

Expert Opinion

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GnRH antagonist, cetrorelix, for pituitary suppression in modern, patient-friendly assisted reproductive technology

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Background: Gonadotropin-releasing hormone (GnRH) analogues are used routinely to prevent a premature luteinizing hormone (LH) surge in women undergoing assisted reproductive technology (ART) treatments. In contrast to GnRH agonists, antagonists produce rapid and reversible suppression of LH with no initial flare effect. **Objective:** To review the role of cetrorelix, the first GnRH antagonist approved for the prevention of premature LH surges during controlled ovarian stimulation in modern ART. **Method:** A review of published literature on cetrorelix. **Results:** Both multiple- and single-dose cetrorelix protocols were shown to be at least as effective as long GnRH agonist regimens for pituitary suppression in Phase II/III clinical trials. Furthermore, cetrorelix co-treatment resulted in similar live birth rates but a shorter duration of gonadotropin stimulation, a lower total gonadotropin dose requirement and lower incidence of ovarian hyperstimulation syndrome compared with long agonist regimens. A single-dose cetrorelix protocol further decreased the number of injections required. Preliminary studies have also produced promising data on the use of cetrorelix in modified ART protocols, such as frozen embryo transfer and donor oocyte recipient cycles. **Conclusion:** Cetrorelix offers a potential therapeutic alternative to GnRH agonists during controlled ovarian stimulation and has become an integral part of modern, patient-friendly reproductive medicine.

Keywords: ART, cetrorelix, COS, gonadotropin-releasing hormone analogue, gonadotropin-releasing hormone antagonist, IUI, IVF

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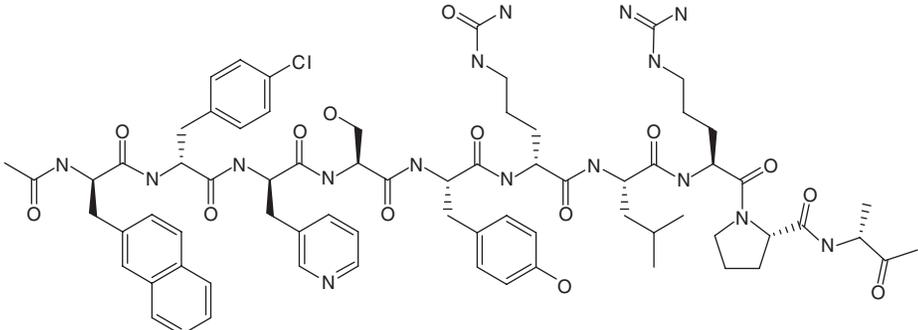
1. Introduction

Subfertility affects 5 – 15% of women worldwide, and ~ 50% of the women affected seek medical care [1]. Assisted reproductive technology (ART) is an effective strategy for infertile couples. During cycles of controlled ovarian stimulation (COS), pituitary suppression reduces the risk of a premature luteinizing hormone (LH) surge and, thus, untimely ovulation. Early ovulation results in cycle cancellation or the retrieval of poor quality oocytes (which adversely affect pregnancy rates).

Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the synthesis and secretion of follicle-stimulating hormone (FSH) and LH from the anterior pituitary. Pituitary suppression during cycles of ART allows ovarian stimulation to be controlled by exogenous FSH and suppresses the mid-cycle LH surge. In modern reproductive medicine, this is achieved by the administration of GnRH analogues. These analogues are synthetic versions of native GnRH and are available as either agonists or antagonists [2]. GnRH antagonists were first introduced to clinical practice in 1999 [3] and have since replaced the use of agonists in many protocols worldwide.

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Box 1. Drug summary.

Drug name	Cetrorelix acetate
Phase	Launched
Indication	Infertility, female
Pharmacology description	LHRH antagonist
Route of administration	Parenteral, subcutaneous
Chemical structure	
Pivotal trial(s)	In Phase III trials, 239/246 of patients receiving cetrorelix acetate reached the day of ovulation induction

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2. Current pharmacotherapy

2.1 GnRH agonists

GnRH agonists available for use in ART include mainly buserelin and triptorelin in Europe and leuprolide acetate in the US. However, the use of GnRH agonist treatment protocols is associated with a number of shortcomings. GnRH agonists exert an initial stimulatory effect on gonadotropin secretion, which leads to the so-called 'flare effect'. A pretreatment interval of 10 – 14 days is required to allow the flare effect to subside before gonadotropin treatment may begin (Figure 1) [2]. The flare effect may also stimulate the development of ovarian cysts, which are associated with the development of poor-quality oocytes and embryos, high rates of cycle cancellation and low implantation and pregnancy rates [4].

Once desensitization is achieved, serum estradiol levels are markedly suppressed and menopausal symptoms such as hot flashes are not uncommon [5]. The use of GnRH agonists necessitates a long duration of treatment (~ 25 – 30 days) and a high total gonadotropin dose requirement [6]. Moreover, the use of GnRH agonists is also associated with risks of ovarian hyperstimulation syndrome (OHSS) [7]. Slow pituitary recovery may be observed after discontinuation of GnRH agonist treatment [8].

Unless a depot formulation is used, GnRH agonists are administered daily by subcutaneous (s.c.) injection or nasal spray [5]. Nasal administration of GnRH agonists may lead to variable absorption into the systemic circulation [9].

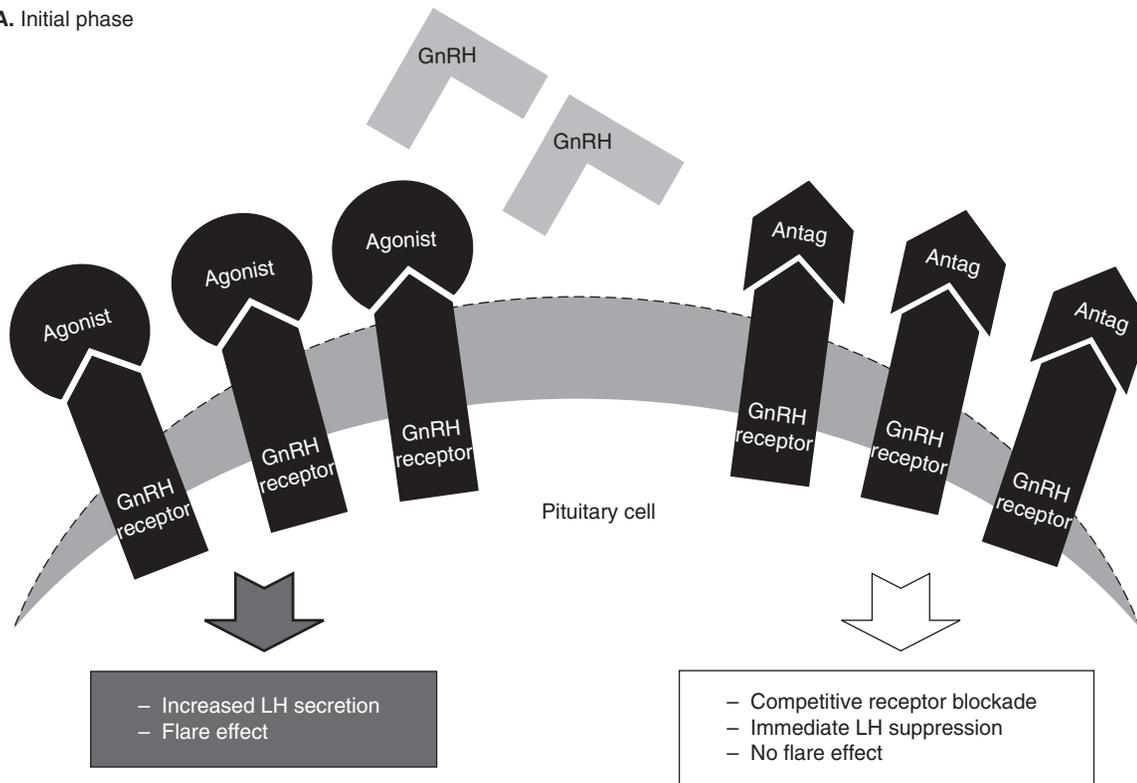
2.2 GnRH antagonists

GnRH antagonists offer a therapeutic alternative to agonists for pituitary suppression. GnRH antagonists achieve an immediate and dose-dependent suppression of LH by competing with native GnRH to bind to pituitary cell membrane receptors (Figure 1) [10]. Third-generation GnRH antagonists, including cetrorelix (Box 1) and ganirelix, are commercially available for use in ART [7].

