Are GnRH antagonists comparable to agonists for use in IVF?

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We believe that appropriate comparison of optimal GnRH agonist and antagonist regimens has not been performed yet. Currently available meta-analyses included all comparative studies between GnRH agonists and antagonists performed so far, including less than optimal GnRH antagonist regimens. After critical appraisal of the various studied GnRH antagonist regimens in terms of follicular development and IVF outcome, we postulate that early suppression of endogenous FSH results in optimal follicular development. Additionally, stable and early suppression of LH and progesterone levels during the entire period of stimulation may be an advantage for implantation and pregnancy outcome. In this respect, single dose and particularly flexible protocols seem to be less advantageous. Early FSH and LH suppression can be achieved by early GnRH antagonist administration (stimulation day 1) or by oral contraceptive (OC) pretreatment. More studies comparing long GnRH agonist protocols with ‘long’ GnRH antagonist protocols, with enough power to identify differences in pregnancy rates, are required before appropriate comparison can be made.

Keywords: GnRH agonists; GnRH antagonists; IVF; stimulation protocols; oral contraceptive pretreatment

The first in vitro fertilization (IVF) therapies were performed in natural unstimulated IVF cycles. Nowadays, gonadotrophins are given to induce multiple follicular development and GnRH analogues for the prevention of premature LH surges in IVF. Without the use of GnRH analogues, LH surges occur in ~20% of stimulated IVF patients (Edwards et al., 1996; Janssens et al., 2000). Preventing LH surges using GnRH analogues improves oocyte yield with more embryos, allowing better selection, leading to an increase in pregnancy rates (Templeton et al., 1998). It took 15 years of experience with the GnRH agonists in IVF to identify the optimal protocol (the long protocol starting in the midluteal phase of the preceding cycle) with regard to the best IVF results in a general population (Daya, 2000; Huirne et al., 2004a). GnRH agonist administration causes gonadotrophin suppression via pituitary desensitization, after an initial short period of gonadotrophin hypersecretion. In contrast, GnRH antagonists cause immediate and rapid gonadotrophin suppression, by competitive occupancy of the GnRH receptor and therefore intuitively a more logical choice to use in IVF for the prevention premature LH surges. Theoretically, GnRH antagonists could be administered at any time during the early or mid-follicular phase of a treatment cycle to prevent a premature LH surge. With this in mind, around a decade ago, the first dose-finding studies in IVF started GnRH antagonist medication on a fixed day late in the follicular phase (Albano et al., 1997; Ganiirelix dose-finding study group, 1998; Olivennes et al., 1998; Huirne et al., 2004b). Initially two general approaches emerged; (i) the single dose protocol, in which one injection is administered late in the follicular phase around stimulation day 7 or 8, and (ii) the multiple dose regimens in which the antagonist is administered daily from stimulation day 6 onwards. Soon, comparative studies with long GnRH agonist protocols were initiated, without certainty about the possible optimal GnRH antagonist administration strategy (Albano et al., 2000; Borm and Mannaerts, 2000; Olivennes et al., 2000; European Middle East Orgalutran study group, 2001; Fluker et al., 2001). Several drawbacks of the GnRH antagonist regimens emerged with these first phase III studies. (i) The numbers of oocytes retrieved were in favour of the long GnRH agonist arms compared with the fixed multiple dose day 6 and fixed single dose GnRH antagonist regimen (Albano et al., 2000; Borm and Mannaerts, 2000; Olivennes et al., 2000; European Middle East Orgalutran study group, 2001; Fluker et al., 2001; Roulier et al., 2003). (ii) The initiation of FSH administration in a GnRH antagonist regimen is cycle dependent. It is mostly started on day 2 or 3 of the natural cycle which made treatment planning and scheduling more difficult (Huirne and Lambalk, 2001; Huirne et al., 2005). (iii) Although the pregnancy rates were not different in various individual studies, a
meta-analysis including the first five comparative studies of fixed GnRH antagonist protocols compared with long agonist protocols, indicated 5% less clinical pregnancies in the antagonist groups (Al-Inany and Aboulghar, 2002). The initial reported results of these comparative studies, together with the results of national large database evaluations (Devaux et al., 2004; Griesinger et al., 2005), which were not in favour of the GnRH antagonist, made the GnRH antagonist for many clinicians a second choice. Is this justified? Analysis of the national IVF registry in Germany from 2000 to 2003 demonstrated that GnRH antagonists were often utilized in cycles with an unfavourable a priori prognosis, in patients with advanced age and with a higher number of previously unfavourable cycles (Griesinger et al., 2005). Sub-analysis of patients with equal demographic and clinical features resulted in similar pregnancy rates independent of whether GnRH agonists or antagonists were used (Engel et al., 2006). Furthermore, the meta-analysis of Al-Inany and Aboulghar (2002), included one study, with different starting doses of FSH in the comparative arms, with a possible risk of confounding (Olivennes et al., 2000). Differences no longer reach statistical significance if this study is left out of the analyses: OR 0.8 (0.63–1.01) (Thesis Al-Inany 2006), although this may also be due to insufficient power once this study is omitted.

