Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 6

GnRH antagonist in assisted reproduction
Cochrane systematic review

Hesham Al-Inany, Mohamed A Aboulghar

Abstract

Objectives: To compare the efficacy of gonadotrophin-releasing hormone (GnRH) antagonists with the standard long protocol of GnRH agonists for controlled ovarian hyperstimulation in assisted conception.

Search strategy: Search strategies included on-line searching of the MEDLINE and EMBASE databases and the Cochrane Menstrual Disorders and Subfertility Group's Specialised Register from 1982 to 2001, and hand searching of bibliographies of relevant publications and reviews, and abstracts of scientific meetings.

Selection criteria: Only randomised controlled studies comparing different protocols of GnRH antagonists with GnRH agonists in assisted conception cycles were included.

Data collection & analysis: Data were extracted into 2 x 2 tables. For the primary outcome, prevention of premature LH surge and clinical pregnancy per woman randomised, the overall common odds ratio (OR) and the risk difference with 95% confidence interval (C.I.) were calculated after verifying the presence of homogeneity of treatment effect across all trials. Secondary outcomes considered were number of oocytes retrieved, clinical pregnancy per oocyte retrieval and per embryo transfer, spontaneous abortion, incidence of severe ovarian hyperstimulation syndrome and the amount of gonadotrophins used. Where relevant data were missing or unclear, the authors have been consulted.

Main results: Five trials comparing the new fixed protocol of GnRH antagonist to the long protocol of GnRH agonist fulfilled the inclusion criteria and were included. In four studies, the multiple low-dose (0.25 mg) antagonist regimen was applied and, in one study, the single high-dose (3 mg) antagonist regimen was investigated. In all trials, reference treatment included a long protocol of GnRHa (buserelin, leuprorelin or triptorelin) starting in the mid-luteal phase of the preceding cycle. In comparison to the long protocol of GnRHa, the overall OR for the prevention of premature LH surges was 1.76 (95% C.I. 0.75-4.16), which is not statistically significant. There was a significantly fewer clinical pregnancies in those treated with GnRH antagonists (OR 95% C.I. 0.62-0.97). The absolute treatment effect (ATE) was calculated to be 5%. The number needed to treat (NNT) was 20. There was no statistically significant reduction in incidence of severe ovarian hyperstimulation syndrome between the two regimens (RR 0.51 (95% C.I. 0.22, 1.18).
Conclusion: The new fixed GnRH antagonist protocol (i.e. with antagonist start fixed on day 6 of gonadotrophin stimulation) is a short and simple protocol with good clinical outcome but the lower pregnancy rate compared to the GnRH agonist long protocol and the non significant difference between both protocols regarding prevention of premature LH surge and prevention of severe ovarian hyperstimulation syndrome necessitates counseling subfertile couples before recommending change from GnRH agonist to antagonist. The clinical outcome may be further improved by developing more flexible antagonist regimens taking into account individual patient characteristics. The GnRH antagonist flexible regimen should be the area of research in the near future.

Introduction

Induction of ovulation is one of the major advances in the treatment of subfertility in the second half of the 20th century. One aspect of ovulation induction that requires attention is the occurrence of an LH surge which may occur prematurely before the leading follicle reaches the optimum diameter for triggering ovulation by human chorionic gonadotrophin (hCG) injection. Such premature LH surge prevents effective induction of multiple follicular maturation for in-vitro fertilisation (IVF) in a significant number of women (1). Gonadotrophin-releasing hormone agonists (GnRHa) have played an important role in reducing the incidence of premature LH surges by reversibly blocking pituitary gonadotrophin secretion. As a result, the rate of cancellation of assisted conception cycles was decreased and pregnancy rates were increased(2,3). However, the use of GnRH agonists is not without disadvantages. The prolonged protocol of GnRH agonists that proved to be the most efficacious (4) needs 2 to 3 weeks for desensitization with relatively high costs due to increased requirement of gonadotrophin injections and increased need for hormonal and ultrasonographic measurements (5).

Gonadotrophin-releasing hormone antagonists have emerged as an alternative in preventing premature LH surges. In comparison with the GnRH agonists, the pharmacological mechanism by which GnRH antagonists suppress the release of gonadotrophins is completely different. While the agonists act on chronic administration through down-regulation of receptors and desensitisation of the gonadotrophic cells, the antagonists bind competitively to the receptors and thereby prevent the endogenous GnRH
from exerting its stimulatory effects on the pituitary cells. The competitive blockade of the receptors leads to an immediate arrest of gonadotrophin secretion (1). This mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonist. This antagonistic effect is highly dose-dependent in contrast with the agonists (6). While the first generation of GnRH antagonists showed allergic side-effects due to an induced histamine release, which hampered the clinical development of these compounds, third generation GnRH antagonists such as ganirelix (NV Organon, Oss, The Netherlands) or cetorelix (ASTA-Medica, Frankfurt am Main, Germany) have solved these problems and have recently been approved for clinical use (5).