The use of GnRH antagonists offers a number of advantages over agonists. GnRH antagonists produce a rapid and reversible suppression of LH and FSH, with no initial flare effect [10]. Therefore, prolonged pretreatment to achieve pituitary down-regulation is not required. As GnRH antagonists are usually administered only when there is a risk of premature LH surge (usually from day 5 to 7 of stimulation), symptoms of hypoenestrogenemia are rare [11]. Furthermore, lower total doses [3] and fewer days of exogenous gonadotropin stimulation are reported with co-treatment with antagonists than agonists [6]. Consequently, the total cycle duration is shorter and subsequent cycles can be initiated more quickly with antagonist than long agonist protocols [6]. Last, the pituitary remains responsive to GnRH stimulation during antagonist co-treatment, and so a bolus dose of agonist can be administered (instead of human chorionic gonadotropin; hCG) to trigger final oocyte maturation while concurrently preventing OHSS [12,13].

GnRH antagonists offer theoretical advantages over agonists for women with specific clinical conditions [14]. Up to a quarter of all patients undergoing *in vitro* fertilization (IVF) respond

A. Initial phase



B. Chronic phase

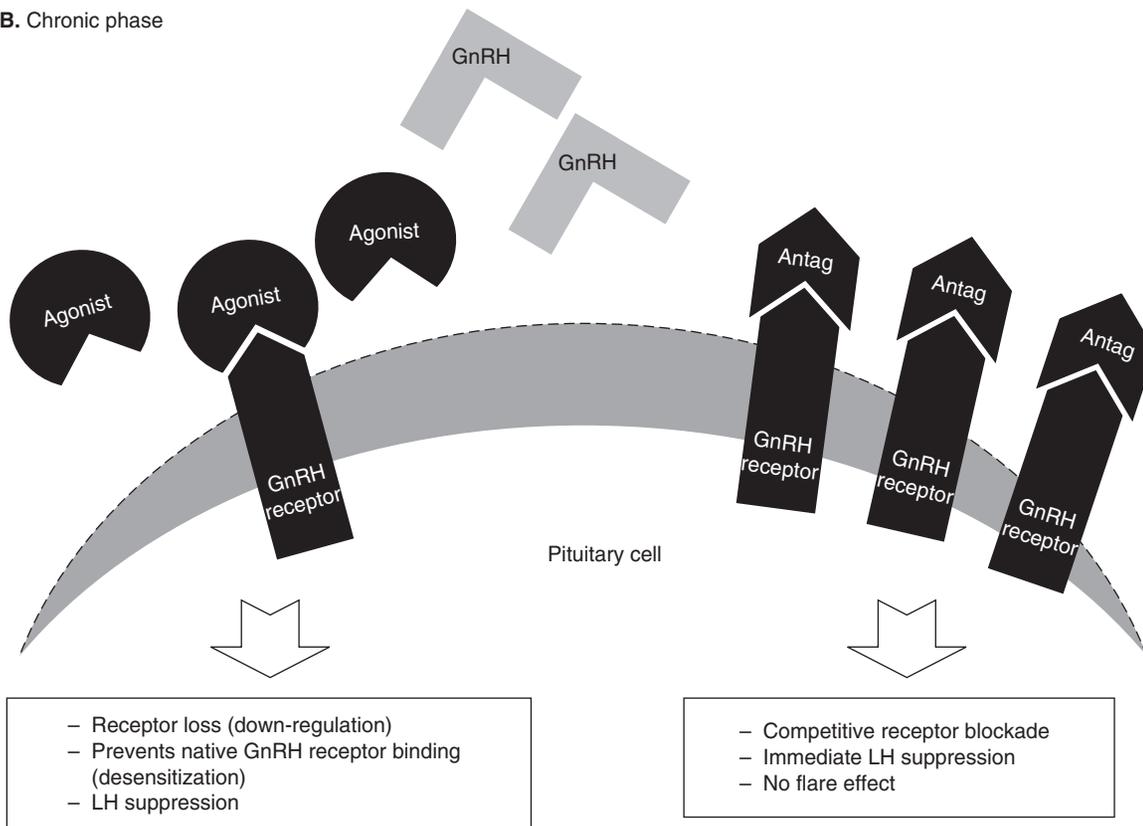


Figure 1. Mechanism of action of GnRH analogs.

Antag: Antagonist; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone.

poorly to gonadotropin stimulation [15]. A poor response may be defined as the development of an inadequate number of follicles following COS [16]. GnRH antagonist-based protocols could provide a useful option for patients with a (expected or proven) poor response to stimulation by avoiding prolonged pituitary suppression [2,7].

The use of GnRH antagonists may also be beneficial during COS for women at high risk of OHSS, such as those with polycystic ovary syndrome (PCOS) [17]. GnRH antagonist co-treatment leads to the development of fewer ovarian follicles than in long agonist protocols [6]. Moreover, there is early evidence to support a reduced incidence of moderate or severe OHSS in high-risk patients following GnRH agonist-induced final oocyte maturation and subsequent transfer of frozen-thawed oocytes [18].

PCOS is characterized by chronic ovulatory dysfunction and hypersecretion of LH. It has been suggested that the rapid and effective suppression of LH afforded by GnRH antagonists could be beneficial during cycles of ovulation induction (OI) for patients with PCOS [7]. Avoidance of an untimely LH surge could also help to schedule intrauterine insemination (IUI) following OI [19]. Indeed, a recent meta-analysis of data from six randomized controlled trials (RCTs) of OI, using recombinant human FSH (r-hFSH), followed by IUI indicates that, compared with conservative monitoring, GnRH antagonist co-treatment significantly increases the clinical pregnancy rate (odds ratio (OR) 1.56, 95% CI 1.05 – 2.33) [19]. Large studies are required to assess further the potential benefits of GnRH antagonists for women undergoing OI.

2.3 GnRH antagonists versus agonists: meta-analysis of clinical trial data

Key outcomes of four meta-analyses to compare pituitary suppression with GnRH antagonists or agonists are summarized in Table 1 [6,20-22]. The first analysis assessed the efficacy of GnRH antagonists versus standard long agonist protocols for COS in women undergoing ART [20]. Combined analysis of data from five RCTs showed a lower clinical pregnancy rate in patients who received a GnRH antagonist compared with a long agonist protocol (OR 0.79, 95% CI 0.63 – 0.99) [20].

A meta-analysis of data from eight comparative studies showed that the use of cetorelix resulted in clinical pregnancy rates comparable with those of agonists (OR 0.91, 95% CI 0.68 – 1.22), although ganirelix did not (OR 0.76, 95% CI 0.59 – 0.98) [21]. The authors also noted a significantly lower incidence of OHSS with the use of cetorelix (OR 0.23, 95% CI 0.10 – 0.54) compared with long agonist protocols [21], whereas the use of ganirelix or agonist co-treatment resulted in similar rates of OHSS (OR 1.13, 95% CI 0.24 – 5.31) [21].

A meta-analysis of data from 22 RCTs demonstrated no significant difference in live birth rates per randomized patient with the use of GnRH agonists or antagonists (OR 0.86, 95% CI 0.72 – 1.02). However, the relative risk of hospital admission because of OHSS was reduced by 54%

with antagonists compared with agonists (OR 0.46, 95% CI 0.26 – 0.82; $n = 7$) [22].

A subsequent meta-analysis of data from 27 RCTs showed significant differences in clinical pregnancy rates in patients treated with GnRH antagonist versus long agonist protocols (OR 0.83, 95% CI 0.72 – 0.95) [6]. However, the relative risk of severe OHSS was reduced by 39% (OR 0.60, 95% CI 0.40 – 0.88) and interventions to prevent OHSS were significantly less frequent (OR 0.43, 95% CI 0.20 – 0.92) with the use of GnRH antagonists than with agonists [6]. Furthermore, the amount of exogenous human menopausal gonadotropin (hMG) required for ovarian stimulation was significantly lower (in terms of the duration of treatment and number of ampoules administered; $p = 0.00001$ for both) with GnRH antagonist than long agonist protocols [6]. The authors concluded that GnRH antagonist protocols are short and simple and are associated with good clinical outcomes and a significant reduction in the incidence of severe OHSS versus standard agonist protocols [6]. However, it was noted that the lower pregnancy rate observed with GnRH antagonist co-treatment must be discussed with patients prior to treatment [6].

