GnRH antagonists in ovarian stimulation for IVF

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The present review describes, on the basis of the currently available evidence, the consensus reached by a group of experts on the use of gonadotropin-releasing hormone (GnRH) antagonists in ovarian stimulation for IVF. The single or multiple low-dose administration of GnRH antagonist during the late-follicular phase effectively prevents a premature rise in serum luteinizing hormone (LH) levels in most women. Although controversy remains, most comparative studies suggest a slight, not significant reduction in the probability of pregnancy after IVF using GnRH antagonist versus GnRH agonist co-treatment. Published meta-analyses suggest that this slight difference in pregnancy rates is not attributed to chance. Further studies applying varying treatment regimens and outcome measures are required. Data are not in favour of a need to modify the starting dose of gonadotropins. Data are not in favour of increasing gonadotropin dose at GnRH antagonist initiation. The addition of LH from the initiation of ovarian stimulation or from GnRH antagonist administration does not appear to be necessary. Replacement of human chorionic gonadotropin (HCG) by GnRH agonist for trig- antagonist initiation. The addition of LH from the initiation of ovarian stimulation or from GnRH antagonist administration does not appear to be necessary. Replacement of human chorionic gonadotropin (HCG) by GnRH agonist for triggering final oocyte maturation is associated with a lower probability of pregnancy. The optimal timing for HCG administration needs to be explored further. GnRH antagonist initiation on day 6 of stimulation appears to be superior to flexible initiation by a follicle of 14–16 mm, although earlier GnRH antagonist administration is worth further evaluation. Luteal phase supplementation in GnRH antagonist protocols remains mandatory in IVF. Effects of GnRH antagonist co-treatment on the incidence of ovarian hyperstimulation syndrome remains uncertain, although a trend is present in favour of the GnRH antagonists. The role of GnRH antagonists in ovarian stimulation for IVF appears to be promising, although many questions regarding preferred dose regimens and effects on clinical outcomes remain.

Key words: GnRH antagonists/IVF/ovarian stimulation/pregnancy rates
Introduction

Gonadotropin-releasing hormone (GnRH) antagonists were introduced in recent years in ovarian stimulation for assisted reproductive technologies (ART) to inhibit a premature rise in luteinizing hormone (LH), a role served by GnRH agonists since 1984 (Porter et al., 1984). The uptake of GnRH antagonists in ART, however, has so far been lower than expected. This has stimulated an ongoing debate and resulted in numerous editorials in the literature (Felberbaum and Diedrich, 2003; Engel et al., 2005; Fauser and Devroye, 2005; Kolibianakis et al., 2005a).

In an attempt to optimize the existing stimulation protocols, several studies have explored various aspects of the use of GnRH antagonist in IVF. Such studies involved the optimal day GnRH antagonist administration should be initiated (Ludwig et al., 2002; Escudero et al., 2004; Mochtar et al., 2004), the effect of the starting dose of exogenous follicle-stimulating hormone (FSH) on pregnancy rates (Wikland et al., 2001; Out et al., 2004), the need to supplement the follicular phase with LH (Cedrin-Durnerin et al., 2004; Griesinger et al., 2005a) as well as the need to increase the gonadotropin dose at GnRH antagonist initiation (Abouighar et al., 2004). In addition, interest has been focused on the effect of the timing of human chorionic gonadotropin (HCG) administration on the probability of pregnancy (Kolibianakis et al., 2004a), the replacement of HCG with GnRH agonist for triggering final oocyte maturation (Fauser et al., 2002; Humaidan et al., 2005; Kolibianakis et al., 2005b) as well as the possibility of direct effects of GnRH antagonists on extra-pituitary tissues (Weiss et al., 2001; Tarlatzis and Kolibianakis, 2002). Finally, alternative stimulation schemes such as the late initiation of FSH in the follicular phase (de Jong et al., 2000; Hohmann et al., 2003), the application of IVF in a modified natural cycle (Rongieres-Bertrand et al., 1999, Kolibianakis et al., 2004b) and the use of GnRH antagonists in ovarian stimulation for intrauterine insemination (IUI) (Ragni et al., 2001, 2004) have been explored.