Applying GnRH antagonists for ovulation induction in assisted conception will result in a dramatic reduction in the duration of GnRH analogue treatment and reduce the amount of gonadotrophin needed for stimulation. Other potential benefits include a lower risk for developing severe OHSS and avoiding estrogen deprivation symptoms (e.g. hot flushes, sleep disturbances, headache) as frequently observed in the pre-stimulation phase of a long protocol. Whether the previously mentioned benefits justify a change in routine treatment from the standard long GnRHa protocol to the newly designed GnRH antagonist regimen depends on whether the clinical outcome using these protocols is equivalent. The present systematic review aims at determining the efficacy of the fixed GnRH antagonist regimen (i.e. with fixed start on day 6 of gonadotrophin stimulation) and the standard long GnRHa protocol in patients undergoing controlled ovarian hyperstimulation for assisted reproduction techniques (ART).

Objectives

To compare the efficacy of gonadotrophin-releasing hormone (GnRH) antagonists and GnRH agonist administration for controlled ovarian hyperstimulation in assisted conception.

Criteria for considering studies for this review

Types of studies

Only randomised controlled studies were included in this review comparing different protocols of GnRH antagonists with GnRH agonists in assisted conception cycles.
Types of participants

Subfertile couples undergoing ovulation induction as part of an assisted reproductive program using GnRH antagonists for the prevention of premature LH surges. The following characteristics of the participants were considered: age of the woman; duration of subfertility; semen analysis results, ovulatory status confirmed with luteal progesterone (P) or sonographic evidence of ovulation; tubal patency.

Types of interventions

Pituitary suppression with GnRH antagonist or GnRHa together with ovarian stimulation with recombinant or urinary human follicle stimulating hormone (hFSH) and/or human menopausal gonadotropin (hMG) as part of an assisted reproduction technique.

Types of outcome measures

Primary outcomes:

- prevention of premature LH surge-pregnancy rate per woman
- pregnancy rate per cycle as determined by serum B-hCG and ultrasound examination for fetal heart activity

Secondary outcomes:

- number of oocyte retrieved per cycle
- pregnancy rate per oocyte retrieval
- pregnancy rate per embryo transfer
- spontaneous miscarriage rate
- E2 level on day of hCG
- duration of GnRH analogue treatment
- amount of gonadotrophins used
- incidence of ovarian hyperstimulation syndrome
- cost effectiveness as determined by the amount of gonadotrophin units used and cost /pregnancy
Search strategy for identification of studies

Search strategy for identification of studies:

1. The Cochrane Menstrual Disorders and Subfertility Review Group specialised register of controlled trials was searched using the key-words: gonadotrophin-releasing hormone antagonists - gonadotrophin-releasing hormone agonists - controlled ovarian hyperstimulation

2. MEDLINE database using the same key-words (MeSH words)

3. EMBASE database using the same key-words

4. Handsearching the reference lists of included studies


6. Contacting pharmaceutical industries in view of possibility of prospective registration of trials. When important information was lacking from the original publications the authors were contacted.
Methods of the review

The present systematic review was done in a prospective manner. The title was registered in 1998 and the protocol was released in 1999 before the results of any RCT was published. This allowed us to have prospective application of selection criteria and a priori statements of intended analyses to be made before the results of individual trials were known.

Included trials data were processed as described in the Cochrane Handbook. The quality of all selected studies were assessed and evaluated for methodological quality and appropriateness for inclusion without consideration of their results. The studies were analysed for the following quality criteria and methodological details:

Trial Characteristics

- Study design.
- Method of randomization.
- Multi-centre or single-centre design.
- Presence or absence of blinding to treatment allocation.
- Number of patients randomised, excluded or lost to follow up.
- Whether an "intention to treat" analysis was done.
- The presence of a power calculation.
- Duration, timing and location of the study.
- Sources of any funding.
- Characteristics of the Study Participants
- Cause and duration of pre-existing subfertility
- Age of the woman
- Body mass index (BMI)
- Number of previous IVF-ET cycles.