The methodology and outcomes of the meta-analyses have been heavily debated, and caution has been advised when interpreting the observed difference in pregnancy rates in some studies [7]. Confounding factors may include the differing study designs and limited clinical experience of physicians with GnRH antagonists [7]. Current evidence suggests that there is no clinically relevant difference in live birth rates achieved with GnRH agonists or antagonists [11,22].

3. Introduction to cetorelix

Cetorelix acetate (Cetrotide[®], Merck Serono S.A. - Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany) was developed in the early 1990s [23,24] and was the first GnRH antagonist to receive regulatory approval (in 1999 in the EU) for the inhibition of premature LH surges and ovulation in women undergoing COS. Cetorelix is now approved for this indication in more than 80 countries worldwide.

Cetorelix is provided as lyophilized powder (0.25 mg/1 mL or 3 mg/3 mL) with a shelf-life of 2 years [25,26]. Vials should be stored at $\leq 25^{\circ}\text{C}$ within the outer carton to protect the peptide from light [25,26]. The solution should be used immediately after reconstitution of the powder in water [25,26]. Cetorelix is administered by s.c. injection during the early to mid-follicular phase of an ART cycle and is suitable for self-administration by the patient [27].

Cetorelix can be used in multiple- or single-dose protocols [25,26]. In multiple-dose protocols, cetorelix 0.25 mg is administered on day 5 or 6 of gonadotropin stimulation and, thereafter, is injected daily until hCG administration. In a single-dose protocol, cetorelix 3 mg is injected when serum estradiol levels indicate an appropriate response to stimulation (usually between days 5 and 7). If hCG is not administered

Table 1. Key objectives and conclusions of four meta-analyses of data on the use of cetrorelix in COS.

Study	Objective	Findings
Al-Inany and Aboulghar [20]	To evaluate the efficacy of GnRH antagonists compared with standard GnRH long agonist protocols for COS	GnRH antagonist protocols are short and simple but associated with a lower pregnancy rate compared with long agonist protocols GnRH antagonist protocols may be improved further by developing more flexible regimens that consider individual patient characteristics
Ludwig <i>et al.</i> [21]	To evaluate if there is a reduction in the incidence of OHSS and/or a reduction in pregnancy rates with cetrorelix or ganirelix compared with long agonist protocols	Compared with a long agonist protocol, cetrorelix but not ganirelix, is associated with a: <ul style="list-style-type: none"> • Significantly lower incidence of OHSS • Similar pregnancy rate
Kolibianakis <i>et al.</i> [22]	To determine whether the choice of GnRH analog for pituitary suppression during COS affects live birth rate	GnRH agonists and antagonist protocols result in similar live birth rates (per randomized patient)
Al-Inany <i>et al.</i> [6]	To update the comparative evidence on the efficacy of GnRH antagonists versus standard long agonist protocols for COS	GnRH antagonist protocols are short and simple, and associated with good clinical outcomes Compared with GnRH agonists, antagonists are associated with a: <ul style="list-style-type: none"> • Significant reduction in the incidence of OHSS • Significantly lower consumption of gonadotropins The slightly lower pregnancy rates associated with GnRH antagonist compared with long agonist protocols must be discussed with patients prior to treatment

COS: Controlled ovarian stimulation; GnRH: Gonadotropin-releasing hormone; OHSS: Ovarian hyperstimulation syndrome.

within 4 days after cetrorelix 3 mg, daily doses of cetrorelix 0.25 mg are injected until hCG administration.

4. Chemistry

Cetrorelix is a decapeptide analog of native GnRH, with amino-acid substitutions at positions 1, 2, 3, 6, and 10 (Figure 2) [10]. Acetyl and amide groups at the C- and N-terminals provide stability and full antagonistic activity [24].

5. Pharmacodynamics

Cetrorelix is a high-affinity GnRH antagonist that competitively blocks binding of GnRH to pituitary cell receptors [28]. The binding affinity of cetrorelix for the GnRH receptor is ~ 20 times greater than that of native GnRH [24]. As demonstrated in preclinical rodent models, the dose-dependent antagonism of GnRH mediated by cetrorelix inhibits secretion of gonadotropins from the pituitary [23].

Cetrorelix has a far greater effect on serum levels of LH than FSH [24]. Serum levels of FSH are largely unaffected at the doses of cetrorelix used in COS [24]. However, immediate suppression of serum LH levels (by 80% of baseline levels) occurs within 24 h of a single s.c. injection of cetrorelix 3 mg [29,30]. Inhibition of the mid-cycle LH surge consequently delays ovulation [31,32]. Repeated treatment with cetrorelix causes sustained suppression of LH (9 days after last administration) but reversal of the effects is observed after cessation of therapy [29].

6. Pharmacokinetics and metabolism

Cetrorelix is rapidly absorbed after s.c. administration; in healthy women, maximal plasma concentrations occur within 1 – 2 h [33]. The mean absolute bioavailability of cetrorelix is ~ 85% after s.c. injection, and 86% of cetrorelix is protein-bound [27]. Cetrorelix has a plasma half-life of ~ 20 h, and at least 2 – 4% of the drug is excreted in urine and 5 – 10% in bile [27]. Cetrorelix is excreted unchanged in urine, but four peptide metabolites are also present in bile [27]. The effects of cetrorelix in cases of hepatic or renal impairment are yet to be determined [27].

7. Clinical efficacy

7.1 Phase II studies

The efficacy of cetrorelix for prevention of the premature LH surge was assessed in a number of Phase II exploratory and dose-finding studies [3,34-36].

An early Phase II study enrolled 20 women undergoing COS to receive treatment with cetrorelix at doses of 3 mg (n = 15) or 1 mg (n = 5) s.c. once daily from cycle day 7 until administration of hCG [3]. None of the women experienced an endogenous LH surge following treatment with cetrorelix (irrespective of the dose administered). Furthermore, the total gonadotropin dose requirement was ~ 50% of the standard dose administered with a long GnRH agonist protocol, and yet oocyte quality was reported to be comparable [3]. The results of a subsequent dose-finding study indicated that cetrorelix

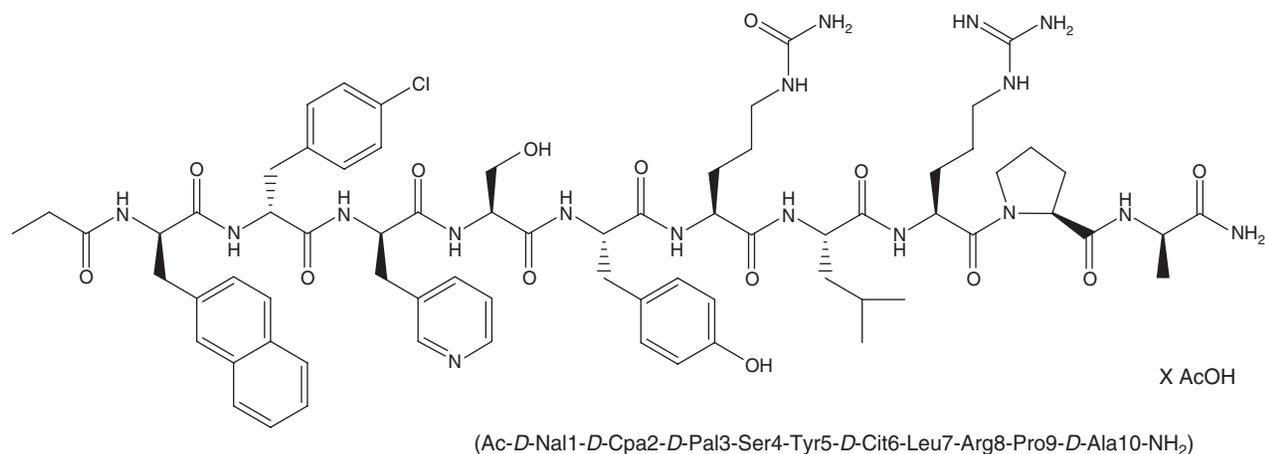


Figure 2. Structure of cetorelix [27].

at 0.25 mg s.c. once daily was adequate to prevent an endogenous LH surge in women undergoing COS [34].