The purpose of the present review was to describe, on the basis of the currently available evidence, the consensus reached by a group of experts on the use of GnRH antagonists in ovarian stimulation for IVF. Before the consensus meeting a systematic literature search was performed by each of the invited speakers on the specific subject of the presentation given.

Molecular and cellular actions of GnRH antagonists

The inhibition of a premature LH rise by GnRH agonists requires at least 7 days, as it is accomplished by an initial stimulation of GnRH receptors before gonadotroph desensitization is achieved. In contrast, GnRH antagonists compete directly with endogenous GnRH for receptor binding and therefore rapidly inhibit secretion of gonadotropin and steroid hormones (Klingmuller et al., 1993). This property conveys a potential advantage over GnRH agonists in the management of ovarian stimulation. However, because of the constant need to block out endogenous GnRH, much higher doses of antagonists are required (mg per day compared with <0.1 mg per day for GnRH agonists).

The GnRH antagonists incorporate a number of amino acid substitutions in the NH₂ terminal domain (involved in receptor activation) combined with a D-amino acid substitution for Gly⁶ which enhances the βII type bend necessary for receptor binding (Millar et al., 2004). These features of GnRH antagonists used in the clinic are shown in Figure 1. The presence (Cheng and Leung, 2005) and cellular effects of GnRH I, GnRH II and GnRH receptor in human ovarian, uterine and placental cells suggests that GnRH analogues may also exert direct actions in these tissues through disruption of autocrine or paracrine signalling of GnRH (Weiss et al., 2001; Tarlatzis and Kolibianakis, 2002).

Recently, certain GnRH antagonists have been shown to act as agonists for some intracellular signalling pathways (Maudsley et al., 2004). Thus they are pure antagonists at the pituitary GnRH receptor (i.e. inhibit GnRH stimulation of Giα and downstream Ca²⁺, and protein kinase C signalling) but are full agonists in stimulating Gαq and the inhibition of proliferation and apoptosis in peripheral reproductive cells (Gqα and Giα are the alpha subunits of the heterotrimeric G-proteins which mediate the GnRH receptor activation of intracellular signalling). Other GnRH antagonists have little or no Gαq activity. GnRH antagonists may therefore have additional effects (negative or positive) when used in IVF. Further laboratory studies and thorough comparative clinical trials with GnRH agonists are required to address this possibility.

A number of non-peptide orally-active GnRH antagonists are currently undergoing clinical trials (Papanikolaou et al., 2005). These compounds are pure antagonists of Gqα and do not activate Gαq (Lu and Millar, personal communication). This singular activity coupled with flexible dosing and ease of administration suggests considerable potential for utilization in IVF. It is interesting that one of these compounds (TAK-013, Takeda) has potent oral activity in inhibiting LH but has no effect on FSH when administered for 80 days (Hara et al., 2003).

GnRH antagonists in ovarian stimulation for IVF

The aim of using GnRH antagonists in IVF is the inhibition of a premature LH rise which could lead to premature luteinization, follicle maturation arrest and asynchrony of oocyte maturation. The use of GnRH antagonists in IVF is characterized both by advantages and disadvantages.
Advantages and disadvantages for the use of GnRH antagonists in IVF

Advantages

(i) Prevention of premature LH increase is easier and takes less time. GnRH antagonists act within a few hours after their administration (Klingmuller et al., 1993) and thus they can be administered only when there is a risk for an LH surge. This is in contrast to GnRH agonists where pituitary down-regulation occurs only after 7–10 days.

(ii) GnRH antagonists are not associated with an acute stimulation of gonadotropins and steroid hormones, which occurs with GnRH agonist administration.

(iii) The initial stimulation by GnRH agonists can induce cyst formation, which is avoided with GnRH antagonists.

(iv) No hot flushes are observed with GnRH antagonists as their use does not result in profound hypo-estrogenaemia observed with GnRH agonists (Varney et al., 1993).