Interventions used

- Method of ovarian hyperstimulation
- Method of GnRH antagonists and agonists administration: timing, route, duration and dose
- Amount of gonadotrophin needed for stimulation

Outcomes:

- Number of oocytes retrieved per cycle
- Success rate (pregnancy / woman, pregnancy, cycle) as determined by serum B-HCG and ultrasound examination for fetal heart activity.
  - pregnancy rate per embryo transfer
- spontaneous miscarriage rate
- E2 level on day of hCG (as a risk factor for ovarian hyperstimulation syndrome (OHSS)
- duration of GnRH analogue treatment
- amount of gonadotrophins used
- Incidence of ovarian hyperstimulation syndrome (OHSS) (detected by clinical grading of OHSS, laboratory investigations as haematocrite, haemoglobin, renal functions and imaging techniques as ovarian and abdominal ultrasound and chest X-ray)
- Number of cycle cancellation
- Cost effectiveness (as determined by cost of medications, cost per pregnancy, cost of complications as severe OHSS)

All assessments of the quality of trials and data extraction were performed independently by two reviewers (HA and MA) using forms designed according to Cochrane guidelines. Additional information on trial methodology and/or actual original trial data were sought from the authors of trials which appeared to meet the eligibility criteria but had aspects of methodology that were unclear, or where the data was in a form unsuitable for meta-analysis. Authors from the five trials were contacted, to request additional information and/or data, and response was obtained from the two sponsoring pharmaceutical companies (Organon, Asta-Medica). Subgroup analysis was done to check the stability of the results reached by pooling data of all studies in general especially that the two drugs tested (cetrorelix and ganerelrix) although close in their chemical structure but are not identical. Also, subgroup analysis according to the regimen of administration was done.

Heterogeneity between the results of different studies were examined by inspecting the scatter in the data points and the overlap in their confidence intervals and more formally by
checking results of chi-square tests. It was planned to look at the possible contribution of differences in trial design to any heterogeneity identified in this manner. Where possible the outcomes were pooled statistically.

The dichotomous data results for each study were expressed as an odds ratio with 95% confidence intervals. These results were combined for meta-analysis with RevMan software (using the Peto-modified Mantel-Haenszel method). Relative risk or absolute risk difference were presented where appropriate.

The review will be updated whenever new randomised controlled trials are published or when a new regimen for GnRH antagonist is applied.

**Description of studies**

Please see the table of included studies for features of the five trials included in the analysis

Five trials were identified to meet our inclusion criteria (7-11). In the first two trials, the GnRH antagonist cetrorelix was applied (sponsor Asta-Medica whereas the remaining three trials the efficacy and safety of the GnRH antagonist ganirelix was investigated by Organon.

In these trials, a fixed protocol of GnRH antagonist (GnRH antagonist was given in a fixed day of the cycle ) was compared to the long protocol GnRH agonist. Olivennes 2000 used the single high dose regimen (3mg) while the other studies used the multiple low dose(0.25mg) antagonist regimen.

In the five trials, GnRH agonist was of the long luteal protocol.

The GnRH agonist regimens applied were a depot formula of 3.75 mg triptorelin (11), daily subcutaneous 0.1 mg triptorelin (8-9), daily subcutaneous 1-0.5 mg leuprorelin (10) and daily intranasal 0.6-1.2 mg buserelin (7;8). Luteal phase support was given to all patients. In all trials only one treatment cycle was performed, thus, there was no modifying effect due to the studied cycle.

In all trials healthy female partners from subfertile couples were included and the inclusion and exclusion criteria were very similar. Main common inclusion criteria were: age at least 18 but not older than 39 years, regular menstrual cycle ranging from 24 to 35 days and FSH < 10 IU/L during the early follicular phase. Patients with PCOD were excluded in
all trials. Albano 2000 and Olivennes 2000 have also excluded cases with moderate or severe endometriosis (see "table of included studies").

**Multiple low-dose regimen**

In the four multiple low-dose antagonist studies, randomisation was performed using a 2:1 ratio (antagonist/agonist).

Patients randomized to treatment with GnRH antagonist started ovarian stimulation with recFSH on day 2 or 3 of the menstrual cycle with a once daily subcutaneous injection. The GnRH antagonist was started on stimulation day 6 by daily SC administration up to and including the day of human chorionic gonadotrophin (hCG) administration.

The GnRH agonist reference treatment was started in the mid-luteal phase (cycle day 21-24) by either daily intranasal or subcutaneous administration. Ovarian stimulation was started after 2 weeks if pituitary downregulation was established (serum estradiol level <50pg/ml). In both treatment groups, ovarian stimulation was started with a fixed daily dose of 150 or 225 IU recFSH or hMG for the first 5 stimulation days. Thereafter, the dose of gonadotrophin was adapted depending on the ovarian response as monitored via ultrasonography. Triggering of ovulation was induced with HCG (10,000 IU) if at least 3 follicles >17mm were observed by USS.

