

## 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 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

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## 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 Devroey, 2005; Kolibianakis *et al.*, 2005a).

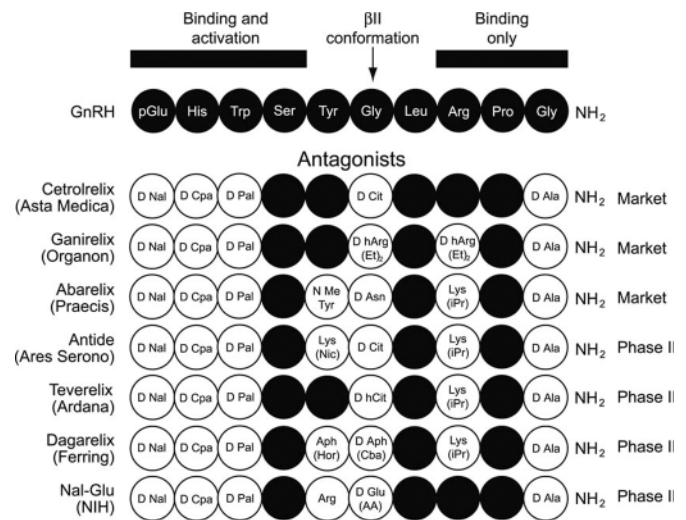
In an attempt to optimize the existing stimulation protocols, several studies have explored various aspects of the use of GnRH antagonist in IVF. Such studies involved the optimal day GnRH antagonist administration should be initiated (Ludwig *et al.*, 2002; Escudero *et al.*, 2004; Mochtar *et al.*, 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 (Aboulghar *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 accompanied 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 NH<sub>2</sub> terminal domain (involved in receptor activation) combined with a D-amino acid substitution for Gly<sup>6</sup> which enhances the  $\beta$ II type bend necessary for receptor binding (Millar



**Figure 1.** Structure of clinically used GnRH antagonists (modified from Millar *et al.*, 2004).

*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 G<sub>αq</sub> and downstream Ca<sup>2+</sup>, and protein kinase C signalling) but are full agonists in stimulating G<sub>αi</sub> and the inhibition of proliferation and apoptosis in peripheral reproductive cells (G<sub>αq</sub> and G<sub>αi</sub> 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 G<sub>αi</sub> 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 G<sub>αq</sub> and do not activate G<sub>αi</sub> (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 (E<sub>2</sub>) 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).

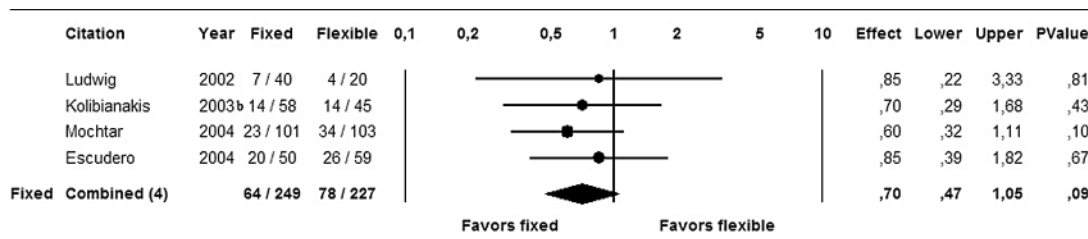


Figure 2. Clinical pregnancy rate in fixed and flexible GnRH antagonist protocols (modified from Al-Inany *et al.*, 2005).

*GnRH agonist versus HCG for triggering final oocyte maturation*

GnRH agonist has been used to trigger final oocyte maturation in GnRH antagonist cycles (Felberbaum *et al.*, 1995). Replacing HCG with GnRH agonist has been claimed to lead to a decreased risk of developing ovarian hyperstimulation syndrome (OHSS) in high risk patients (Kol, 2004). However, GnRH agonist administration induces an LH surge which is not identical to that occurring in the natural cycle, especially regarding its duration (Fauser *et al.*, 2002; Beckers *et al.*, 2003).

The existing literature suggests that a lower probability of pregnancy is to be expected when a single dose of GnRH agonist is used instead of HCG for triggering final oocyte maturation (Humaidan *et al.*, 2005; Griesinger *et al.*, 2005b; Kolibianakis *et al.*, 2005b). Thus, if GnRH agonists are used instead of HCG in high-risk patients to prevent OHSS, the reduced probability of pregnancy that might be associated with their use has to be considered. However, it remains to be explored whether the dose of the GnRH agonist administered, the repeated administration of the agonist or the use of alternative luteal support schemes would improve the pregnancy outcome. On the other hand, alternative existing methods shown to reduce the risk of OHSS such as coasting or cryopreservation of all embryos and transfer of the thawed embryos in a subsequent cycle can also be applied (Delvigne and Rozenberg, 2002; Aboulghar and Mansour, 2003). A comparison between various methods used to prevent OHSS is currently lacking.