(v) Inadvertent administration of the GnRH analogue in early pregnancy can be avoided as GnRH antagonist is administered in the mid-follicular phase.

(vi) Requirements for exogenous gonadotropins are reduced, rendering ovarian stimulation less costly.

(vii) Duration of ovarian stimulation protocols is shortened, improving patient discomfort.

Disadvantages

(i) GnRH antagonist co-treatment represents a novel approach in ovarian stimulation for IVF and knowledge accumulation is necessary for its optimization.

(ii) GnRH antagonists offer less flexibility regarding cycle programming as compared with the long, but not with the short, GnRH agonist protocol.

(iii) Most comparative studies report a minor reduction in pregnancy rates per cycle with GnRH antagonists as compared with GnRH agonists.

It should be noted that for units that manage starting dates of cycles to gain an orderly daily volume of oocyte retrievals the use of GnRH agonists has been an advantage. With GnRH antagonist protocols, sufficient flexibility regarding the starting dates and the ability to achieve a daily volume control is still present, although this can be improved by using the oral contraceptive pill (OCP) (Hwang et al., 2004).

Important aspects of GnRH antagonist use in ovarian stimulation for IVF

Single versus multiple dose GnRH antagonist protocol

Two GnRH antagonist protocols were developed involving either multiple (Diedrich et al., 1994) or single administration (Olivennes et al., 1994). In the multiple dose protocol, the GnRH antagonist was administered continuously until the day of HCG administration, starting 5 days after stimulation with gonadotropins. The minimal dose shown to prevent the occurrence of a premature LH rise in the great majority of patients was shown to be 0.25 mg (Albano et al., 1997; The Ganirelix dose finding study group, 1998).

In the single dose protocol, a 3 mg dose of GnRH antagonist given on cycle day 7 during ovarian stimulation was shown to prevent a premature LH surge (Olivennes et al., 1998). In case of the need to delay HCG, low daily doses of GnRH antagonists could be added 4 days after the single antagonist dose.

Pros for the single dose GnRH antagonist protocol: Potential for fewer injections, although in 10% of cycles additional daily doses of GnRH antagonist are necessary (Olivennes et al., 2000).

Cons for the single dose: Besides inhibiting premature LH surge, the single dose protocol results in an excessive and potentially harmful suppression of endogenous LH. However, no significant difference in pregnancy rates was shown in a randomized-controlled trial (RCT) which compared the two antagonist protocols (Wilcox et al., 2005).

Fixed versus flexible antagonist administration

In all phase three comparative trials in which the daily GnRH antagonist protocol was used, initiation of GnRH antagonist was performed on day 6 of stimulation. However, this choice was not evidence-based and, in principle, GnRH antagonist administration should commence when there is follicular development and/or production of estradiol (E2) by the developing follicles which might give rise to a premature elevation in pituitary LH release due to positive feedback mechanisms. Thus the idea of a flexible GnRH antagonist initiation is worth evaluating and might lead to even further simplification of this protocol.

Four RCTs have so far been performed comparing a fixed (on day 6) versus a flexible (by a follicle diameter of 14–15 mm) protocol of GnRH antagonist administration (Al-Inany et al., 2005). Although currently the difference is not significant, all published studies show a lower pregnancy rate in the flexible as compared to the fixed protocol (odds ratio 0.70, 95% CI: 0.47–1.05; Figure 2).

However, the criteria on which the initiation of GnRH antagonist is based on as well as the first day on which patients should start evaluation, in order to examine if these criteria are satisfied, have not been assessed so far. Earlier initiation of GnRH antagonist needs to be further explored (Kolibianakis et al., 2003a, 2004c). Moreover, dose and timing of gonadotropin administration may have an impact on the optimal day of starting GnRH antagonist to inhibit the premature LH rise (Hohmann et al., 2003).

