Comparisons of GnRH antagonist versus GnRH agonist protocol in poor ovarian responders undergoing IVF

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Introduction

IVF and ICSI are widely accepted as effective treatments for most causes of infertility. Generally, for IVF to be successful, adequate follicular recruitment and maturation is essential. The first poor responder was described in 1983, in which Garcia assessed the poor responder having a low peak estradiol level (Garcia et al., 1983). Most clinicians now regard poor ovarian response as those patients with <500 pg/l peak estradiol levels and/or <4 dominant follicles on day of hCG, and therefore, a smaller number of embryos are transferred (Garcia et al., 1983). It is estimated that the incidence of poor response varies from 9 to 24% (Keay et al., 1997). Poor ovarian response is defined as reduced follicle/oocyte production after controlled ovarian hyperstimulation (COH) IVF treatment (Keay et al., 1997; Turhan, 2006). In comparison to normal responders, these patients have impaired fertilization rates and lower embryo quality (Mahutte and Arici, 2002). Moreover, the poor response to ovulation induction results in high cancellation and failure rates, which thus influences significantly the overall IVF success rates as well as cost-effectiveness (Keay et al., 1997). Therefore, the management of poor responders has been one of the most difficult challenges in assisted reproductive technology (ART), with disappointing overall IVF success rates. With Fleming (Fleming et al., 1982) who was first using the GnRH agonists (GnRH-a) in ovulation induction, the success rate in IVF started to increase. But for poor responders, GnRH-a may cause over-suppression without aiding the IVF outcome. The treatment of poor responders has challenged many in the field of assisted

BACKGROUND: In view of the discrepancies about the GnRH antagonist (GnRH-ant) ovarian stimulation protocols having some potential advantages compared with the GnRH agonist (GnRH-a) protocols in poor ovarian responders IVF/ICSI, a meta-analysis of the published data was performed to compare the efficacy of GnRH-ant versus GnRH-a protocols for ovarian stimulation in IVF poor response patients.

METHODS: We searched for all published articles indexed in MEDLINE (1950–2010), EMBASE (1974–2010) and China National Knowledge Infrastructure (CNKI, 1994–2010). Any randomized controlled study that compared the GnRH-ant with GnRH-a in ovarian stimulation protocols for poor responders undergoing IVF/ICSI was included, and data were extracted independently by two reviewers. The searches yielded 64 articles, from which 14 studies met the inclusion criteria. We performed this meta-analysis involving 566 IVF patients in a GnRH-ant protocol group and 561 patients in a GnRH-a protocol group with Review Manager 4.2 software. Odds ratio (OR) and weighted mean difference (WMD) with 95% confidence intervals (CIs) were used to evaluate dichotomous and continuous data, respectively.

RESULTS: Fourteen eligible studies were included in this meta-analysis. GnRH-ant protocols resulted in a statistically significantly lower duration of stimulation compared with GnRH-a protocols (P = 0.04; WMD: −1.88, 95% CI: −3.64, −0.12), but there was no significant difference in the number of oocytes retrieved (P = 0.51; WMD: −0.17, 95% CI: −0.69, 0.34) or the number of mature oocytes retrieved (P = 0.99; WMD: −0.01, 95% CI: −1.14, 1.12). Moreover, no significant difference was found in the cycle cancellation rate (CCR, P = 0.67; OR: 1.01, 95% CI: 0.71–1.42) or clinical pregnancy rate (CPR, P = 0.16; OR: 1.23, 95% CI: 0.92, 1.66).

CONCLUSIONS: Clear advantage was gained in duration of stimulation with GnRH-ant in poor ovarian responders undergoing IVF, although there was no statistical difference in the number of oocytes retrieved, the number of mature oocytes retrieved, the CCR and CPR between GnRH-ant and GnRH-a protocols. These results may be helpful to our clinical practice. However, further controlled randomized prospective studies with larger sample sizes are needed.