Now that over 200 clinical trials involving GnRH antagonists in IVF have been published, it is a good time to compare results with those achieved with the long GnRH agonist protocol, the most commonly adopted protocol for assisted reproductive treatment cycles worldwide. Tables 1 and 2 provide an overview of all currently available comparative RCT’s (published as full papers), including their design and regimen used, with or without oral contraceptive (OC) pretreatment.

Very recently, two meta-analyses have been published with conflicting interpretations (Al-Inany et al., 2006; Kolibianakis et al., 2006).

### Table 1: Characteristics of current published randomized controlled trials comparing GnRH agonist and antagonists in IVF without OC pretreatment

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients (ITT)</th>
<th>Population</th>
<th>Type of agonist used</th>
<th>Type of antagonist used</th>
<th>Antagonist protocol</th>
<th>Starting dose FSH (IU)</th>
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<tr>
<td>Long agonist versus fixed MD</td>
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<tr>
<td>Albano et al. (2000)</td>
<td>95/198</td>
<td>General</td>
<td>Busulrelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Fixed S6 MD</td>
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<td>European study (2000)</td>
<td>244/486</td>
<td>General</td>
<td>Busulrelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Fixed S6 MD</td>
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<tr>
<td>European Middle East Ovulatran Study Group (2001)</td>
<td>119/236</td>
<td>General</td>
<td>Triptorelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Fixed S6 MD</td>
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<td>Different criteria for hCG administration in both groups, 18 versus 20 mm.</td>
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<td>Fruette et al. (2001)</td>
<td>105/208</td>
<td>General</td>
<td>Leuprolin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Fixed S6 MD</td>
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<tr>
<td>Lee et al. (2005)</td>
<td>41/20 (20/20/21)</td>
<td>General</td>
<td>Busulrelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Fixed S6 MD</td>
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<td>Simon et al. (2005)</td>
<td>14/14/14</td>
<td>Oocyte donors</td>
<td>Buserelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Fixed S6 MD</td>
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<td>Long agonist versus fixed SD</td>
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<tr>
<td>Olivennes et al. (2000)</td>
<td>43/126</td>
<td>General</td>
<td>Triptorelin</td>
<td>Long SD</td>
<td>Cetrorelix</td>
<td>Fixed SD (S7)</td>
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<td>Long agonist versus flexible antagonist (MD)</td>
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<td>Hohmann et al. (2003)</td>
<td>58/111 (45/48/49)</td>
<td>General</td>
<td>Triptorelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
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<tr>
<td>Check et al. (2004)</td>
<td>30/30</td>
<td>General</td>
<td>Leuprolide</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Flex (≥14 mm)</td>
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<td>Loutradis et al. (2004)</td>
<td>58/58</td>
<td>General</td>
<td>Triptorelin</td>
<td>Long MD hCG (18 mm)</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
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<td>Badrwy et al. (2005)</td>
<td>50/50</td>
<td>General</td>
<td>Buserelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
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<tr>
<td>Xavier et al. (2005)</td>
<td>65/66</td>
<td>General</td>
<td>Buserelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
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<tr>
<td>Marcia et al. (2005)</td>
<td>30/30</td>
<td>Poor resp</td>
<td>Leuprolin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
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<tr>
<td>Rombauts et al. (2006)</td>
<td>111/111</td>
<td>General</td>
<td>Nafarelin</td>
<td>Long MD</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
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<td>Short agonist versus fixed antagonist multiple dose (MD)</td>
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<td>Martinez et al. (2003)</td>
<td>23/21</td>
<td>Poor resp</td>
<td>Triptorelin</td>
<td>Short MD</td>
<td>Cetrorelix</td>
<td>Fixed S7 MD</td>
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<td>Short agonist versus flexible antagonist multiple dose (MD)</td>
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<tr>
<td>Akman et al. (2001)</td>
<td>24/24</td>
<td>Poor resp</td>
<td>Leuprolin</td>
<td>O/C short MD (CD2)</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
</tr>
<tr>
<td>Malmsi et al. (2005)</td>
<td>30/30</td>
<td>Poor resp</td>
<td>Triptorelin</td>
<td>Short MD (CD1)</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm)</td>
</tr>
<tr>
<td>Schmidt et al. (2005)</td>
<td>24/24</td>
<td>Poor resp</td>
<td>Leuprolin</td>
<td>O/C short MD</td>
<td>Cetrorelix</td>
<td>Flex MD (≥12 mm)</td>
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<tr>
<td>De placido et al. (2006)</td>
<td>67/66</td>
<td>Poor resp</td>
<td>Triptorelin</td>
<td>Flare up MD (S1)</td>
<td>Cetrorelix</td>
<td>Flex MD (≥14 mm), 2 days 0.125 mg/day or less than 0.25 mg/day</td>
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<td>Short agonist versus flexible antagonist single dose (SD)</td>
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<td>Roulier et al. (2003)</td>
<td>364/307</td>
<td>General</td>
<td>Triptorelin</td>
<td>Short SD (CD1)</td>
<td>Cetrorelix</td>
<td>Flex SD (≥14 mm)</td>
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</table>