**Single high-dose regimen**

In the single high-dose antagonist study, randomisation was performed using a 3:1 ratio (antagonist/agonist). In the single high-dose antagonist regimen a single dose of 3 mg antagonist was administered on day 7 of hMG stimulation unless the E2 level was below 400 pg/mL, in which case the injection was delayed. If triggering of ovulation was not done within 4 days of administration of the 3-mg dose of antagonist, a daily injection of 0.25 mg was given until hCG administration.

The GnRH agonist reference treatment was started in the mid-luteal phase (cycle day 21-24) by administering the triptorelin depot formula and ovarian stimulation was started after 2 weeks if pituitary downregulation was established (serum estradiol level <50pg/ml).
In both treatment groups, ovarian stimulation was started with a fixed daily dose of 150 or 225 IU hMG for the first 4 stimulation days. Thereafter, the dose of gonadotrophin was adapted depending on the ovarian response. Triggering of ovulation was induced with HCG (10,000 IU) when at least 1 follicle >18 mm were observed by USS and the E2 level was ≥ 1200 pg/ml.

Thirty to thirty-six hours after triggering, oocyte pick-up was performed. This was followed by IVF or ICSI and no more than 3 embryos were to be replaced 2 to 5 days thereafter. Luteal-phase support was given per the clinic's routine practice and was started no later than the day of embryo transfer.

**Methodological quality of included studies**

In general, the quality of the five trials was high. All were multicenter randomized controlled trials. Olivennes et al 2000 included 7 study centers in France (11) whereas the others were multinational in Europe (9 centers in Albano et al 2000 and 20 centers in European Orgalutran study group 2000 and 12 centers in the European-Middle East 2001 trial) (1-9). The North American trial was done in nine centers in USA and two centers in Canada.(10) All trials had parallel design with true randomisation. Albano 2000 used centralized telephone procedure as a method of randomization (7). European Orgalutran study group 2000, The North American trial 2001 and European-Middle East 2001 trial used an Interactive Voice Response System (IVRS) which stratified for age, type of subfertility and planned fertilization procedure. Randomization was done at time of recruitment of participants.(8-10) None of the trials used double blinded treatment allocation as blinding was difficult to be conducted in such trials, because, in the GnRH long protocol, ovarian suppression is required before starting ovulation induction by gonadotrophins. In contrast, the GnRH antagonist is given after starting gonadotrophin stimulation. All trials were randomized in ratios that favored GnRH antagonist (2:1, 2:1, 3:1, 2:1, 2:1 respectively) to retrieve as much information as possible about the new treatment regimen. (7-11) In all trials, healthy female partners from subfertile couples were included and the inclusion and exclusion criteria were very similar. The antagonist regimen was identical in the European trial, European-Middle -East and the North American trials except for the starting dose of FSH (fixed for the first 5 days), which was 150IU per day in the European...
trial, European-Middle-East and 225 IU per day in the North American trials. In the single high-dose regimen the starting dose was either 150 IU or 225 IU per day (8-10).

In each trial, the two treatment groups were similar with respect to age, height, weight and body mass index (BMI). In the European Middle-East trial, women were on average 2 years younger than in the other trials. In each trial, the two treatment groups were similar with respect to cause of subfertility, duration of subfertility, and the percentage of subjects with primary subfertility. In the European Middle-East trial, the incidence of primary subfertility was highest (71-73%) as was the incidence of male factor (60-63%) (9). Participants of these trials had different types of subfertility (see "Description of Studies"). However, subgroup analysis to compare the outcomes within the various categories of subfertility was not possible because such detailed data were not available. Consequently, the effect of clinical heterogeneity was not discernible.

None of these trials used power calculation to detect differences in pregnancy rates. A comparative study designed to assess a 5 percentage point difference in pregnancy rate situated in the region of 20% would require over 1200 women in each treatment group to draw a conclusion on pregnancy rate (11). Thus, each trial was not designed to adequately test the null hypothesis of no difference in pregnancy rates between the new GnRH antagonist regimen and the long protocol of GnRHa.

All trials reported subjects who did withdraw during the study. In all trials, collected data included only one treatment cycle. Center adjusted analysis was done in all trials. However, Intention-to-treat analysis was done for efficacy analysis in the ganirelix studies only. These trials were designed as non-inferiority trials to show that the efficacy of antagonist is not clinically inferior to the current care i.e. GnRH agonist treatment in a long protocol. Only in the ganirelix studies, implantation rates were included in the results, whereas endometrial thickness was not reported in any trial. The authors of the trials were contacted for extra information.