Key words: GnRH agonist / GnRH antagonist / ovarian stimulation / poor responder
reproduction. Various treatment regimens and interventions have been investigated in an effort to improve ovarian response and IVF outcome. These include the use of high doses of gonadotrophins (Land et al., 1996), the change to a ‘flare-up’ protocol with OC pretreatment (Karanade et al., 1997) and the use of growth hormone or growth hormone-releasing factor (Howles et al., 1999) or aspirin (Lok et al., 2004) as adjunct therapies. However, most of these interventions have only limited success in poor responders. The availability of effective GnRH antagonists (GnRH-ant) has offered an alternative protocol for poor responders (Craft et al., 1999; Chang et al., 2002). Since approval from the US Food and Drug Administration was acquired in 1999, clinical experience with GnRH-ant in assisted reproduction has continued to accumulate. However, uptake by clinicians was slow because women receiving GnRH-ant have been shown to have a lower probability of clinical pregnancy per treatment cycle compared with women receiving GnRH-a (Al-Inany and Aboughar, 2002). Since GnRH-ant avoids suppression of endogenous gonadotrophin secretion at the stage of follicular recruitment, it appears rational to use antagonists in patients with expected or proven decreased ovarian response to exogenous gonadotrophins (Craft et al., 1999; Tarlatzis et al., 2003). GnRH-ant have several theoretical advantages over the GnRH-a. They act by the mechanism of competitive binding to the GnRH receptors in pituitary which allows a modulation of the degree of hormonal suppression by adjustment of the dose (Reissmann et al., 1995). Furthermore, GnRH-ant suppress gonadotrophin release within a few hours have no flare-up effect and gonadal function resumes without a lag effect following their discontinuation (Homburg, 2004).

Recently, several studies about the comparing the effectiveness of GnRH-ant and GnRH-a in poor responder IVF patients were performed, and the results have been publicized, which were still conflicting (Akman et al., 2001). In the light of this development, we collected all the articles to date published on comparing the GnRH-ant protocol with a conventional GnRH-a protocol in poor responders undergoing IVF. A meta-analysis of all relevant published randomized and cohort studies was carried out to estimate effect size to determine the extent of heterogeneity in the strength of associations between studies.

Materials and Methods

Search strategy, inclusion and exclusion criteria

The MEDLINE (1950–2010), EMBASE (1974–2010) and China National Knowledge Infrastructure (CNKI, 1994–2010) were searched in a systematic and diligent manner for all randomized controlled studies on comparing GnRH-ant with GnRH-a in ovarian stimulation protocols for poor responders undergoing IVF. The search used the following keywords ‘poor responder’, ‘ovarian stimulation’, ‘GnRH-ant’, ‘GnRH-a’ and ‘randomized controlled trial’. The references of all computer-identified publications were searched for additional studies, and the MEDLINE option related articles was used to search for potentially relevant articles. Review articles and references of other relevant studies identified were hand-searched to find additional eligible studies. Articles published in all languages were selected if they met all of the following criteria: (i) study was a randomized, controlled trial to compare GnRH-a or GnRH-ant usage for pituitary down-regulation during ovarian stimulation in poor responder patients, (ii) study reported on clinical outcomes, (iii) if a review article, new data were presented.

Data extraction and outcome measures

The data were extracted from eligible studies: author’s name, region/country where the study was conducted, year of publication, numbers of cases/patients and controls, diagnostic criteria, mean age and standard deviation or age range in GnRH-ant and GnRH-a in ovarian stimulation protocols for poor responders undergoing IVF. In addition, the IVF outcome data for each patient were requested from all studies: method of ovarian stimulation, the duration of stimulation, the number of oocytes retrieved and mature oocytes retrieved, the cycle cancellation rate (CCR) due to poor response and clinical pregnancy rate (CPR). Clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat by ultrasound after embryo transfer. All data were independently abstracted in duplicate by two researchers. If the researchers disagreed, a final result was reached by discussion. For data not provided in table form or the main text, the required information was obtained by contacting corresponding authors as possible as we can.