<table>
<thead>
<tr>
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<th>Year</th>
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<th>Flexible</th>
<th>0.1</th>
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<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
<th>Lower</th>
<th>Upper</th>
<th>P Value</th>
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<td>7 / 40</td>
<td>4 / 20</td>
<td></td>
<td></td>
<td></td>
<td>.85</td>
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<td>3.33</td>
<td>.81</td>
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<td></td>
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<tr>
<td>Kolibianakis</td>
<td>2003</td>
<td>14 / 58</td>
<td>14 / 45</td>
<td></td>
<td></td>
<td></td>
<td>.70</td>
<td>.29</td>
<td>1.69</td>
<td>.43</td>
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<td>2004</td>
<td>23 / 101</td>
<td>34 / 103</td>
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<td>.56</td>
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<td>1.11</td>
<td>.10</td>
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<tr>
<td>Escudero</td>
<td>2004</td>
<td>20 / 50</td>
<td>29 / 59</td>
<td></td>
<td></td>
<td></td>
<td>.85</td>
<td>.39</td>
<td>1.62</td>
<td>.87</td>
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<td>78 / 227</td>
<td></td>
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<td>.70</td>
<td>.47</td>
<td>1.05</td>
<td>.08</td>
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Figure 2. Clinical pregnancy rate in fixed and flexible GnRH antagonist protocols (modified from Al-Inany et al., 2005).
B.C. Tarlatzis et al.

**GnRH agonist versus HCG for triggering final oocyte maturation**

GnRH agonist has been advocated as a mean for programming IVF cycles using GnRH antagonists (Fischl et al., 2001; Cedrin-Durnerin et al., 2004). In addition, it has been speculated that the use of OCP pretreatment may result in improved synchronization of the recruitable cohort of ovarian follicles. Its use in ovarian stimulation for IVF is associated with advantages and disadvantages.

**Pros:**
- Easier scheduling of the cycle which is not based in this case on the occurrence of menstruation but on the discontinuation of the OCP.

**Cons:**
1. Pretreatment with OCP has been associated with a longer duration of treatment (van Loenen et al., 2001).
2. An increased gonadotropin requirement has been observed with the use of OCP (Bendikson et al., 2003).
3. Administration of OCP might be emotionally disturbing, since OCP is mainly used to prevent conception.

No significant effect of OCP pretreatment on the probability of pregnancy in GnRH antagonist cycles was shown in a large RCT (Kolibianakis et al., 2006), suggesting that programming of IVF cycles with the use of OCP is feasible. The effect of the time interval from OCP discontinuation to initiation of stimulation on IVF outcome (van Heusden and Fauser, 2002) still needs to be assessed.

**Use of exogenous FSH in GnRH antagonist co-treatment cycles**

On a physiological basis, the required starting dose of FSH in GnRH antagonist cycles is lower compared to GnRH agonist, due to the presence of higher endogenous FSH levels during the intercycle phase (Fauser and van Heusden, 1997). However, a lower number of cumulus-oocyte complexes (COCs) was retrieved with the use of GnRH antagonists in phase III comparative trials with GnRH agonists (Al-Inany and Aboulghar, 2002). The concept of a higher starting FSH dose that might compensate for this difference has been tested so far in two RCTs. It was shown that a higher starting dose of FSH results in an increased number of COCs retrieved but it does not appear to be associated with higher pregnancy rates (Wikland et al., 2001; Out et al., 2004; Table I). In addition, the increase of gonadotropin doses at GnRH antagonist initiation did not appear to result in higher probability of pregnancy (Aboulghar et al., 2004).

It has been shown that it is possible to start FSH stimulation later in the follicular phase by extending the FSH window for multifollicular development (Hohmann et al., 2001, 2003). This would lead to the development of milder stimulation protocols. In the same direction is the use of the modified natural cycle for IVF in which the development of a single follicle is supported by exogenous FSH in combination with GnRH antagonist to control the endogenous LH production (Rongieres-Bertrand et al., 1999). The application of the modified natural cycle in poor prognosis groups is debatable (Kolibianakis et al., 2004b; Elizur et al., 2005).