One Phase II study was conducted to establish the optimum single-dose protocol in COS [35]. Of the 65 women who received cetorelix 3 or 2 mg s.c. on day 8 of the stimulation cycle, only 1 (in the 2 mg dose group) experienced an LH surge [35]. There were no differences in the magnitude of change in LH levels between groups, but the LH surge was suppressed for a shorter duration in the 2 mg group [35]. ART outcomes were similar in both groups [35].

7.2 Phase III studies

As a result of the promising Phase II data, cetorelix was investigated further in five prospective Phase III trials (Table 2) [37-41]. Two dosing regimens of cetorelix were evaluated: a multiple-dose protocol (0.25 mg s.c. once daily, starting on day 5 or 6 of gonadotropin stimulation) and a single-dose protocol (3 mg on day 7 of stimulation; Figure 3).

Data on the efficacy and safety of cetorelix versus GnRH agonist co-treatment for prevention of premature LH surges are available from two randomized, multi-center, Phase III clinical trials [37,38]. A randomized study of cetorelix 0.25 mg s.c. once daily ($n = 188$) versus buserelin (nasal spray; 0.15 mg four times daily; $n = 85$) in women aged up to 39 years was published in 2000 [37]. Pregnancy rates per started cycle were comparable between the cetorelix and buserelin groups (22.3 versus 25.9%, respectively). However, cetorelix was associated with the administration of significantly fewer hMG ampoules and fewer days of stimulation than buserelin ($p < 0.01$ for both). Cetorelix co-treatment also involved fewer days of pituitary suppression (5.7 versus 26.6, respectively; $p < 0.001$) and led to the development of fewer small follicles (11 – 14 mm in diameter) that are associated with an increased risk of OHSS than did buserelin (3.2 versus 4.3, respectively; $p = 0.02$) [37].

In another Phase III study, patients undergoing COS were randomized to co-treatment with cetorelix 3 mg s.c. once

daily ($n = 115$) or depot triptorelin 3.75 mg ($n = 39$) [38]. Although fewer oocytes were retrieved and the total number of embryos transferred was lower with cetorelix than depot triptorelin, similar clinical pregnancy rates were obtained in both treatment groups. The single-dose cetorelix protocol required a shorter duration of stimulation and administration of fewer ampoules of hMG.

Additional data are available from one uncontrolled, open-label study [39] and two randomized, single-center studies comparing the efficacy of cetorelix with buserelin or leuprolide acetate [40,41]. The findings of these studies were generally consistent with those of the multi-center Phase III trials, and showed that multiple- or single-dose protocols of cetorelix achieved similar clinical outcomes as did GnRH agonists (Table 2).

Two large Phase IIIb studies were subsequently conducted to compare the efficacy of cetorelix in multiple- ($n = 1066$) and single-dose ($n = 541$) protocols in routine clinical practice [5]. In these studies, multiple- and single-dose cetorelix protocols were associated with similar efficacy and safety profiles [5]. Although more oocytes were retrieved with single- than multiple-dose protocols (10.1 versus 9.0; $p = 0.005$), the total number of embryos obtained (IVF: 4.7 versus 4.7) and transferred (2.3 versus 2.5), and pregnancy rates per started cycle (24 and 23%, respectively) were similar using the two regimens [5].

Cetorelix was administered in combination with hMG in most clinical trials. However, limited experience suggests that cetorelix has similar efficacy when used with r-hFSH [11,13,42,43].

7.3 Experience in modified ART protocols

A number of studies have been conducted to evaluate the efficacy and safety of cetorelix in oral contraceptive (OC)-programmed stimulation cycles [42,44]. In a study of 182 patients who were randomized to receive an OC pretreatment cetorelix (0.25 mg s.c. a day) regimen or

Table 2. Key outcomes of five prospective, randomized Phase III clinical trials of cetrorelix for pituitary suppression in cycles of controlled ovarian stimulation.

	Albano et al. 2000 [37]	Olivennes et al. 2000 [38]	Felberbaum et al. 2000 [39]	Xavier et al. 2005 [41]	Hsieh et al. 2008 [40]*
Study design	Prospective, open-label, randomized, multi-center	Prospective, randomized, open-label, multi-center	Prospective, open-label, multinational	Prospective, randomized, open-label, single center	Prospective, open-label, randomized, single center
GnRH analog	Cetrorelix 0.25 mg (n = 188) Buserelin 0.6 mg (n = 85)	Cetrorelix 3 mg (n = 115) Triptorelin 3.75 mg (n = 39)	Cetrorelix 0.25 mg (n = 346)	Cetrorelix 0.25 mg (n = 66) Buserelin 0.6 mg (n = 65)	Cetrorelix 0.25 mg* (n = 86) LA 0.5 mg (n = 58)
Patients who experienced an LH surge, % [†]	1.6 0.0	0.0 2.8	0.9	NR	3.5 3.4
Mean serum estradiol levels on the day of hCG administration (s.d.), pg/mL	1625 (836)	1786 (808)	1544 (NR)	1269 (615)	1191 (330)
Mean number of oocytes (s.d.)	8.0 (4.9) [§]	9.2 (5.1)	NR	10.1 (4.6)	9.4 (5.5)
Mean number of embryos transferred (s.d.)	2.2 (0.6)	2.6 (0.9)	NR	2.6 (0.6)	7.9 (4.1)
Clinical pregnancy rate, %	22.3 (per started cycle)	22.6 (per patient who progressed to oocyte pick-up)	23.6 (per embryo transfer)	15.1 (per started cycle)	12.3 (4.5)
	25.9 (per started cycle)	28.2 (per patient who progressed to oocyte pick-up)		2.4 (0.6)	8.9 (2.7)
				16.9 (per started cycle)	NR
				NR	NR
				8.9 (2.7)	8.4 (2.5)
				NR	NR

*Clinical outcomes for additional doses of cetrorelix (0.15 and 0.2 mg) evaluated in the study were not included in the comparative analysis with LA.

[†]LH level > 10 U/L and progesterone level > 1 ng/L.

[§]Per patient with at least one fertilized oocyte.

GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; LA: Leuprolide acetate; LH: Luteinizing hormone; NR: Not reported.