**Results**

The included studies enrolled 1796 subjects who were randomised although the sample size varied across the trials. In total 1211 subjects were randomised to treatment with the GnRH
antagonist and 585 subjects were randomized to treatment with GnRHa. The analysis was done on the number of women randomised not on all subjects treated.

**Individual trials**

subjects treated with the GnRH antagonist required significant less FSH/hMG and the duration of stimulation was significantly shorter in each trial. On the day of triggering ovulation, the cohort of follicles was smaller and serum E2 levels were significant lower after treatment with the GnRH antagonist in all trials. Accordingly, significant fewer oocytes were retrieved in subjects treated with the antagonist regimen.

The individual trials showed no statistically significant differences between the agonist and antagonist regime regarding clinical pregnancy rate.

**Premature LH surge**

The overall OR for premature LH surge was 1.76 (95%C.I. 0.75-4.16) demonstrating the non significant difference between the GnRH agonist and antagonist in the prevention of premature LH surge. The chi-square test for homogeneity of treatment effect was not statistically significant. The relative risk was 1.54 (0.65,3.64). Risk difference was 0.01 (0.00, 0.02). Subgroup analysis was done after exclusion of Olivennes trial (used single high dose regimen) and the relative risk was 2.02 (0.76-5.33). Subgroup analysis was also done for ganerilix trials and relative risk was estimated to be 2.16 (0.73, 6.38).

**Number of oocytes retrieved**

There was a statistically significant lower number of oocytes retrieved in the antagonist protocol. The over all OR was -1.86 (95% C.I. -2.47 , -1.25). The chi-square test for heterogeneity of treatment effect was not statistically significant. This result was consistent in the subgroup analysis

**Clinical pregnancy per woman**
After pooling the data from all five included studies, the clinical pregnancy rate was significantly lower in the antagonist group. The overall OR for clinical pregnancy per woman randomised was 0.79 (95% C.I., 0.63-0.99) in favor of the long GnRHa protocol. The chi-square test for heterogeneity of treatment effect was not statistically significant. The absolute treatment effect (ATE) was calculated to be 5%. The number needed to treat (NNT) was 20. This means that for every 20 subfertile couples undergoing IVF/ICSI program, one additional successful pregnancy can be expected in the GnRH agonist treated group.

Subgroup analysis was done to check the stability of the results. In Ganerilix sponsored trials, the OR was 0.78 (0.61, 1.01) just reaching the unity. The ATE and NNT were not different from those of the included five trials. On estimating the results after excluding Olivennes trial (which used single high dose administration), the OR was 0.80 (0.63, 1.01). Again the ATE and NNT were not different.

Clinical pregnancy per oocyte retrieval

The overall OR was 0.77 (95% C.I., 0.61-0.96) in favor of the long protocol over the antagonist protocols. The chi-square test for heterogeneity of treatment effect was not statistically significant.
Clinical pregnancy per embryo transfer

The overall OR was 0.76 (95% C.I., 0.60-0.97) in favor of the long protocol over the antagonist protocols. The chi-square test for heterogeneity of treatment effect was not statistically significant. The Olivennes study was not included as the number of transfer could not be obtained.

Spontaneous miscarriage rate

Comparison of spontaneous miscarriage per clinical pregnancy in the five trials showed that the overall OR was 1.03 (95% C.I., 0.52, 2.04), demonstrating a non significant difference between the two protocols. Risk difference was 0.00. This result was consistent in the different subgroup analysis.

Multiple pregnancy rate

There was no statistically significant difference between the two protocols regarding the incidence of multiple pregnancy. The overall OR is 0.74 (0.48, 1.16). Olivennes trial was not included as data were not mentioned in the text and could not be obtained.

Cycle cancellation

There was no significant difference between both groups regarding cycle cancellations (OR 0.88 (0.56-1.40). However, the chi-square test for heterogeneity of treatment effect was statistically significant. (P=0.004)

E2 level on day of hCG:

Data of the level of E2 on day of hCG were available in all trials, but variance estimates were only provided in two trials (Albano 2000, Olivennes 2000 (as shown in the analysis figure). The weighted mean difference in amount of gonadotropin used was -570.25 (95% C.I. -662.95, -477.54 ) pg less for the antagonist protocols. It should be noted that this estimate was calculated by pooling the data from the 2 trials which provided variance estimates and may not be a true representation of the difference in E2 level between the long protocol and the antagonists. However, observing the level of E2 in the remaining three trials (European Orgalutran study group 2000, North American trial 2001 and Europan-Middle
one can recognize that lower E2 level in the antagonist protocol which is consistent with the weighted mean difference mentioned above. Consequently, it can be concluded GnRH antagonist protocol is associated with a statistically significant lower level of E2 on day of hCG.