Statistical analysis

Summary statistics were estimated in the Review Manager 4.2 software (RevMan 4.2, The Nordic Cochrane Center, Rigshospitalet). Continuous variables were expressed as weighted mean difference (WMD) with 95% confidence intervals (CIs). Dichotomous data for each unit of analysis were expressed as an odds ratio (OR) with 95% CIs. The authors considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. The heterogeneity between studies was tested using the Q statistic (Zamora et al., 2006). Statistical heterogeneity was assessed by the measure of the I². An I² measurement greater than 50% was taken to indicate a substantial heterogeneity (The Cochrane Collaboration, 2011). If substantial heterogeneity was detected, a random effect model was used instead of a fixed effect model.

Results

With the search strategy applied, 64 published articles were identified that could possibly compare the GnRH-ant with GnRH-a in ovarian stimulation protocols for poor responders undergoing IVF/ICS. After reading the full papers, only 14 studies (ten English papers, three Chinese papers and one Spanish paper) finally met our inclusion criteria (Fig. 1), involving 1127 poor responder patients treated with GnRH-a or GnRH-ant for ovarian stimulation in randomized controlled studies. Detailed characteristics of each study are described in Table I. The definition of ‘poor response’ was heterogenous, in which 12 studies defined poor response as ‘inappropriate ovarian response’ to ovarian stimulation in a previous cycle (Akman et al., 2001; Martínez et al., 2003; Cheung et al., 2005; Malmsi et al., 2005; Marci et al., 2005; Schmidt et al., 2005; Demirol and Gurgan, 2007; Tazegul et al., 2008; Wang et al., 2008; Kahraman et al., 2009; Liu et al., 2009; Devesa et al., 2010) and/or six studies defined it as fewer than four mature oocytes retrieved (Akman et al., 2001; Martínez et al., 2003; Cheung et al., 2005; Malmsi et al., 2005; Marci et al., 2005; Schmidt et al., 2005; Demirol and Gurgan, 2007; Tazegul et al., 2008; Kahraman et al., 2009). All studies (Akman et al., 2001; Martínez et al., 2003; Cheung et al., 2005; Malmsi et al., 2005; Marci et al., 2005; Schmidt et al., 2005; De Placido et al., 2006; Demirol and Gurgan, 2007; Tazegul et al., 2008; Wang
et al., 2008; Tian et al., 2008; Kahraman et al., 2009; Liu et al., 2009; Devesa et al., 2010) used a fixed protocol with multiple dose regimens of GnRH-ant (cetrorelix and triptorelin), while GnRH-a protocol was used long/short agonist protocol with multiple dose regimens of GnRH-a (leuprorelin, triptorelin, buserelin and ganirelix).

The duration of stimulation was significantly lower in GnRH-ant than that in GnRH-a cycles ($P = 0.04$; WMD: $-1.88$, 95% CI: $-3.64$, $-0.12$; Fig. 2). As shown in Fig. 3, when the meta-analysis was performed with the 10 studies, there was no significant difference in the number of oocytes retrieved between GnRH-ant and GnRH-a protocols ($P = 0.51$; WMD: $-0.17$, 95% CI: $-0.69$, 0.34). Similarly, there was no significant difference in the number of mature oocytes retrieved between the GnRH-ant and the GnRH-a groups from five studies ($P = 0.99$; WMD: $-0.01$, 95% CI: $-1.14$, 1.12; Fig. 4).

Figure 5 shows that the CCR was similar for antagonist and agonist protocols from the meta-analysis evaluated with all studies ($P = 0.67$; OR: 1.01, 95% CI: 0.71–1.42). Finally, there was no statistically significant difference between GnRH-ant and GnRH-a with respect to CPR, although it appears lower in the antagonist than in the agonist group ($P = 0.16$; OR: 1.23, 95% CI: 0.92–1.66; Fig. 6).