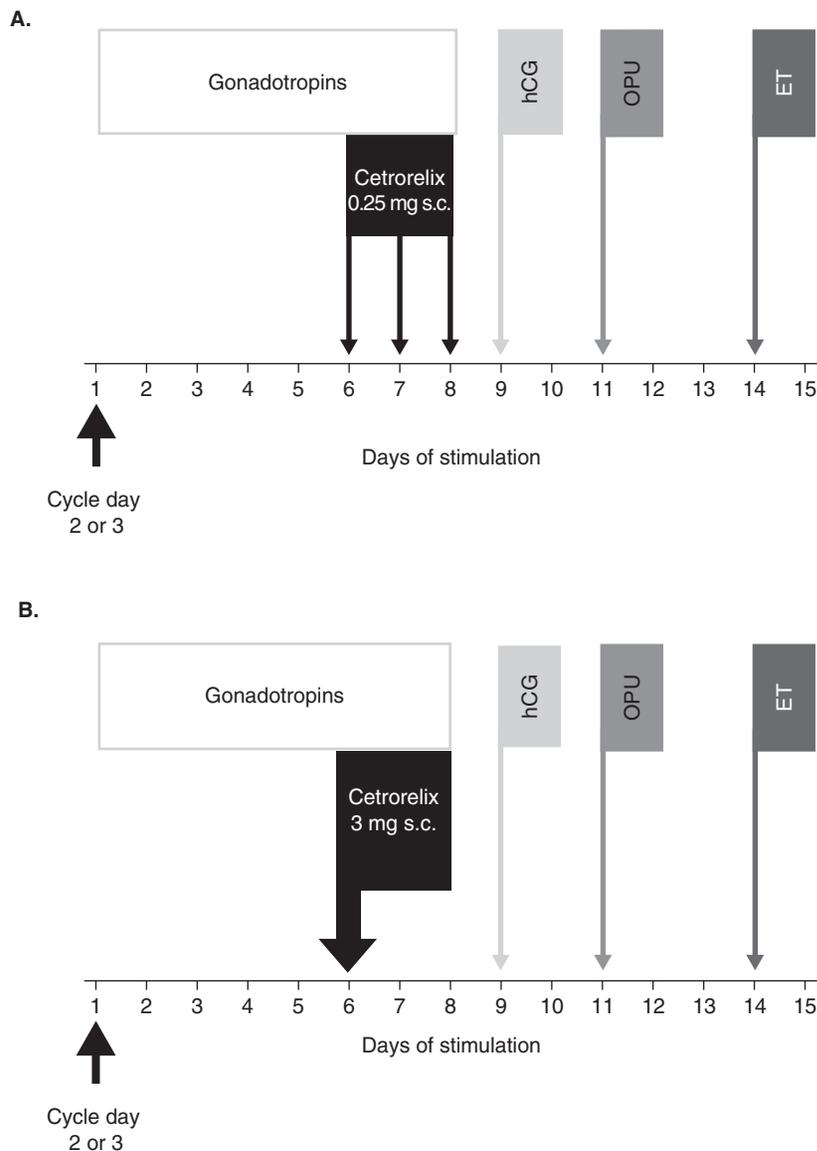


Figure 3. (A) Multiple- and **(B)** single-dose cetorelix protocols.

ET: Embryo transfer; hCG: Human chorionic gonadotropin; OPU: Oocyte pick-up; s.c.: Subcutaneous.

buserelin (500 µg for ≥ 10 days, and 200 µg thereafter), similar outcomes were reported in both groups, including the mean number of oocytes retrieved (11.4 with cetorelix versus 10.9 with buserelin) [42]. Body mass index was higher in the cetorelix group but this did not affect the treatment outcomes [42].

A randomized study of 185 infertile women receiving the combined OC pill for cycle programming showed similar efficacy of single-dose cetorelix (3 mg s.c.) and daily doses of ganirelix 0.25 mg in preventing premature LH surges (LH < 5 IU/L: 97.7 versus 96.6% of patients, respectively) and achieving a pregnancy (51.7 versus 48.9%, respectively) [44]. The single-dose cetorelix protocol required a significantly lower median number of injections than did ganirelix co-treatment

(1 versus 4 injections; $p < 0.001$), which is expected to confer convenience benefits for patients [44].

A prospective, randomized study of 120 women undergoing COS for ART was performed to identify the optimal starting dose of r-hFSH (follitropin alfa; GONAL-f[®], Merck Serono S.A. - Geneva) for COS for IVF or intracytoplasmic sperm injection when combined with cetorelix (0.25 mg daily from day 6 of stimulation) [43]. A significantly greater mean number of oocytes were obtained using a starting dose of r-hFSH 225 IU compared with 150 IU (11.0 versus 9.1; $p = 0.024$), although this was judged to be of minimal clinical significance [43]. The authors concluded that cetorelix simplifies ART treatment protocols and reduces the overall exposure to medication [43].

Early studies have also produced promising data on the use of cetrorelix (at single or multiple doses of 0.25, 0.5 or 1 mg) administered in the late follicular phase of natural or mild IVF cycles [45-47]. In a pilot study of 33 women who received cetrorelix (at a single dose of 0.5 or 1 mg) when plasma estradiol levels reached 100 – 150 pg/mL and a lead follicle of 12 – 14 mm in diameter was detected, only 4/44 natural cycles were cancelled and a pregnancy rate of 32% per embryo transfer was achieved [45].

7.4 Experience in special patient populations

Specific groups of patients may benefit most from pituitary suppression with cetrorelix, including women who respond poorly to gonadotropin stimulation or those at high risk of developing OHSS.

Data on pituitary suppression using cetrorelix compared with a GnRH agonist in patients with an expected or proven poor response to stimulation are available from four RCTs [48-51]. Comparable implantation (15.1 versus 11.4%, respectively) and clinical pregnancy rates (26.3 versus 22.2% per embryo transfer, respectively) were demonstrated in an early study of 48 poor responders who received OC pretreatment plus leuprolide acetate (40 µg s.c. once daily) or cetrorelix alone (0.25 mg once daily during the late follicular phase) [48]. Similarly, pregnancy and implantation rates did not differ when cetrorelix (alone or as co-treatment with clomiphene citrate plus r-hFSH or hMG) or a short GnRH agonist protocol was administered to 90 patients with proven poor response [51].

In a third randomized trial, 66 patients received cetrorelix (0.25 mg once daily starting on day 6 of stimulation) or busarelin (600 µg once daily starting in the mid-luteal phase of the previous cycle). The use of cetrorelix was associated with a higher mean number of embryos being transferred (2.32 versus 1.50; $p = 0.01$), although clinical pregnancy rates were not significantly different [49]. The most recently published study compared a flexible cetrorelix protocol (0.125 mg for 2 days and thereafter 0.25 mg once daily) with a short GnRH agonist regimen (triptorelin 0.1 mg s.c. once daily) in 133 women at risk of a poor response [50]. Pituitary suppression with cetrorelix resulted in a significantly higher mean number of metaphase II oocytes than did triptorelin (5.73 versus 4.64; $p < 0.05$) [50].

Data are available from four RCTs comparing down-regulation with cetrorelix or a GnRH agonist in patients with PCOS who received OC pretreatment [52-55]. A meta-analysis of data from these studies showed no significant differences in the number of oocytes retrieved or clinical pregnancy rate achieved with either cetrorelix or long GnRH agonist protocols in patients with PCOS [14]. However, multiple-dose cetrorelix resulted in a significantly shorter stimulation period than did long GnRH agonist protocols (OR -8.6, 95% CI -1.14 to -0.59; $p < 0.01$) [14].

There is evidence to support a significant reduction in the incidence of OHSS in high-risk populations with cetrorelix compared with agonist protocols. Data from a prospective,

multi-center, comparative study (using historical controls) suggest that cetrorelix may reduce the incidence of OHSS and, thus, the number of cancelled cycles among patients at high risk of an excessive response [56]. A meta-analysis of data from eight comparative studies demonstrated a significantly lower incidence of OHSS with the use of cetrorelix (OR 0.23, 95% CI 0.10 – 0.54) compared with long agonist protocols [21]. Whereas, the use of ganirelix or agonist co-treatment resulted in similar rates of OHSS (OR 1.13, 95% CI 0.24 – 5.31) [21].

Additional studies are required to evaluate prospectively the efficacy of cetrorelix with a GnRH agonist to trigger final oocyte maturation in high-risk patients [14].

8. Safety and tolerability

Given the pharmacologic and physiologic effects of GnRH antagonists, their use has been postulated to reduce the risk of adverse effects associated with long GnRH agonist protocols, such as hormone withdrawal symptoms and OHSS. Clinical evidence shows that cetrorelix (in multiple- or single-dose protocols) is generally well tolerated in women undergoing COS [27,38]. Hormone withdrawal symptoms such as tachycardia, hot flushes, headaches, vaginal bleeding, or decreased libido occur only rarely with cetrorelix [38].

Few systemic adverse events were reported (by at least 1%) among 949 patients aged 19 – 40 years who received multiple or single doses of cetrorelix (0.1 – 5 mg) in key clinical trials [27]. Overall, only 1.1% experienced headache, 1.3% nausea, and 3.5% moderate or severe OHSS [27]. While the risk of OHSS is not completely eliminated with the use of GnRH antagonists [57], the incidence of OHSS is significantly lower with the use of cetrorelix than GnRH agonists [37,38,56].

As observed with other s.c. administered GnRH analogs, mild and transient injection-site reactions are commonly observed with cetrorelix [25,26]. Hypersensitivity reactions are uncommon but cases have been reported [25,26]. No adverse effects have been detected on the health of children conceived from oocytes collected during cycles of COS in which cetrorelix was used for pituitary suppression [58].