In theory, the type of gonadotropin preparation used (recombinant versus urinary, containing LH or not) for ovarian stimulation is not expected to result in a different probability of pregnancy.

**LH supplementation**

An abrupt suppression of endogenous LH by GnRH antagonist occurs in the mid-follicular phase, at a critical stage for follicular development. In view of the decreased probability of pregnancy associated with low LH levels, which was observed using high GnRH antagonist doses (The Ganirelix dose finding group, 1998) and the increased pregnancy loss observed with low LH levels in GnRH agonist cycles (Westergaard et al., 2000), it was assumed that LH supplementation might improve pregnancy outcome in GnRH antagonist cycles. However, data from RCTs suggest that the addition of 75 IU of recombinant LH to recombinant

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Antagonist</th>
<th>Rec FSH starting doses</th>
<th>Ongoing pregnancy rate</th>
<th>Vital pregnancy rate</th>
<th>Difference</th>
<th>95% CI of the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 IU</td>
<td>225 IU</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 IU</td>
<td>200 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wikland et al. (2001)</td>
<td>120</td>
<td>Daily dose, starting on day 6 of stimulation</td>
<td>25% (15/60)</td>
<td>25% (15/60)</td>
<td>0.0%</td>
<td>−15.3% to +15.3%</td>
<td></td>
</tr>
<tr>
<td>Out et al. (2004)</td>
<td>264</td>
<td>Daily dose, starting on day 6 of stimulation</td>
<td>31.1% (41/132)</td>
<td>24.2% (32/132)</td>
<td>+6.8%</td>
<td>−3.9% to +17.43%</td>
<td></td>
</tr>
</tbody>
</table>
FSH at GnRH antagonist initiation (Cedrin-Durnerin et al., 2004) or from initiation of stimulation (Griesinger et al., 2005a) does not appear to enhance pregnancy rates (Table II). Similarly, no improvement in pregnancy rates could be shown by increasing the dose of HMG by 75 IU at GnRH antagonist initiation (Aboulghar et al., 2004).

Moreover, no indication that low endogenous LH levels after GnRH antagonist initiation are associated with a decreased probability of pregnancy in IVF cycles was provided by both retrospective (Merviel et al., 2004) and prospective studies (Kolibianakis et al., 2004d). On the contrary, it was suggested that the lower the LH levels on day 8 of stimulation for IVF, the higher the probability of pregnancy (Kolibianakis et al., 2004d).

On the basis of the currently available data it appears that LH supplementation in ovarian stimulation for IVF using GnRH antagonist cycles is not necessary.

Criteria for HCG administration
There is a marked variation in the criteria used for triggering final oocyte maturation in IVF both in GnRH agonists and antagonist cycles (Kolibianakis et al., 2004a). Recent data indicate that the timing of HCG administration might be important for the probability of pregnancy. Prolongation of the follicular phase was shown to be associated with decreased pregnancy rates (Kolibianakis et al., 2004a). Further studies are necessary to explore the optimal timing of HCG administration. It should be noted that criteria for HCG administration should be strict, especially in clinical trials, in order to ensure that the follicular phase ends in the same way in all patients treated.

Luteal phase supplementation
An initial attempt to not support the luteal phase in GnRH antagonist cycles indicated that luteal supplementation was necessary (Albano et al., 1998; de Jong et al., 2000). Further support to this concept was offered by data showing that endometrial development during a non-supplemented luteal phase is abnormal (Kolibianakis et al., 2003c). In addition, extremely low pregnancy rates and continuously suppressed pituitary gonadotropin release were observed in an unsupported luteal phase after GnRH antagonist co-treatment during ovarian stimulation (Beckers et al., 2003). The existing evidence in GnRH antagonist cycles suggests that luteal supplementation remains mandatory as is the case with GnRH agonists.

