies included in the present review were conducted in non-selected populations. Thus, the findings from this meta-analysis are not necessarily valid to the same extent in a certain subset of ART patients. As regards likelihood of pregnancy achievement, it still appears rational to assume that the mechanisms accounting for the lower chance of clinical pregnancy achievement after GnRH agonist treatment in a general population will also be relevant in patients at risk of OHSS. However, the size of effect might be less pronounced (and thus obscured in uncontrolled,
observations trials), as patients at risk of OHSS are usually patients with a good prognosis (e.g. young age, high ovarian response, high number of oocytes and thus option for embryo selection etc.). Itskovitz et al. (2000), triggered final oocyte maturation with 0.2 mg leuprorelin in eight patients at risk of OHSS in an uncontrolled study and reported 0% pregnancy rate from eight fresh transfers. Kol and Muchtar (2005) used a similar approach in six patients considered at OHSS risk and achieved one clinical pregnancy from six fresh transfers (16.6%). Bankowski et al. (2004) reported a prospective, non-randomized study (abstract publication) in which in 97 cycles final oocyte maturation was triggered with GnRH agonist in case patients were considered at risk of OHSS and compared the outcome to standard treatment with HCG in 317 cycles in normally responding patients. The pregnancy rate was 21.5% for HCG and 11.3% for GnRH agonist cycles. Bracero et al. (2001) reported two clinical pregnancies in eight women (25%) considered at risk of OHSS after GnRH agonist triggering in a retrospective, cohort study (abstract publication). In another observational study (abstract publication) by Meltzer et al. (2002), 35 women with either polycystic ovary

Figure 2. Forest plots of standardized differences of the mean with 95% confidence intervals (CIs) comparing GnRH agonist versus HCG for triggering final oocyte maturation in IVF. Homogeneity of treatment effect was observed except for the proportion of metaphase II oocytes (P < 0.01).
syndrome (PCOS) or previous history of OHSS were triggered with 0.25 mg of triptorelin. Clinical pregnancy rate was reported as 31.4%. Finally, Carone et al. (2005) reported three clinical pregnancies in 10 cycles (33%) after GnRH agonist triggering of final oocyte maturation in 10 PCOS patients (abstract publication).

These latter results do not necessarily contrast the main conclusion from the present analysis, as uncontrolled trials tend to overestimate the size of effect of an intervention. Furthermore, taking the relatively small sample sizes into account, the CIs of the reported pregnancy rates most likely include the pregnancy rate after GnRH agonist triggering estimated herein, which was 7.9% per randomized patient (calculated from pooled data; 11/139 Figure 1).

Given that the present authors were investigators in one of the studies (Kolibianakis et al., 2005) included in the analysis, our objectivity (inclusion/exclusion of trials) and thus the validity of our review may be questioned. Herein, only a small number of publications (fully published papers) could be assessed for appropriateness for inclusion. From the literature search, no hint for publication bias was found (Table I). In conference proceedings, a single abstract from a randomized controlled trial was found (Ossina et al., 2004), reporting similar clinical outcome after 0.1 mg of triptorelin and 10,000 IU hCG in 101 patients treated in a GnRH antagonist protocol. As it was not possible to obtain further information from the authors, full publication of this trial has to be awaited until further conclusions can be drawn.

**Conclusions**

GnRH agonist administration in GnRH antagonist protocols to triggering final oocyte maturation yields a number of oocytes capable of undergoing fertilization and subsequent embryonic cleavage, which is comparable to that achieved with HCG. However, GnRH agonist usage for this purpose as assessed by the available studies is associated with decreased pregnancy likelihood.

**Implications for research**

Smaller sized feasibility studies could aim to find forms of luteal phase support associated with better clinical outcome after GnRH agonist triggering in GnRH antagonist protocols. The feasibility of GnRH agonist triggering of final oocyte maturation in oocyte donation cycles has as yet not been investigated, but possibly represents a safe treatment concept for the oocyte donor, while providing developmental competent oocytes for the recipient.

**Potential conflict of interest**

The authors of the present manuscript have been investigators in one of the trials included in the meta-analysis.

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**References**


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