Cetrorelix is contraindicated for use in patients who have experienced hypersensitivity reactions to cetrorelix, extrinsic peptide hormones or mannitol, or are pregnant, breast-feeding or postmenopausal, or have moderate or severe renal or hepatic impairment. Caution is advised for use in patients with hypersensitivity to GnRH; patients should be monitored carefully after the first injection [27].

9. Cetrorelix versus ganirelix

There are few comparative studies of cetrorelix versus ganirelix (the other available GnRH antagonist) co-treatment during ART [44]. Similar efficacy and safety profiles of cetrorelix 3 mg (single-dose protocol) and ganirelix 0.25 mg daily were demonstrated in a randomized study of 185 infertile women

who received OC pretreatment in a modified ART regimen [44]. However, administration of cetrorelix 3 mg required a significantly lower median number of injections than did ganirelix 0.25 mg (1 versus 4, respectively; $p < 0.001$) [44]. A single-dose protocol cannot be used with ganirelix as the drug is available only in a 0.25 mg dosage [21].

One meta-analysis that compared GnRH antagonists and long agonist protocols further analyzed specific data on cetrorelix and ganirelix [21]. The analysis showed that clinical pregnancy rates per cycle were similar with the use of cetrorelix or long agonist protocols (OR 0.91; 95% CI 0.68 – 1.22) [21]. However, the pregnancy rate with ganirelix co-treatment was significantly lower than in long agonist protocols (OR 0.76; 95% CI 0.59 – 0.98) [21]. The analysis also demonstrated a significantly lower incidence of OHSS with the use of cetrorelix than GnRH agonists (OR 0.23; 95% CI 0.10 – 0.54), whereas this was not the case for ganirelix (OR 1.13; 95% CI 0.24 – 5.31) [21]. Currently, both antagonists are used widely in clinical practice and additional RCTs are needed to clearly distinguish between them.

10. Conclusions

GnRH antagonists offer several advantages over agonists for pituitary suppression. Antagonists achieve rapid and reversible suppression of LH without a flare effect, which eliminates the need for prolonged pretreatment to achieve pituitary suppression. Furthermore, lower doses and fewer days of gonadotropin stimulation may be required and antagonists are less likely than GnRH agonists to cause hypoestrogenic symptoms.

Clinical trials have demonstrated that cetrorelix, in multiple- or single-dose protocols, is at least as effective as long GnRH agonist regimens for pituitary suppression. Unlike the other GnRH antagonist, ganirelix, the single-dose cetrorelix protocol further reduces the number of injections needed. Cetrorelix adds to the increasing number of treatment options available for use in ART, and may help to improve the convenience of therapy for women undergoing cycles of ART.

11. Expert opinion

GnRH antagonists have replaced agonists in most ART cycles worldwide. The use of cetrorelix for pituitary suppression in COS is associated with a favorable efficacy and safety profile. Clinical trials and meta-analyses have shown that GnRH antagonists are associated with similar live birth rates but a reduced treatment burden (in terms of cycle duration and side effects) and a lower risk of OHSS compared with long agonist protocols [11]. Therefore, GnRH antagonists, such as cetrorelix, are considered to represent patient-friendly ART treatments.

The use of GnRH antagonists has replaced agonists in many fresh IVF cycles but their introduction into routine clinical practice has been surprisingly slow [14,59]. This attitude may have resulted from early Phase III studies and small meta-analyses, which suggested that GnRH antagonists were

associated with lower clinical pregnancy rates than were long luteal agonist protocols [6,60].

Current evidence suggests that there is no clinically relevant difference in live birth rates with GnRH agonists or antagonists [11], and the apparent discrepancy in clinical pregnancy rates in early studies has been the subject of much debate. Indeed, it has been proposed that differences in study populations [61] and inadequate clinical experience with GnRH antagonists may have contributed to these outcomes [7]. However, it has also been suggested that GnRH antagonist co-treatment may adversely affect oocyte or embryo quality, or endometrial receptivity [62].

The results of a recent retrospective analysis of data on fresh intracytoplasmic sperm injection cycles from a single-center suggested a higher rate of early pregnancy loss (miscarriage before 12 weeks gestation) in women aged under 35 years who received cetrorelix compared with a GnRH agonist for pituitary suppression [63]. However, the investigators acknowledge that multiple factors, such as the etiology of infertility and ovarian response as measured by estradiol levels, could have affected the fate of implanted embryos in this study.

Oocyte donor programs provide an opportunity to evaluate in isolation the potential effects of GnRH antagonists on oocytes or the endometrium. Data from two such studies suggest that the quality of donor oocytes and resulting embryos are similar after GnRH agonist or antagonist co-treatment [64,65]. Moreover, significantly more metaphase II oocytes were obtained from women treated with cetrorelix 0.25 mg s.c. daily ($n = 51$) than a long leuprolide acetate protocol ($n = 90$) in a retrospective study of oocyte donation cycles [66].

The direct effect of GnRH antagonists on the endometrium was specifically evaluated in a prospective randomized trial, in which sibling oocytes from 49 donors were shared between two matched recipients [67]. Oocyte recipients were randomized to receive standard endometrial priming with estradiol and progesterone only ($n = 49$) or co-treatment with cetrorelix 0.25 mg/day ($n = 49$) [67]. Administration of cetrorelix during the proliferative phase had no effect on the implantation (24.4% without cetrorelix; 26.1% with cetrorelix) or overall pregnancy rates (59.2% without cetrorelix; 55.1% with cetrorelix) [67]. Furthermore, no association was found between serum cetrorelix levels on the day of r-hCG administration and clinical pregnancy outcome in a retrospective case-control study of 130 women who received cetrorelix 3 mg for COS in ART [68].

Conversely, the authors of a recent study who compared the outcomes of fresh and frozen ART cycles proposed a potentially deleterious effect of GnRH antagonists on the endometrium [69]. In this study, implantation and pregnancy rates were significantly higher in fresh ART cycles following GnRH agonist versus antagonist suppression [69]. However, implantation and pregnancy rates of frozen–thawed embryos created using GnRH antagonist were slightly higher than in the agonist group [69].

The association between changes in estradiol levels and clinical outcomes of GnRH antagonist cycles is unclear. In a recent prospective, observational study of 113 women in which cetrorelix 2.5 mg was administered when the leading follicle was 14 mm in diameter, serum estradiol levels increased in 45% of cycles, approached a plateau in 24.5% and declined in 30.2% [70]. No correlation was found between the serum estradiol pattern and clinical outcomes, including the number of oocytes retrieved, or implantation or clinical pregnancy rates [70]. Importantly, a decline in serum estradiol levels was not associated with adverse effects.

A wide variety of GnRH antagonist protocols have been proposed. Flexible dosing, which involves administration of antagonist according to follicular size, rather than the administration of fixed doses on pre-determined days of the menstrual cycle, may offer an alternative approach. A meta-analysis of data from four RCTs showed similar pregnancy rates following fixed or flexible GnRH antagonist co-treatment, and flexible protocols required the use of significantly fewer ampoules of GnRH antagonist (OR -1.2, 95% CI -1.26 to -1.15) and lower doses of r-hFSH (OR 95.5 IU, 95% CI 74.8 – 116.1) [71]. Nonetheless, administration of cetrorelix is still recommended to be started on day 5 or 6 of FSH administration.

Compared with GnRH agonist co-treatment, cetrorelix is expected to facilitate the use of simpler ART treatment regimens, lower total doses of gonadotropins, and shorter treatment cycles. Pituitary suppression with cetrorelix avoids most symptoms of hypoenestrogenism and the formation of ovarian cysts. GnRH antagonists also offer the possibility of cycle programming using OCs and enable the use of agonists instead of hCG to induce final oocyte maturation. Compared with GnRH agonists, antagonist IVF protocols

can be initiated more quickly and require fewer injections (~ 5 versus 25). Thus, the use of antagonists may be more suitable than agonists for use in frozen embryo transfers and oocyte donation programs, which now comprise a quarter of all ART cycles [72].

Patients undergoing ART are exposed to health risks and experience a substantial treatment burden and psychologic distress. Efforts have been made to devise simple and 'patient-friendly' treatment regimens [11]. The routine use of GnRH antagonists, such as cetrorelix, instead of agonists could help improve the ART experience. In view of the favorable efficacy, safety and tolerability profile of cetrorelix, GnRH antagonists should be considered as a first-line therapeutic option in modern, patient-friendly ART treatment.