**Incidence of severe OHSS**

Using the Peto modified Mantel-Haenszel Method, data were combined across the five studies showing statistically non significant reduction in incidence of severe OHSS. The common odds ratio was 0.47 (95% C.I. 0.18, 1.25). Relative risk was estimated (RR) was 0.51 (95% C.I. 0.22, 1.18). The chi-square test for heterogeneity of treatment effect was not statistically significant.

Risk difference was estimated to be -0.01 (-0.02, 0.00). Subgroup analysis was done after exclusion of Olivennes trial (used single high dose regimen) and the relative risk was 0.56 (0.22-1.42). Subgroup analysis was also done for ganerilix trials and relative risk was estimated to be 1.46 (95% C.I. 0.33, 6.41).

**Duration of ovarian stimulation**

After pooling the data from all five included studies, the duration of ovarian stimulation was significantly shorter in the antagonist treated group. The overall OR was -1.12 (95% C.I., -1.45, -0.80) in favor of the antagonist regimen. The chi-square test for heterogeneity of treatment effect was not statistically significant. This result was consistent in the different subgroup analysis.

**Duration of cycle treatment**

After pooling the data from all five included studies, the duration of cycle treatment was significantly shorter in the antagonist treated group. There was a dramatic reduction in the duration of the cycle, OR was -20.69 (95% C.I., -21.33, -20.06) in favor of the antagonist regimen. This result was consistent in the different subgroup analysis.
Amount of Gonadotropin used

Data of the average amount of gonadotrophin used were available in all trials, but variance estimates were only provided in two trials (Albano 2000, Olivennes 2000 (as shown in the analysis figure). The weighted mean difference in amount of gonadotrophin used was -3.34 (95% C.I. -5.2, -1.47) ampoules more for the long protocol compared to the antagonist protocols.

It should be noted that this estimate is calculated by pooling the data from the 2 trials which provided variance estimates and may not be a true representation of the difference in total gonadotrophin use between the long protocol and the antagonists. However, observing the dose of gonadotrophins in the remaining three trials one can recognise that on average 300 IU more recombinant FSH was required in the long protocol which is consistent with the weighted mean difference mentioned above. Consequently, it can be concluded that with the use of the long protocol, more gonadotrophin is required for ovarian stimulation.

Cost effectiveness

This outcome could not be estimated as no available data in the text and no extra information on this issue could be obtained. Ideally, cost effectiveness should be expressed in term of cost / pregnancy. Then cost of complications should be added (OHSS, multiple pregnancy).
Discussion

This is the first prospective meta-analysis on GnRH antagonist and the first prospective systematic review in the field of gynecology. The protocol has been designed and released before any of the included studies has been published. It was designed to compare the efficacy of the GnRH agonist and the newly introduced GnRH antagonists. Over the last two decade, GnRH agonists have been used in ovarian stimulation protocols in assisted reproductive techniques (ART) in combination with gonadotrophins to prevent a premature LH surge. The concept of suppressing gonadotrophins by competitive receptor blockage rather than through pituitary desensitization with its inevitable flare-up is compelling. (12). Controlling the endogenous LH surge by GnRH antagonists may increase the efficiency both in an unstimulated and clomiphene citrate cycles (13).

In total five, randomized, controlled trials were included. All studies were multi-centre trials, with significant differences between the participating centres (10). There was no significant difference between the agonist and antagonist treated groups regarding the prevention of premature LH surge. However, the number of oocytes retrieved was consistently smaller in subjects treated with the GnRH antagonist, which was in good agreement with the smaller cohort of growing follicles, the lower amount of gonadotrophin used and the shorter duration of stimulation.

It can be recognized that there was a consistent trend in favor of GnRH agonists whether in terms of oocytes retrieved at OPU or number of embryos obtained. These findings together with lower concentrations of serum oestradiol during ovarian stimulation with the antagonists may support the hypothesis that GnRH antagonists interact with the mitotic programming of cells involved in folliculogenesis, blastomere formation and endometrium development. (14) However, Most of the studies cited in support of this suggestion are in-vitro studies (15)

There was also a consistent lower pregnancy rate in the GnRH antagonist treated subjects in the five trials but did not reach statistical significance in any of them. On pooling the results of these studies, there was a statistically significant reduction in pregnancy rate in GnRH antagonist group. This reduction was despite of transfer of an equivalent number of good quality embryos in both groups. This observation may raise questions on the impact of
GnRH antagonist on the endometrium and subsequently on implantation. In the current studies no data on endometrial thickness were retrieved. However, further controlled research including examination of endometrium biopsies may provide further insight into the possible effects of GnRH antagonists on endometrial development.