**Discussion**

Although the results of GnRH-ant ovarian stimulation protocols offer a number of potential advantages (Tarlatzis et al., 2006) compared with the accepted conventional GnRH-a protocol, the efficacy of GnRH-ant and GnRH-a in poor responder IVF patients is still controversial. So we searched the published articles and found some studies on comparisons of GnRH-ant versus GnRH-a protocol in poor ovarian responders undergoing IVF for analysis. Although there were already several similar papers (including reviews and meta-analysis articles) published, this topic was so interesting to the readership that we re-searched the electronic databases and the journals and/or magazines in libraries carefully and made an update. Compared with the recent Cochrane review (Pandian et al., 2010), our meta-analysis newly included four latest papers (Tazegül et al., 2008; Demirol et al., 2009; Kahraman et al., 2009; Devesa et al., 2010) in MEDLINE and three Chinese studies (Tian et al., 2008; Wang et al., 2008; Liu et al., 2009) which reached our criteria.

As all known, the use of GnRH-ant into clinical practice and their addition to ovarian stimulation during the late follicular phase would prevent the premature LH surges while not causing any suppression in the early follicular phase, which is a critical period for those patients with decreased ovarian reserves. Cheung et al. suggested that GnRH-ant would be a reasonable option for patients with poor ovarian response in previous stimulation cycles (Cheung et al., 2005). GnRH-ant bind competitively to GnRH receptors, resulting in an immediate suppression of gonadotrophin release. In comparison with a traditional long GnRH-a protocol, treatment with a GnRH-ant resulted in faster initial follicular growth but a slightly lower number of follicles on the day of HCG (Borm and Mannaerts, 2000; De Jong et al., 2001; Mannaerts et al., 2001; Fluker et al., 2001; Hohmann et al., 2003). Unlike GnRH-ant, GnRH-a exert their effect by producing a pituitary down-regulation phenomenon (Reissmann et al., 1995).