*aStarting dose was 225 IU in the Cetrorelix and 150 IU hMG in the Triptorelin.

*bDifferent criteria for hCG administration in both groups, 18 versus 20 mm.

*cInadequate randomization.

MD, multiple dose; SD, single dose; flex, flexible protocol; OC, oral contraceptives; E2, estradiol; S6, stimulation day 6 etc.; CD2, cycle day 2; hMG, human menopausal gonadotrophine; rFSH, recombinant follicle stimulating hormone; LH, luteinizing hormone; hCG, human chorion gonadotrophin.
Authors Number of patients Population Type of agonist used Agonist protocol Type of antagonist used Antagonist protocol Start FSH: number of days after last OCP Starting dose FSH

OC/long agonist versus OC/ fixed antagonist protocol
Hwang et al. (2004)a 29/27 PCOS Buserelin Long MD (± OC) Cetrorelix OC/MD fixed (0.125 mg/day OCP+4 to OCP+9) (0.25 mg/day OCP+10 to hCGd) OC/ fixed SD S7 4 150 hMG
Sauer et al. (2004)b 25/24 (25/24/25) General Leuprolin OC/long SD Cetrorelix Cetrorelix OC/ fixed SD S7+ LH OC/ fixed MD S6 5 225 rFSH
Cheung et al. (2005) 33/33 Poor responders Buserelin OC/long MD Cetrorelix Cetrorelix OC/ fixed MD S6 2 or 3 300 rFSH
Huierne et al. (2006a) 91/91 General Oocyte donors Buserelin Triptorelin Long MD OC/long MD Cetrorelix Ganirelix OC/ fixed MD S6 OC/ fixed MD S8 5 150–225 rFSH 300 rFSH

OC/long agonist versus OC/flexible antagonist protocol
Bahceci et al. (2005) 75/73 PCOS Leuprolin OC/long MD Cetrorelix Cetrorelix OC/ flex MD (≥ 14 mm) 3 150–300 uFSH/hMG 300 rFSH
Barmat et al. (2005) 40/40 General Leuprolin OC/long MD Ganiirelix Ganiirelix OC/ flex MD (≥ 14 mm) 5 200 rFSH
Rombauts et al. (2006) 111/111 General Nafarelin Long MD Ganiirelix Ganiirelix OC/ flex MD (≥ 14 mm) 2 225–300 uFSH
Koichi et al. (2006)c 66/63/63 General Buserelin OC/long MD Cetrorelix Cetrorelix OC/ flex MD (≥ 14 mm) 5 150–225 rFSH
Vlaisavljevic et al. (2003) 236/226 General Goserelin OC/long SD Cetrorelix Cetrorelix OC/ flex MD (≥ 12–14 mm) 5 300 rFSH + 150 hMG