Pooling of the results of the included trials showed that there was no significant difference in the reduction in the incidence of severe OHSS between the antagonist or the agonist.

We could not evaluate the economic differences between the two protocols. We may assume that the significant reduction of the amount of gonadotrophines and the much shorter duration of GnRH analogue treatment, could have direct impact on reduction of the cost of the cycle in favor of the antagonist regimen. However, it should be noted that cost effectiveness should be estimated by cost per pregnancy rather than cost per cycle. One should also keep in mind the Indirect costs: e.g. absence from work (both partners), Productivity loss, other indirect costs due to differences in treatment duration

As Olivennes 2000 trial used single or dual high dose GnRH antagonist which was different from the multiple dose protocol in the remaining trials, we performed subgroup analysis excluding this study. However, the exclusion of the data from this trial did not affect the overall conclusion of this meta-analysis.

Although the methodological quality of the trials was high, the following points can be made. The use of a fixed protocol that starts GnRH administration on a fixed day of the cycle with a fixed dose should be re-evaluated. The open label of all studies might bias the stimulation strategy and concomitantly the results and complications. Recently it has been reported that serum antagonist levels have a linear inverse relationship with body weight. Therefore slightly lower doses may be required for smaller women and increased doses may be required for substantially larger women. The included trials were restricted to normal healthy patients with a regular cycle and a normal BMI ( > 18 and <30kg/m2). Similarly, data on women with polycystic ovary syndrome and baseline FSH values >10IU/L need to be obtained. In addition, there was no evaluation of menopausal symptoms that develop with agonist administration.
It is expected that with the developing experience in using the antagonist, clinicians will be able to finely tune its use. The time of the antagonist administration needs to be managed through the size of the leading follicle rather than on oestradiol levels, meaning that GnRH antagonist regimen should be flexible rather than fixed. Pretreatment with an oral contraceptive may be valuable in cycle programming which is of practical importance to physicians. Conclusions

**Implications for practice**

GnRH antagonists' fixed protocol facilitates short and simple protocol for ovarian stimulation in assisted conception. However, in view of the available data, there is a small but statistically significant lower pregnancy rate that necessitates counseling subfertile couples before recommending change from GnRH agonist to antagonist.