Our current finding suggested that there was no significant difference on the number of oocytes retrieved and mature oocytes retrieved in both the GnRH-ant and GnRH-a protocols, which was similar to the results of previous studies (Cheung et al., 2005; Kahraman et al., 2009). However, Malmusi et al. (2005) reported that the number of oocytes retrieved ($3.5 \pm 1.4$ versus $2.5 \pm 1.2$) and mature oocytes retrieved ($3.2 \pm 1.5$ versus $1.7 \pm 1.2$) in
### Table I Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Region (province, country)</th>
<th>Inclusion criteria</th>
<th>Number of patients</th>
<th>Protocol</th>
<th>Gn type &amp; initial dosage (IU/d)</th>
<th>Total dosage of Gn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akman et al (2001)</td>
<td>Istanbul, Turkey</td>
<td>At least two failed IVF cycles due to: basal FSH &gt; 15 IU/l or E2 (dHCG) &lt; 500 pg/ml, or COC ≤ 4</td>
<td>24/24</td>
<td>Multiple dose (cetrorelix)</td>
<td>OC/short, multiple dose (leuprolelin)</td>
<td>pFSH 300 &amp; HMG 300</td>
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<tr>
<td>Martinez et al (2003)</td>
<td>Barcelona, Spain</td>
<td>Previous ‘poor response’</td>
<td>21/23</td>
<td>Multiple dose (cetrorelix)</td>
<td>Short, multiple dose (tripotrelin)</td>
<td>rFSH 150 &amp; HMG 150</td>
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<tr>
<td>Cheung et al (2005)</td>
<td>Hong Kong, China</td>
<td>Repeated basal FSH &gt; 10 IU/l or previous IVF cycle with mature follicles &lt; 3</td>
<td>31/32</td>
<td>OC/multiple dose (cetrorelix)</td>
<td>OC/long, multiple dose (buserelin)</td>
<td>rFSH 300</td>
</tr>
<tr>
<td>Malmusi et al (2005)</td>
<td>Modena, Italy</td>
<td>Basal FSH &lt; 15 IU/l, previous IVF cycle: &lt; 3 COC, or no ovarian response when FSH ≥ 300 IU for ≥ 15 days</td>
<td>25/30</td>
<td>Multiple dose (ganirelix)</td>
<td>Short, multiple dose (tripotrelin)</td>
<td>rFSH 450</td>
</tr>
<tr>
<td>Marci et al (2005)</td>
<td>Rome, Italy</td>
<td>Previous cycle: E2 (dHCG) &lt; 600 pg/ml and COC &lt; 3</td>
<td>30/30</td>
<td>Multiple dose (cetrorelix)</td>
<td>Long, multiple dose (leuprolelin)</td>
<td>rFSH 375</td>
</tr>
<tr>
<td>Schmidt et al (2005)</td>
<td>Connecticut, USA</td>
<td>Previous cycle: E2(dHCG) &lt; 850 pg/ml and/or ≤ 4 COC and basal FSH &lt; 13 IU/l</td>
<td>24/24</td>
<td>Multiple dose (ganirelix)</td>
<td>OC/short, multiple dose (leuprolelin)</td>
<td>rFSH 300 &amp; HMG 150</td>
</tr>
<tr>
<td>De Placido et al (2005)</td>
<td>Naples, Italy</td>
<td>≥ 37 years or basal FSH ≥ 9 IU/l, regular cycle</td>
<td>67/66</td>
<td>Multiple dose (cetrorelix)</td>
<td>Flare up, multiple dose (tripotrelin)</td>
<td>rFSH 300</td>
</tr>
<tr>
<td>Tazegul et al (2008)</td>
<td>Konya, Turkey</td>
<td>Basal FSH &lt; 13 IU/l, previous IVF cycle: E2 (dHCG) &lt; 500 pg/ml and poor response (COC ≤ 4)</td>
<td>44/45</td>
<td>Multiple dose (cetrorelix/ganirelix)</td>
<td>Long, multiple dose (leuprolelin)</td>
<td>rFSH 300 &amp; HMG 300</td>
</tr>
<tr>
<td>Tian et al (2008)</td>
<td>Beijing, China</td>
<td>Previous IVF cycle: COC ≤ 5</td>
<td>21/23</td>
<td>Multiple dose (cetrorelix)</td>
<td>Short, multiple dose (tripotrelin)</td>
<td>rFSH</td>
</tr>
<tr>
<td>Wang et al (2008)</td>
<td>Jiangsu, China</td>
<td>≥ 38 years, or basal FSH &gt; 10 IU/l, or antral follicle (d3) ≤ 5, or previous IVF cycle COC ≤ 5</td>
<td>63/58</td>
<td>OC/multiple dose (cetrorelix)</td>
<td>OC/long, micro-dose (leuprolelin)</td>
<td>rFSH 300</td>
</tr>
<tr>
<td>Demiroglu et al (2009)</td>
<td>Ankara, Turkey</td>
<td>Basal FSH &gt; 15 IU/l, previous IVF cycle: &lt; 4 COC, and at least two previous IVF cycles with poor ovarian response (E2 &lt; 500 pg/ml or COC &lt;4)</td>
<td>45/45</td>
<td>Multiple dose (cetrorelix)</td>
<td>OC/flare-up, microdose (leuprolelin)</td>
<td>HMG 450</td>
</tr>
<tr>
<td>Kahraman et al (2009)</td>
<td>Ankara, Turkey</td>
<td>Previous IVF cycle: COC &lt; 4, E2 (dHCG) &lt; 500 pg/ml, or cancelled for poor ovarian response</td>
<td>21/21</td>
<td>Multiple dose (cetrorelix)</td>
<td>Flare-up, microdose (leuprolelin)</td>
<td>rFSH 300 – 450</td>
</tr>
<tr>
<td>Liu et al (2009)</td>
<td>Guangxi, China</td>
<td>Previous IVF cycle failure</td>
<td>58/60</td>
<td>Multiple dose (cetrorelix)</td>
<td>Short, multiple dose (tripotrelin)</td>
<td>HMG</td>
</tr>
<tr>
<td>Devesa et al (2010)</td>
<td>Barcelona, Spain</td>
<td>≤ 45 years, previous IVF cycle: follicle &lt; 4, poor response to COH, pathologic CCCT and/or AFC ≤ 7</td>
<td>92/80</td>
<td>OC/multiple dose (ganirelix)</td>
<td>OC/flare-up, (leuprolide)</td>
<td>rFSH 375 / rFSH 300 &amp; HMG 75</td>
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</table>

IFV, in vitro fertilization; GnRH-ant, GnRH antagonist; GnRH-a, GnRH agonist; COC, cumulus oocyte complexes; OC, oral contraception; FSH, follicle stimulating hormone; HCG, human chorionic gonadotrophin; CCCT, clomiphene citrate challenge test; AFC, antral follicle count; Gn, gonadotrophin; pFSH, pure FSH; rFSH, recombinant FSH; HMG, human menopausal gonadotrophin.
Figure 2  Meta-analysis of GnRH-ant versus GnRH-a treatments in poor responders for the duration of stimulation. WMD = weighted mean difference.