*Oral contraceptive pill pretreatment in ovarian stimulation with GnRH antagonists*

The use of OCP 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:

(i) Pretreatment with OCP has been associated with a longer duration of treatment (van Loenen *et al.*, 2001).

(ii) An increased gonadotropin requirement has been observed with the use of OCP (Bendikson *et al.*, 2003).

(iii) 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 inter-cycle 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 I.** Randomized-controlled trials evaluating the need for an increase in the starting dose of rec FSH in patients treated for IVF using GnRH antagonists

Study	n	Antagonist	Rec FSH starting doses				Difference	95% CI of the difference
			Ongoing pregnancy rate		Vital pregnancy rate			
			150 IU	225 IU	150 IU	200 IU		
Wikland <i>et al.</i> (2001)	120	Daily dose, starting on day 6 of stimulation	25% (15/60)	25% (15/60)			0.0%	-15.3% to +15.3%
Out <i>et al.</i> (2004)	264	Daily dose, starting on day 6 of stimulation			31.1% (41/132)	24.2% (32/132)	+6.8%	-3.9% to +17.43%

**Table II.** Randomized-controlled trials evaluating the addition of LH in patients stimulated with rec FSH and GnRH antagonists for IVF

Study	n	Rec FSH	Antagonist starting dose	Dose of rec LH	Delivery rate		Clinical pregnancy rate		Difference	95% CI of the difference
					Rec FSH	Rec FSH + rec LH	Rec FSH	Rec FSH + rec LH		
Cedrin-Durnerin <i>et al.</i> (2004)	218	150–300 IU	Single dose, flexible initiation by a follicle of 14–16mm	75 IU, starting at antagonist initiation	22.1% (23/104)	23.7% (27/114)			-1.6%	-12.6% + 9.7%
Griesinger <i>et al.</i> (2005)	127	150 IU	Daily dose, starting on day 6 of stimulation	75 IU, starting with rec FSH			18.5% (12/65)	12.9% (8/62)	+5.6%	-7.4% + 18.3%

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 ( $20 \times 21$  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

**Table III.** Modifications of the standard GnRH antagonist protocol

Modification	Studies	Current evidence
Increase of the starting dose LH supplementation	2 RCTs (Out <i>et al.</i> , 2004; Wikland <i>et al.</i> 2001) 384 patients 2 RCTs (Cedrin-Durnerin, 2004; Griesinger <i>et al.</i> , 2005a) 345 patients	Increase of FSH dose does not appear to be necessary LH supplementation does not appear to be necessary
Increase of gonadotrophin dose at antagonist initiation	1 RCT (Aboulghar <i>et al.</i> , 2004) 151 patients	Increase of gonadotropin dose does not appear to be necessary
Flexible antagonist administration	4 RCTs (Ludwig <i>et al.</i> , 2002; Mochtar <i>et al.</i> , 2004; Kolibianakis <i>et al.</i> , 2003b; Escudero <i>et al.</i> , 2004) 476 patients	Fixed protocol appears to be associated with a higher pregnancy rate
OCP pre-treatment	2 RCTs (Fischl <i>et al.</i> , 2001; Kolibianakis <i>et al.</i> , 2006) 575 patients	OCP pretreatment appears feasible for programming an antagonist cycle
Replacement of HCG by GnRH agonist	3 RCTs, (Fauser <i>et al.</i> , 2002; Humaidan <i>et al.</i> , 2005; Kolibianakis <i>et al.</i> , 2005b) 275 patients 1 meta-analysis (Griesinger <i>et al.</i> , 2003b)	Replacement of hCG is associated with a lower probability of pregnancy
Luteal supplementation	3 observational studies (Albano <i>et al.</i> , 1998; de Jong <i>et al.</i> , 2000; Kolibianakis <i>et al.</i> , 2003c) 56 patients	Luteal support is necessary in GnRH antagonist cycles
Prolongation of follicular phase	1 RCT (Kolibianakis <i>et al.</i> , 2004a) 413 patients	Prolongation is associated with a lower probability of pregnancy

*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 pre-treatment 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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