Short agonist versus OC/flexible antagonist
Schmidt et al. (2005) 24/24 Poor responders Leuprolin Flare up MD Ganiirelix OC/ flex MD (≥ 12 mm) 2 200 rFSH

aDose of antagonist was increased from 0.125 to 0.25 mg/day on day 10 after last OCP.
bThree arm study; Leuprolin (n = 25) versus Cetrorelix (n = 24) versus Cetrorelix + LH (n = 25).
cSome women were used twice as donorsd 3 arm study; Buserelin (n = 66) versus Cetrorelix, startdose 225 IU FSH, FSH increase to 300 if follicle ≥ 14 mm (n = 63) versus Cetrorelix, startdose 225 IU FSH, FSH decreased to 75IU + 200 hCG/day if follicle ≥ 14 mm (n = 63). MD, multiple dose; SD, single dose; flex, flexible protocol; OC, oral contraceptives; OCP, oral contraceptive pill; E2, estradiol; S6, stimulation day 6 etc.; CD2, cycle day 2; hMG, human menopausal gonadotrophin; rFSH, recombinant follicle stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotrophin.
dInadequate randomization.

et al., 2006a). Both studies reported highly significantly shorter duration of stimulation (−1.5 and −1.1 days) and less oocytes (−1.6 and −1.1) retrieved using GnRH antagonists compared with agonists (Al-Inany et al., 2006; Kolibianakis et al., 2006a). The first meta-analysis including 27 relevant published papers, abstracts and proceedings, showed significant differences with respect to clinical (OR = 0.84, 95% CI 0.72–0.97) and ongoing pregnancy/live birth rate (OR = 0.82, 95% CI: 0.69–0.98) in favour of the agonist regimen (Al-Inany et al., 2006). However, the quality, method of design and analysis could not be assessed for all of the individual papers used. The other meta-analysis, with 22 RCT’s published as full papers in peer reviewed journals, could not identify significant differences with respect to the probability of live birth independent of population studied, gonadotrophin type used for stimulation, type of agonist protocol or whether a fixed or flexible GnRH antagonist regimen was used (Kolibianakis et al., 2006a). In the latter meta-analysis, an expected live birth was calculated on the basis of clinical and ongoing pregnancies for all studies not reporting live birth rate, which remains an estimate. OC pretreatment (OCP) was only sub-analysed (in a subgroup ‘additional intervention group’), if OCP was given in only one of the treatment arms, but not when it was applied in both arms. We think that this is not entirely correct as OCP may have a bigger effect in a GnRH antagonist regimen with mostly high fluctuation in hormonal levels during the treatment compared with the long GnRH agonist regimen in which hormonal levels are more or less stably suppressed. It may be an effect modifier and should, in our opinion, be taken into account in the analyses. Thus the question is still unanswered; what is the current place of the GnRH antagonist in IVF/ICSI?

After critical appraisal of currently available studies using GnRH antagonists, we think that the differences in reported outcome measurements could be the consequence of the large variation of employed GnRH antagonist regimens (Fig. 1). In this respect, it is likely that two phenomena play an important role to facilitate optimal IVF results when GnRH analogues are used:

(i) Stable and low LH and progesterone levels throughout the stimulation phase to achieve optimal conditions for implantation and
(ii) Sustained low levels of endogenous FSH before stimulation is started to allow optimal synchronization of the follicular cohort.

What are the facts that may help to determine the optimal GnRH analogue regimen?

Long versus short or ultra-short GnRH agonist regimen

Many treatment schedules with the use of GnRH agonists in IVF therapy have been designed and studied (for review see
Huirne et al. (2004a). Several investigators tried to shorten the duration of GnRH agonist administration by later administration or early cessation. However, the long protocol (starting in the midluteal phase of the preceding cycle) gave the best IVF results with regard to oocyte yield and pregnancy rates (Daya, 2000). This protocol induces profound suppression of endogenous release of gonadotrophins during the early follicular phase, allowing the early antral follicles to grow co-ordinately in response to exogenous gonadotrophins to accomplish simultaneous maturation (Fig. 2a). This leads to an extended widening of the FSH window, increased FSH requirement and in the end more mature follicles and retrieved oocytes (Daya, 2000).