Figure 3  Meta-analysis of GnRH-ant versus GnRH-a treatments in poor responders for the number of oocytes retrieved. WMD = weighted mean difference.

Figure 4  Meta-analysis of GnRH-ant versus GnRH-a treatments in poor responders for the number of mature oocytes retrieved. WMD = weighted mean difference.
GnRH-a group was significantly greater ($P < 0.05$) than that in the GnRH-ant group ($3.5 \pm 1.4$ versus $2.5 \pm 1.2$). Additionally, the use of GnRH-ant was associated with the shorter duration of stimulation from our data, and the difference was statistically significant ($P = 0.04$). Wang et al.’s analysis showed that the GnRH-ant protocol could result in the shorter duration of stimulation than that in GnRH-a ($9.65 \pm 1.60$ versus $19.85 \pm 3.94$, $P < 0.05$; Wang et al., 2008). Therefore, advantages of the GnRH-ant regimen versus the long agonist protocol include the absence of an initial ‘flare-up’, a considerably reducing treatment duration is accepted (Borm and Mannaerts, 2000; De Jong et al., 2001; Mannaerts et al., 2001; Fluker et al., 2001; Hohmann et al., 2003).
Concerning the CCR, our finding showed that there was no difference in both GnRH-ant regimen and GnRH-a protocol, which was very similar to the results of the previous meta-analysis (Franco et al., 2006). Also, the current analysis did not show better clinically pregnancy rates following GnRH-ant; in other words, GnRH-ant could cause a non-significant trend for a reduction in clinical pregnancy for IVF patients with poor response. Many randomized controlled trial (RCT) studies showed the similar results (Akman et al., 2001; Martínez et al., 2003; Cheung et al., 2005; Malmusi et al., 2005; Marci et al., 2005; Schmidt et al., 2005; De Placido et al., 2006; Demirol and Gurgan, 2007; Tazegül et al., 2008; Tian et al., 2008; Wang et al., 2008; Kahraman et al., 2009; Liu et al., 2009; Devesa et al., 2010).

As a relative shortcoming of the present meta-analysis is the lack of a uniform definition of ‘poor ovarian responders’, it made difficult to compare IVF treatment outcomes and assess protocols for management (Kailasam et al., 2004). Therefore, an international standardization of criteria to define ‘poor ovarian responders’ should be very important and urgent. The best stimulation protocol for poor responders should have an acceptable rate of cycle cancellation and duration of stimulation and yield the maximum number of possible of mature good-quality oocytes with satisfactory pregnancy rates (Craft et al., 1999; Nikolettos et al., 2001; Al-Inany and Aboughar, 2002).

In conclusion, our meta-analysis demonstrated that the duration of stimulation was significantly lower in GnRH-ant protocols than GnRH-a protocols in poor responder IVF patients, although no improvements were found in the number of oocytes and mature oocytes retrieved, the CCR and CPR with the use of GnRH-ant. These results may be helpful to our clinical practice. All of these results were consistent with the Cochrane Review by Pandian et al. (2010). In addition, the findings of a slightly lower CPR (although not significant) in GnRH-ant suggest that much work remains to be done in optimizing the GnRH-ant/GnRH-a protocols and individualizing these to different cycle characteristics. Future more studies which should include a larger sample size are needed.

Authors’ roles
D.P. was the first author who acquired and analyzed the data and drafting the article. J.L. revised the paper for some important content. J.W., as the correspondence author of this manuscript, designed the study and finally approved the version.

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GnRH antagonist versus agonist in poor responders


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