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Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007;22:1506-12
2. Hayden C. GnRH analogues: applications in assisted reproductive techniques. *Eur J Endocrinol* 2008;159(Suppl 1):S17-25
3. Diedrich K, Diedrich C, Santos E, et al. Suppression of the endogenous luteinizing hormone surge by the gonadotrophin-releasing hormone antagonist Cetrorelix during ovarian stimulation. *Hum Reprod* 1994;9:788-91
4. Qublan HS, Amarín Z, Tahat YA, et al. Ovarian cyst formation following GnRH agonist administration in IVF cycles: incidence and impact. *Hum Reprod* 2006;21:640-4
5. Olivennes F, Diedrich K, Frydman R, et al. Safety and efficacy of a 3 mg dose of the GnRH antagonist cetrorelix in preventing premature LH surges: report of two large multicentre, multinational, phase IIIb clinical experiences. *Reprod Biomed Online* 2003;6:432-8
6. Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review. *Reprod Biomed Online* 2007;14:640-9
 - **A meta-analysis.**
7. Olivennes F, Cunha-Filho JS, Fanchin R, et al. The use of GnRH antagonists in ovarian stimulation. *Hum Reprod Update* 2002;8:279-90
8. Broekmans FJ, Hompes PG, Lambalk CB, et al. Short term pituitary desensitization: effects of different doses of the gonadotrophin-releasing hormone agonist triptorelin. *Hum Reprod* 1996;11:55-60
9. Holland FJ, Fishman L, Costigan DC, et al. Pharmacokinetic characteristics of the gonadotrophin-releasing hormone analog D-Ser(TBU)-6EA-10luteinizing hormone-releasing hormone (buserelin) after subcutaneous and intranasal administration in children with central precocious puberty. *J Clin Endocrinol Metab* 1986;63:1065-70
10. Reissmann T, Felberbaum R, Diedrich K, et al. Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of infertility: an overview. *Hum Reprod* 1995;10:1974-81
11. Devroey P, Aboulghar M, Garcia-Velasco J, et al. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. *Hum Reprod* 2009;24:764-74
 - **An expert opinion and review of the literature.**
12. Bodri D, Guillen JJ, Galindo A, et al. Triggering with human chorionic gonadotropin or a gonadotropin-releasing hormone agonist in gonadotropin-releasing hormone antagonist-treated oocyte donor cycles: findings of a large retrospective cohort study. *Fertil Steril* 2009;91:365-71
13. Griesinger G, Diedrich K, Devroey P, Kolibianakis EM. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. *Hum Reprod Update* 2006;12:159-68
14. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. *Reprod Biomed Online* 2006;13:628-38
15. Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. *Br J Obstet Gynaecol* 1997;104:521-7
16. Sunkara SK, Coomarasamy A, Khalaf Y, Braude P. A three-arm randomised controlled trial comparing Gonadotrophin Releasing Hormone (GnRH) agonist long regimen versus GnRH agonist short regimen versus GnRH antagonist regimen in women with a history of poor ovarian response undergoing in vitro fertilisation (IVF) treatment: Poor responders intervention trial (PRINT). *Reprod Health* 2007;4:12
17. Lainas TG, Sfontouris IA, Zorzovilis IZ, et al. Management of severe OHSS using GnRH antagonist and blastocyst cryopreservation in PCOS patients treated with long protocol. *Reprod Biomed Online* 2009;18:15-20
18. Griesinger G, von Otte S, Schroer A, et al. Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective, observational proof-of-concept study. *Hum Reprod* 2007;22:1348-52
19. Kosmas IP, Tatsioni A, Kolibianakis EM, et al. Effects and clinical significance of GnRH antagonist administration for IUI timing in FSH superovulated cycles: a meta-analysis. *Fertil Steril* 2008;90:367-72
 - **A meta-analysis.**
20. Al-Inany H, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. *Cochrane Database Syst Rev* 2001;4:CD001750
 - **A meta-analysis.**
21. Ludwig M, Katalinic A, Diedrich K. Use of GnRH antagonists in ovarian stimulation for ART compared to the long protocol: a meta-analysis. *Arch Gynecol Obstet* 2001;265:175-82
 - **A meta-analysis.**
22. Kolibianakis EM, Collins J, Tarlatzis BC, et al. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. *Hum Reprod Update* 2006;12:651-71
 - **A meta-analysis.**
23. Bokser L, Bajusz S, Groot K, Schally AV. Prolonged inhibition of luteinizing hormone and testosterone levels in male rats with the luteinizing hormone-releasing hormone antagonist SB-75. *Proc Natl Acad Sci USA* 1990;87:7100-4
24. Reissmann T, Schally AV, Bouchard P, et al. The LHRH antagonist cetrorelix: a review. *Hum Reprod Update* 2000;6:322-31
25. Cetrotide 0.25 mg Summary of Product Characteristics. Available from: <http://emc.medicines.org.uk/medicine/8744/SPC/Cetrotide+0.25+mg/> [Accessed 28 May 2009]
26. Cetrotide 3 mg Summary of Product Characteristics. Available from: <http://emc.medicines.org.uk/medicine/8745/SPC/Cetrotide+3+mg/> [Accessed 28 May 2009]
27. Cetrotide Package Insert. Cetrotide 0.25 mg and 3 mg (cetrorelix acetate for injection). USA: EMD Serono, Inc., 2004
28. Fekete M, Bajusz S, Groot K, et al. Comparison of different agonists and antagonists of luteinizing