**Fixed versus flexible and short versus long GnRH antagonist regimens**

The initially developed GnRH antagonist regimens started relatively late in the follicular phase on a fixed day, mostly stimulation day 6. Under these circumstances, the luteo-follicular transitory rise of endogenous FSH starts the stimulation of a cohort of follicles that vary in stage of development. Subsequently exogenous FSH allows further development of a few leading large follicles and several smaller follicles (Albano et al., 2000; Borm and Mannaerts, 2000; European Middle East Orgalutran study group, 2001; Fluker et al., 2001; Huirne et al., 2004a; Huirne et al., 2005). As the criteria to administer hCG are based on the size of the leading largest follicles, consequently a number of follicles will still be immature at that time (Fig. 2b). Logically, the stimulation period will be shorter with less FSH required but also the number of oocytes will be reduced compared with the long GnRH agonist protocol (Albano et al., 2000; Borm and Mannaerts, 2000; Olivennes et al., 2000; European Middle East Orgalutran study group, 2001; Fluker et al., 2001). We think that the relatively higher levels of FSH during the early follicular phase in various initially developed GnRH antagonist regimens, results in less synchronization of the follicular cohort with less oocytes retrieved (Fig. 2b). More oocytes may result in increased pregnancy rates due to increased number of embryos available for improved embryo selection (Templeton and Morris, 1998) and cryopreservation. However, differences in number of oocytes are in the range of 1 or 2 and it is debatable if this slightly smaller number of oocytes retrieved can be held responsible for possible differences in pregnancies.

Yet another feature of the originally employed GnRH antagonist protocols may have contributed negatively. It is likely that the higher LH, estradiol and progesterone levels during the early follicular phase in most of these GnRH antagonist regimens compared with the long agonist regimen (Fig. 3a and b) may play a role. Significantly lower ongoing pregnancy rates are seen in patients with elevated progesterone at initiation of stimulation of fixed day 6 GnRH antagonist cycles (Kolibianakis et al., 2004b). The level of LH suppression 2 days after commencement of GnRH antagonist therapy in a fixed day 6 protocol is possibly associated with ongoing pregnancy, the higher the LH levels the lower the probability of achieving an ongoing pregnancy (Kolibianakis et al., 2004a). Possibly early closure of the implantation window occurs (Develioglu et al., 1999) through earlier expression of progesterone receptors in the follicular phase and down-regulation of estrogen receptors by the exposure to supraphysiological steroid hormone levels (Kolibianakis et al., 2002; Papanikolaou et al., 2005). These findings support the proposed facilitating/activating mode of hormonal control of endometrial receptivity (de Ziegler, 1995). According to this theory, once endometrium is primed by estradiol,
the duration of progesterone exposure is the crucial point leading to a receptive endometrium. Other studies could not find an effect of the absolute LH concentrations on stimulation day 8 or the day of hCG administration during a fixed GnRH antagonist regimen on ovarian response and IVF outcome (Bosch et al., 2003; Penarrubia et al., 2003; Merviel et al., 2004). Differences between the various studies, with regard to the level of LH suppression, study populations and type of GnRH antagonist regimen used, may play a role in the conflicting results. Furthermore, one study indicates that the stability of LH levels rather than absolute LH values are associated with clinical pregnancy as no pregnancies occurred if the LH and progesterone levels changed too markedly (either increase or decrease) during GnRH antagonist administration (Huirne et al., 2005).

In order to reduce the number of antagonist injections and the duration of stimulation, flexible protocols were developed. Instead of starting with the GnRH antagonist on a fixed day, administration was made dependent on the follicular size. GnRH antagonist injections were started as soon as the follicles reach a size of ≥14, 15 or 16mm after 5 days of stimulation (Ludwig et al., 2002; Hohmann et al., 2003; Kolibianakis et al., 2003b; Escudero et al., 2004; Klipstein et al., 2004; Mochtar et al., 2004). Overall, this implies that almost 50% of the patients will start with a GnRH antagonist beyond day 6 of FSH stimulation (Kolibianakis et al., 2003b; Escudero et al., 2004; Mochtar et al., 2004). Such protocols in particular allow higher LH, estradiol and progesterone levels, especially when antagonist treatment is started beyond day 6 and are associated with lower pregnancy rates (Kolibianakis et al.,

Figure 2: (a) Synchronized follicular development after FSH administration in a long GnRH agonist regimen and (b) Follicular development in a fixed day 6 GnRH antagonist regimen without OC pretreatment