### Efficacy of GnRH antagonists in IVF

**The evidence**

In the meta-analysis of five phase III randomized comparative trials between GnRH analogues, the absolute treatment effect of clinical pregnancy rate on an intention-to-treat basis was 5% in favour of the GnRH agonists (Al-Inany and Aboulghar, 2002). In the published meta-analysis, the additional period of treatment required with GnRH agonists was 21 days and the number needed to treat (inverse of the absolute risk difference) was 20 (Al-Inany and Aboulghar, 2002). Based on those data, it is necessary to treat patients for an extra 420 days (20 × 21 days = 420 days) to obtain one additional pregnancy with GnRH agonists. Since then a further three trials have been reported (Hohmann et al., 2003; Vlaisavljevic et al., 2003; Cheung et al., 2005).

In a similar meta-analysis including these trials, the difference in pregnancy rate per cycle was 3.3% (95% CI –0.4, 6.9) in favour of GnRH agonists (J. Collins, personal communication). If this difference were significant, the number needed to treat would be 31, which means that it would take 31 cycles to get one more pregnancy using GnRH agonist compared to GnRH antagonists.

#### Advantages of GnRH antagonists from meta-analysis of phase III trials (Al-Inany and Aboulghar, 2002)

(i) A shorter duration of stimulation is required with the use of GnRH antagonists.

(ii) Gonadotropin requirements are decreased as compared with GnRH agonists.

(iii) Considering OHSS incidence, the odds ratio is in favour of GnRH antagonists, however, it includes unity (0.51, 95% CI 0.22–1.18).

Cost studies on the use of GnRH agonists and antagonists are necessary for further assessment of the two analogues of GnRH in ART. For evaluation of GnRH antagonists the clinical end point of interest needs to be agreed and justified (Germond et al., 2004; Griesinger et al., 2004; Heijnen et al., 2004; Min et al., 2004; Tiitinen et al., 2004; Fauser et al., 2005). A pragmatic approach with broad relevance for clinical practice should probably adopt as primary outcome measure live birth rate (Arce et al., 2005).

### GnRH antagonists in ovarian stimulation for IUI

The issue of ovarian stimulation in combination with IUI in unexplained infertility is still not solved (Hughes et al., 2000; Fauser...
B.C.Tarlatzis et al.

Table III. Modifications of the standard GnRH antagonist protocol

<table>
<thead>
<tr>
<th>Modification</th>
<th>Studies</th>
<th>Current evidence</th>
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</thead>
<tbody>
<tr>
<td>Increase of the starting dose LH</td>
<td>2 RCTs (Out et al., 2004; Wikland et al. 2001) 384 patients</td>
<td>Increase of FSH does not appear to be necessary</td>
</tr>
<tr>
<td>LH supplementation</td>
<td>2 RCTs (Cedrin-Durnerin, 2004; Griesinger et al., 2005a) 345 patients</td>
<td>LH supplementation does not appear to be necessary</td>
</tr>
<tr>
<td>Increase of gonadotrophin dose at</td>
<td>1 RCT (Aboulghar et al., 2004) 151 patients</td>
<td>Increase of gonadotropin dose does not appear to be</td>
</tr>
<tr>
<td>antagonist initiation</td>
<td></td>
<td>necessary</td>
</tr>
<tr>
<td>Flexible antagonist administration</td>
<td>4 RCTs (Ludwig et al., 2002; Mochtar et al., 2004; Kolibianakis et al.,</td>
<td>Fixed protocol appears to be associated with a higher</td>
</tr>
<tr>
<td></td>
<td>2003b; Escudero et al., 2004) 476 patients</td>
<td>pregnancy rate</td>
</tr>
<tr>
<td>OCP pre-treatment</td>
<td>2 RCTs (Fischl et al., 2001; Kolibianakis et al., 2006) 575 patients</td>
<td>OCP pre-treatment appears feasible for programming an</td>
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<tr>
<td></td>
<td></td>
<td>antagonist cycle</td>
</tr>
<tr>
<td>Replacement of HCG by GnRH agonist</td>
<td>3 RCTs, (Fauser et al., 2002; Huamadn et al., 2005; Kolibianakis et al.,</td>
<td>Replacement of hCG is associated with a lower</td>
</tr>
<tr>
<td></td>
<td>2005b) 275 patients 1 meta-analysis (Griesinger et al., 2003b)</td>
<td>probability of pregnancy</td>
</tr>
<tr>
<td>Luteal supplementation</td>
<td>3 observational studies (Albano et al., 1998; de Jong et al., 2000;</td>
<td>Luteal support is necessary in GnRH antagonist cycles</td>
</tr>
<tr>
<td></td>
<td>Kolibianakis et al., 2003c) 56 patients</td>
<td></td>
</tr>
<tr>
<td>Prolongation of follicular phase</td>
<td>1 RCT (Kolibianakis et al., 2004a) 413 patients</td>
<td>Prolongation is associated with a lower probability of</td>
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<tr>
<td></td>
<td></td>
<td>pregnancy</td>
</tr>
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et al., 2005). If ovarian stimulation in combination with IUI is performed, GnRH antagonists can be used for preventing the premature LH surge (Ragni et al., 2001, 2004; Gomez-Palomares et al., 2005). In addition, they may be helpful in cycle programming and avoidance of inseminations during weekends. However, the hypothesis that avoiding LH surge in this case is associated with a higher probability of pregnancy needs to be tested in prospective trials.