- hormone-releasing hormone for receptor-binding ability to rat pituitary and human breast cancer membranes. *Endocrinology* 1989;124:946-55
29. Sommer L, Zanger K, Dyong T, et al. Seven-day administration of the gonadotropin-releasing hormone antagonist Cetrorelix in normal cycling women. *Eur J Endocrinol* 1994;131:280-5
 30. Pechstein B, Nagaraja NV, Hermann R, et al. Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers. *J Clin Pharmacol* 2000;40:266-74
 31. Bokser L, Srkalovic G, Szepeshazi K, Schally AV. Recovery of pituitary-gonadal function in male and female rats after prolonged administration of a potent antagonist of luteinizing hormone-releasing hormone (SB-75). *Neuroendocrinology* 1991;54:136-45
 32. Ayalon D, Farhi Y, Comaru-Schally AM, et al. Inhibitory effect of a highly potent antagonist of LH releasing hormone (SB-75) on the pituitary gonadal axis in the intact and castrated rat. *Neuroendocrinology* 1993;58:153-9
 33. Engel J, Rieger L, Dietl J, Honig A. The GnRH antagonist cetrorelix: established indications and future potential. *Exp Rev Obstet Gynecol* 2007;2:431-40
 34. Albano C, Smitz J, Camus M, et al. Comparison of different doses of gonadotropin-releasing hormone antagonist Cetrorelix during controlled ovarian hyperstimulation. *Fertil Steril* 1997;67:917-22
 35. Olivennes F, Alvarez S, Bouchard P, et al. The use of a GnRH antagonist (Cetrorelix) in a single dose protocol in IVF-embryo transfer: a dose finding study of 3 versus 2 mg. *Hum Reprod* 1998;13:2411-4
 36. Felberbaum R, Reissmann T, Kupker W, et al. Hormone profiles under ovarian stimulation with human menopausal gonadotropin (hMG) and concomitant administration of the gonadotropin releasing hormone (GnRH)-antagonist Cetrorelix at different dosages. *J Assist Reprod Genet* 1996;13:216-22
 37. Albano C, Felberbaum RE, Smitz J, et al. Ovarian stimulation with HMG: results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin. *European Cetrorelix Study Group. Hum Reprod* 2000;15:526-31
 38. Olivennes F, Belaisch-Allart J, Empeire JC, et al. Prospective, randomized, controlled study of in vitro fertilization-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (cetrorelix) or a depot formula of an LH-RH agonist (triptorelin). *Fertil Steril* 2000;73:314-20
 39. Felberbaum RE, Albano C, Ludwig M, et al. Ovarian stimulation for assisted reproduction with HMG and concomitant midcycle administration of the GnRH antagonist cetrorelix according to the multiple dose protocol: a prospective uncontrolled phase III study. *Hum Reprod* 2000;15:1015-20
 40. Hsieh YY, Chang CC, Tsai HD. Comparisons of different dosages of gonadotropin-releasing hormone (GnRH) antagonist, short-acting form and single, half-dose, long-acting form of GnRH agonist during controlled ovarian hyperstimulation and in vitro fertilization. *Taiwan J Obstet Gynecol* 2008;47:66-74
 41. Xavier P, Gamboa C, Calejo L, et al. A randomised study of GnRH antagonist (cetrorelix) versus agonist (busereline) for controlled ovarian stimulation: effect on safety and efficacy. *Eur J Obstet Gynecol Reprod Biol* 2005;120:185-9
 42. Huirne JA, Hugues JN, Pirard C, et al. Cetrorelix in an oral contraceptive-pretreated stimulation cycle compared with buserelin in IVF/ICSI patients treated with r-hFSH: a randomized, multicentre, phase IIIb study. *Hum Reprod* 2006;21:1408-15
 43. Wikland M, Bergh C, Borg K, et al. A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI. *Hum Reprod* 2001;16:1676-81
 44. Wilcox J, Potter D, Moore M, et al. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. *Fertil Steril* 2005;84:108-17
 - **An RCT comparing the two clinically available antagonists.**
 45. Rongjeres-Bertrand C, Olivennes F, Righini C, et al. Revival of the natural cycles in in-vitro fertilization with the use of a new gonadotrophin-releasing hormone antagonist (Cetrorelix): a pilot study with minimal stimulation. *Hum Reprod* 1999;14:683-8
 - **Minimal stimulation study.**
 46. Pelinck MJ, Vogel NE, Hoek A, et al. Minimal stimulation IVF with late follicular phase administration of the GnRH antagonist cetrorelix and concomitant substitution with recombinant FSH: a pilot study. *Hum Reprod* 2005;20:642-8
 - **Minimal stimulation study.**
 47. Pelinck MJ, Vogel NE, Arts EG, et al. Cumulative pregnancy rates after a maximum of nine cycles of modified natural cycle IVF and analysis of patient drop-out: a cohort study. *Hum Reprod* 2007;22:2463-70
 - **Minimal stimulation study.**
 48. Akman MA, Erden HF, Tosun SB, et al. Comparison of agonistic flare-up-protocol and antagonistic multiple dose protocol in ovarian stimulation of poor responders: results of a prospective randomized trial. *Hum Reprod* 2001;16:868-70
 49. Cheung LP, Lam PM, Lok IH, et al. GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial. *Hum Reprod* 2005;20:616-21
 50. De Placido G, Mollo A, Clarizia R, et al. Gonadotropin-releasing hormone (GnRH) antagonist plus recombinant luteinizing hormone vs. a standard GnRH agonist short protocol in patients at risk for poor ovarian response. *Fertil Steril* 2006;85:247-50
 51. Martínez F, Coroleu B, Marqués L, et al. Comparison of "Short Protocol" versus "Antagonists" with or without Clomiphene Citrate for stimulation in IVF of patients with "low response". *Revista Iberoamericana de Fertilidad (in Spanish with English abstract)* 2003;20:355-60
 52. Hwang JL, Seow KM, Lin YH, et al. Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study. *Hum Reprod* 2004;19:1993-2000

53. Bahceci M, Ulug U, Ben-Shlomo I, et al. Use of a GnRH antagonist in controlled ovarian hyperstimulation for assisted conception in women with polycystic ovary disease: a randomized, prospective, pilot study. *J Reprod Med* 2005;50:84-90
54. Kim C-H, Lee Y-J, Hong S-H, et al. Efficacy of a GnRH antagonist during early and late controlled ovarian hyperstimulation period in women with polycystic ovary syndrome undergoing IVF-ET. *Hum Reprod* 2004;19(Suppl 1):i104-5
55. Ashrafi M, Mohammadzadeh A, Ezabadi Z, Baghestani AR. A comparative study of GnRH-ant and GnRH-ag protocols in IVF-ICSI in PCOD patients. *Iranian J Reprod Med* 2005;3:14-18
56. Ragni G, Vegetti W, Riccaboni A, et al. Comparison of GnRH agonists and antagonists in assisted reproduction cycles of patients at high risk of ovarian hyperstimulation syndrome. *Hum Reprod* 2005;20:2421-5
57. Papanikolaou EG, Pozzobon C, Kolibianakis EM, et al. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. *Fertil Steril* 2006;85:112-20
58. Ludwig M, Katalinic A, Felberbaum RE, Diedrich K. Safety aspects of gonadotrophin-releasing hormone antagonists in ovarian stimulation procedures: ovarian hyperstimulation syndrome and health of children born. *Reprod Biomed Online* 2002;5(Suppl 1):61-7
59. Fauser BC, Devroey P. Why is the clinical acceptance of gonadotropin-releasing hormone antagonist cotreatment during ovarian hyperstimulation for in vitro fertilization so slow? *Fertil Steril* 2005;83:1607-11
60. Al-Inany H, Aboulghar M. GnRH antagonists in assisted conception: a Cochrane Review. *Hum Reprod* 2002;17:874-85
- **A meta-analysis.**
61. Griesinger G, Felberbaum R, Diedrich K. GnRH antagonists in ovarian stimulation: a treatment regimen of clinicians' second choice? Data from the German national IVF registry. *Hum Reprod* 2005;20:2373-5
62. Rackow BW, Kliman HJ, Taylor HS. GnRH antagonists may affect endometrial receptivity. *Fertil Steril* 2008;89:1234-9
63. Bahceci M, Ulug U, Sismanoglu A, et al. Early pregnancy loss rates were different among singleton gestations conceived by ICSI using GnRH agonist and antagonist. *J Assist Reprod Genet* 2009;26:227-9
64. Prapas N, Prapas Y, Panagiotidis Y, et al. GnRH agonist versus GnRH antagonist in oocyte donation cycles: a prospective randomized study. *Hum Reprod* 2005;20:1516-20
- **Demonstrated that the antagonist does not adversely affect the embryos.**
65. Vlahos NE, Bankowski BJ, Zacur HA, et al. An oocyte donation protocol using the GnRH antagonist ganirelix acetate, does not compromise embryo quality and is associated with high pregnancy rates. *Arch Gynecol Obstet* 2005;272:1-6
- **Demonstrated that the antagonist does not adversely affect the embryos.**
66. Saucedo de la Llata E, Moraga Sanchez MR, Batiza RV, et al. Comparison of GnRH agonists and antagonists in an ovular donation program. *Ginecol Obstet Mex* (in Spanish with English abstract) 2004;72:53-6
67. Prapas N, Tavaniotou A, Panagiotidis Y, et al. GnRH antagonists and endometrial receptivity in oocyte recipients: a prospective randomized trial. *Reprod Biomed Online* 2009;18:276-81
- **Demonstrated that the antagonist does not adversely affect the embryos.**
68. Bukulmez O, Carr BR, Doody KM, Doody KJ. Serum cetrorelix concentrations do not affect clinical pregnancy outcome in assisted reproduction. *Fertil Steril* 2008;89:74-83
69. Bahceci M, Ulug U, Erden HF, et al. Frozen-thawed cleavage-stage embryo transfer cycles after previous GnRH agonist or antagonist stimulation. *Reprod Biomed Online* 2009;18:67-72
70. Lin YH, Seow KM, Chen HJ, et al. Impact of estradiol patterns in clomiphene citrate/human menopausal gonadotropin/cetrorelix protocol. *Gynecol Endocrinol* 2007;23:45-9
71. Al-Inany H, Aboulghar MA, Mansour RT, Serour GI. Optimizing GnRH antagonist administration: meta-analysis of fixed versus flexible protocol. *Reprod Biomed Online* 2005;10:567-70
- **A meta-analysis.**
72. Tur-Kaspa I, Cohen A, Tkachenko N, et al. GnRH antagonist (Cetrorelix) instead of agonist to prepare recipients for embryo transfer: a prospective, randomized, controlled trial. *Fertil Steril* 2008;90:S382
- **The first to suggest antagonist for FET and demonstrated that the antagonist does not adversely affect the endometrium.**

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