The long GnRH agonist protocol suppresses endogenous FSH levels, leading to a follicular cohort of all small follicles at the initiation of FSH administration without leading larger follicles. After exogenous FSH administration, FSH levels remain above the threshold, resulting in a synchronized follicular development. As soon as one or two follicles meet the hCG administration criteria, most follicles will be of more or less similar size and sensitive for hCG. In the fixed GnRH antagonist protocol, endogenous FSH levels are not suppressed during the early follicular phase. The luteo-follicular transition induces FSH levels above the threshold for a short period until hormonal feedback occurs, leading to the initiation of follicular growth of a few leading follicles. After exogenous FSH administration, FSH levels arise above threshold again and will initiate several additional follicles to grow. As soon as the leading follicles meet the hCG criteria, several other follicles will be of smaller sizes and may not be sensitive for hCG yet. Such an asynchronous cohort may therefore result in less oocytes retrieved, compared to the long agonist protocol.
2003b), whereas an earlier start (cycle day 4 or 5) of GnRH antagonists in these protocols is associated with improved pregnancy rates (Lainas et al., 2005). In this respect, starting with a GnRH antagonist on day 1 compared with day 6 will even further decrease the exposure to LH and estradiol during the early follicular phase (Kolibianakis et al., 2003a). However, the rather high-pregnancy rates (52% per embryo transfer) were not different in this small study. Additionally, this regimen will increase the cost due to the extended period of GnRH antagonist administration.

The long GnRH agonist protocol is favourable to flexible start antagonist protocols with respect to the number of follicles on the day of hCG and number of oocytes retrieved (Hohmann et al., 2003; Weghofer et al., 2004; Ragni et al., 2005). Again asynchronous follicle development through absent suppression of early endogenous FSH secretion could explain this (Figs 2 and 3a and b). Overall, it seems that the low gonadotrophin levels prior to stimulation created by the long agonist protocol are of particularly favourable with regard to IVF/ICSI yield and outcome.

**OCP or estrogen pretreatment versus GnRH antagonist only protocols**

GnRH antagonist regimen with estrogen or OC pretreatment offers a simple alternative to achieve gonadotrophin suppression during the early follicular phase (De Ziegler et al., 1998, Van Heusden et al., 1999). This mechanism can be used to overcome the cycle dependency of GnRH antagonist regimens by inducing a withdrawal bleeding so that starting time of hormonal stimulation can be planned. OC or estrogen pretreatment has been evaluated over the past several years. In some studies, gonadotrophin administration was started 2 or 3 days (Cedrin-Durnerin et al., 2004; Cheung et al., 2005; Bahceci et al., 2005; Huirne et al., 2006b; Huirne et al., 2006c; Rombaerts et al., 2006) and others, 4 or 5 days after OC withdrawal (Obruca A et al., 2000; Vlaisavljevic et al., 2003; Hwang et al., 2004; Sauer et al., 2004; Barmat et al., 2005; Huirne et al., 2006a; Koichi et al., 2006; Kolibianakis et al., 2006b) in either flexible or fixed GnRH antagonist protocols. OC pretreatment using GnRH antagonists with subsequent starting of FSH 2 or 3 days after the last OC intake is associated with deep suppression of LH and FSH levels and improved synchronization of the follicular cohort development compared with GnRH antagonist only protocols (Huirne et al., 2006b; Rombaerts et al., 2006). Similarly, improvement of the synchronization of the follicular cohort was also observed if stimulation was started 3 days after estradiol pretreatment in GnRH antagonist protocols in a general population (Franchin et al., 2003) and in poor responders with promising pregnancy rates (Dragisic et al., 2005). Whereas this effect is not seen when FSH stimulation was started on day 5 after the last OC (Obruca A et al., 2000; Kolibianakis et al., 2006b). Apparently, timing the start of exogenous gonadotrophin administration after OC-pretreatment affects follicular development (Cedrin-Durnerin et al., 2007). Fig. 3c and d show a schematic presentation of the expected patterns of LH and FSH levels during the follicular phase if stimulation is started on day 2 or day 5 after the last OC intake. Straightforward comparison of starting with

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**Figure 3:** Schematic overview of expected FSH and LH concentrations in various GnRH analogue regimens