**Recommended use of GnRH antagonists co-treatment during ovarian stimulation for IVF on the basis of the best estimate from the available data in the literature (Table III)**

(i) Currently, data are not in favour of a need to increase the starting dose of gonadotropins or to increase gonadotropin dose at antagonist initiation.

(ii) Clinical evidence generated so far suggests that OCP pretreatment can be used for planning IVF cycles.

(iii) Addition of LH from initiation of stimulation or from antagonist administration does not appear to be necessary.

(iv) Replacement of HCG by GnRH agonist for triggering final oocyte maturation is associated with lower probability of pregnancy.

(v) The optimal timing for HCG administration needs to be further explored.

(vi) GnRH antagonist initiation on day 6 of stimulation appears to be superior to flexible initiation by a follicle of 14–16 mm, although earlier GnRH antagonist administration is worth further evaluation.

(vii) The role of GnRH antagonists in ovarian stimulation for IUI as well as their application in mild stimulation protocols for IVF appears to be promising.

(viii) Luteal phase supplementation is required following GnRH antagonist co-treatment protocols.

**Coda**

(i) GnRH antagonist co-treatment during ovarian hyperstimulation for IVF is effective in preventing an undesirable premature rise in serum LH. The daily low-dose protocol should be preferred over a single high-dose regimen for theoretical reasons. In addition, much more clinical experience exists with this protocol.

(ii) There is a general resistance in the clinic to further explore the use of GnRH antagonist because of the reported lower pregnancy rates associated with their use (Fauser and Devroey, 2005). This is based, however, on a non-significant difference of 3.3% in the pregnancy rate per cycle in favour of GnRH agonists, in case more recently published studies are also included in the meta-analysis.

(iii) GnRH antagonist co-treatment results in shorter and more cost-effective ovarian stimulation protocols. Many further studies are required for its optimization. Several aspects of GnRH antagonist use need to be further explored, such as: potential pharmacological differences in existing compounds, direct effects of GnRH antagonists on extra pituitary tissues (such as corpus luteum, endometrium, ovary, embryo) and optimization of the currently used stimulation protocols (compounds, initiation, doses).

(iv) The possibility of a reduced incidence of OHSS following ovarian stimulation with GnRH antagonist co-treatment deserves further evaluation.

(v) The impact of timing and dose of HCG for inducing final oocyte maturation on IVF outcomes deserves further studies.

(vi) Further research needs to be carried out on the value of assessing hormonal levels on day 2 of the cycle (Kolibianakis et al., 2004e), prior to initiation of stimulation, and on the importance of hormonal values present on the day of HCG administration (Bosch et al., 2003).

(vii) Finally, the use of GnRH antagonist co-treatment should be viewed in the context of a broader discussion regarding how to assess IVF outcomes (healthy children, term births, chances for success in relation to side effects, complications and cost).

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