(a) and (b) are regimens without oral contraceptive pill (OCP) pretreatment: (a) long GnRH agonist protocol and (b) fixed day 6 GnRH antagonist protocol. (c) FSH is started 2 days after the last OCP and (d) FSH is started 5 days after the last OCP in a fixed day 6 GnRH antagonist regimen.
gonadotrophin administration on day 2 versus day 5 after the last OC intake indeed showed stronger gonadotrophin suppression and less large follicles in the early stimulation period, if stimulation was started earlier after OC withdrawal (Huirne et al., 2007). The drawbacks of OC pretreatment are that the stimulation period is increased and more gonadotrophins are needed. Several RCT’s comparing OC pretreated GnRH antagonist with long agonist protocols could not observe significant differences with respect to the number of oocytes retrieved and pregnancy rates (Hwang et al., 2004; Sauer et al., 2004; Barmat et al., 2005; Cheung et al., 2005; Bahceci et al., 2005; Huirne et al., 2006a; Rombauts et al., 2006). Although some studies indicate lower implantation rates after OC pretreatment (Huirne et al., 2006b; Rombauts et al., 2006) or increased pregnancy loss compared with GnRH antagonist only regimens (Kolibianakis et al., 2006b), similar luteal endometrial development was found in OC pretreated flexible GnRH antagonist protocol in comparison to a long GnRH agonist protocol (Saadat et al., 2004) or a short GnRH agonist protocol (Schmidt et al., 2005) and in addition when a fixed day 6 antagonist was compared to a long agonist protocol (Simon et al., 2005).

GnRH agonists and antagonists: have we compared them in the optimal way?

Taken all together, the optimal GnRH analogue regimens seem to be regimens ensuring stable FSH and LH suppression during the entire stimulation period. In this respect, the long agonist or long fixed antagonist regimen seemed to be preferred (i.e. long OC pretreated fixed GnRH antagonist protocol or a long GnRH antagonist protocol from stimulation day 1 onwards). We stress that an optimal comparison of GnRH agonists versus antagonist requires the comparison of the optimal regimens of both compounds. So far, only a few individual studies compared the long GnRH agonist protocol with OC pretreated fixed GnRH antagonist protocols (Table 2). Most individual RCT’s comparing OC pretreated GnRH antagonist (fixed or flexible) with a long GnRH agonist protocol, could not identify significant differences in number of oocytes retrieved and pregnancy rates in a general IVF population (Vlaisavljevic et al., 2003; Hwang et al., 2004; Sauer et al., 2004; Barmat et al., 2005; Huirne et al., 2006a; Rombauts et al., 2006), PCO patients (Bahceci et al., 2005) or poor responders (Cheung et al., 2005). Most studies comparing OC pretreated flexible GnRH antagonist protocols with long GnRH agonist protocols in a general IVF population, are in favour of the agonist with respect to number of oocytes retrieved and pregnancy rates. OC pretreated fixed GnRH antagonist protocols may be more favourable than OC pretreated flexible GnRH antagonist protocol, although this has so far not been studied in a direct way. On the basis of the lower number of side effects and lower number of required (GnRH analogue) injections with similar ability to schedule ovum pickup, OC pretreated GnRH antagonist regimen may be an attractive alternative for the commonly used long GnRH agonist protocol (Huirne et al., 2006a).

To further explore our idea that the OC pretreated fixed GnRH antagonist regimen is comparable to the long GnRH agonist protocol, more large RCT’s comparing these regimens are required. Only thereafter can a fair comparison be made by a meta-analysis of sufficient power to identify significant differences in pregnancy rates. To identify a difference in clinical pregnancy rate of 5% (with pregnancy rates in the region of 25%), using β of 0.2 and α of 0.05 with a two-tailed hypothesis test, over 1252 patients would be required in each treatment arm.

Conclusion

After critical appraisal of the current GnRH antagonist studies, we believe that stable and early suppression of endogenous gonadotrophins may be advantageous to achieve follicular synchronization and the highest clinical pregnancy rates. This may be achieved by either a long GnRH agonist protocol or a ‘long’ GnRH antagonist protocol (i.e. OC pretreated fixed GnRH antagonist protocol). In this respect, short or flexible regimens seem to be far from optimal. Appropriate comparison of GnRH agonist and antagonist regimens requires the inclusion of the optimal regimens of both compounds. Most meta-analyses that have been performed so far included all GnRH antagonist regimens performed, including the less then optimal regimens.

More (larger) randomized controlled trials of sufficient power to identify significant differences in pregnancy rates comparing OC pretreated fixed GnRH antagonist regimen or a long (starting stimulation day 1) fixed GnRH antagonist regimen with long GnRH agonist regimen are required to allow optimal comparison between GnRH agonists and antagonists for their use in IVF or ICSI therapy.

References