**Implications for research**

The GnRH antagonist flexible protocol should be the area of research in the future through adjusting the dose of GnRH antagonists according to the LH levels during stimulation and according to the body weight. Cost effectiveness analysis should be carried out to evaluate the difference between the two protocols regarding cost per pregnancy.
## Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
</tr>
</thead>
</table>
| Albano 2000 | Randomized controlled trial  
  Method of randomization: central telephone (true)  
  Multicentre (7 centres)  
  Location: Europe (multinational)  
  Open-label, parallel design  
  2:1 randomization ratio  
  no power calculation  
  Number of participants at randomization: 293 (Cetrorelix 198/ Buserlin 95)  
  Number of participants at stimulation: 273 (Cetrorelix 188/ Decapeptyl 85)  
  Number of participants at OPU: 258 (Cetrorelix 181/ Decapeptyl 77)  
  Details on inclusion and exclusion criteria provided  
  Intention to treat analysis: not done  
  Supported by pharmaceutical company  
  Center adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian | Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI with no more than three previous IVF-ET attempt with all causes of infertility (except polycystic ovary and moderate or severe endometriosis)  
  Age Cetrorelix 31.9 ± 3.7 Decapeptyl 31.6±3.8  
  Duration of infertility: not stated  
  FSH: not stated  
  BMI: not stated | A multiple dose regimen of 0.25 mg of GnRH antagonist (Cetrorelix) was administered SC starting from day 6 of hMG treatment to 115 participants up to and including day of hCG administration  
  Midluteal GnRH analogue (Buserlin 150ug four times daily intranasally)  
  Ovarian suppression was confirmed by E2 >50pg/ml / FSH and LH <10IU/L, P <1 ug/ml  
  hMG (menogon, humegon, pergonal) was started at 2 or 3 ampoules for 4 days and the dose was adjusted according to response  
  Luteal phase support using daily vaginal progesterone or HCG injections | Premature LH surge defined as (LH >10 IU/L) and progesterone level >1ng/L  
  Stimulation length no. of hMG ampoules E2 on hCG no of oocytes retrieved clinical preg/OPU clinical preg/ET Miscarriage Ectopic OHSS moderate or severe OHSS Clinical pregnancy was defined as fetal heart beat on ultrasonography  
  Ongoing pregnancy was defined as pregnancy ongoing after 12 weeks of amenorrhea | Number of ICSI cases was not stated the Cetrorelix group and in the Buserlin group.  
  Implantation rate was not mentioned as an outcome variable also, no of embryos obtained and no of embryos transferred was not stated  
  Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text.  
  Tolerability was not mentioned | A |
| European Orgalutran | Randomized controlled trial Method of randomization: interactive response voice system (true) Multicentre (20 centres ) Location: Europe multinational Open-label Parallel design 2:1 randomization ratio no power calculation Number of participants at randomization: 730 (Ganerilix 486 / Buserlin 244) Number of participants at stimulation: 701 (Ganerilix 463 / Buserlin 238 ) Number of participants at OPU: (Ganerilix 440 / Buserlin 221) Details on inclusion and exclusion criteria provided Intention to treat analysis : was done for efficacy analysis and all-subjects treated analysis for safety analysis Supported by pharmaceutical company Center adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome | Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI with all causes of infertility Age Ganerilix 31.9 ± 3.6 Buserlin 31.9±8 Duration of infertility: Ganerilix 4.5±2.7 Buserlin 4.4±2.7 FSH: Ganerilix 7.7 Buserlin 8.4 BMI Ganerilix 23 ±2.9 Buserlin 23±2.7 | A multiple dose regimen of 0.25 mg of GnRH antagonist (Ganerilix) was administered SC starting from day 6 of hMG treatment to 115 participants up to and including day of hCG administration midluteal GnRH analogue (Buserlin 0.6mg four times daily intranasally) Ovarian suppression was confirmed by E2 ≥50pg/ml / FSH and LH <10IU/L, P <1 ug/ml Then rFSH (Puregon) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted accordingly in response Luteal phase support was done according to the center routine practice IVF was done in 357 cases and ICSI was done in 291 cases and 10 cases had both IVF and ICSI | Premature LH surge defined as (LH >10IU/L) and progesterone level<1mg/L. Stimulation length no. of hMG ampoules E2 on hCG no of oocytes retrieved no of embryos obtained no of embryos transferred Implantation rate clinical preg/OPU clinical preg/ET Miscarriage Ectopic OHSS moderate or severe OHSS Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text. Tolerability was not mentioned in the table of outcomes but stated in the text The authors used the estimated difference of ganerlix and buserlin in ongoing pregnancy rate was compared with the margin of -5%, And for cumulus- oocyte complexes, the estimated treatment difference was compared with the equivalence margin of -3 oocytes. |
Method of randomization: interactive response voice system (true)
Multicentre (12 centres, 9 countries)
Location: Europe-middle east multinational
Open-label Parallel design 2:1 randomization ratio
no power calculation stratified randomization
Number of participants at randomization: 355 (Ganerilix 236 / triptorelin 119)
Number of participants at stimulation: (Ganerilix 226 / triptorelin 108 )
Number of participants at OPU: (Ganerilix 214 / triptorelin 105)
Details on inclusion and exclusion criteria provided
Intention to treat analysis: was done for efficacy analysis and all-subjects treated analysis for safety analysis
Supported by pharmaceutical company
Center adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome
undergoing ovarian stimulation for IVF-ET with or without ICSI with all causes of infertility
Age Ganerilix? triptorelin?
Duration of infertility: Ganerilix 4.3 triptorelin 4.1
FSH: Ganerilix 5.8 iu/ml triptorelin 2.8
BMI Ganerilix ± triptorelin ±
mg of GnRH antagonist (Ganerilix) was administered SC starting from day 6 of rec FSH treatment to 215 participants up to and including day of hCG administration midluteal GnRH analogue (triptorelin 0.1mg sc) to 106 participants of the control group Ovarian suppression was confirmed by E2 >50pg/ml / FSH and LH <10IU/L, P <1 ug/ml Then rFSH (Puregon) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted according to response Luteal phase support was done according to the center routine practice
(LH >10IU/L) and progesterone level >1ng/L Ganerilix group 1 vs triptorelin group 0
Stimulation length Ganerilix group 9 vs triptorelin group 26 recFSH:Ganerilix group 1350iu vs triptorelin group 1800iu
E2 on hCGGanerilix group 1090pg/ml vs triptorelin group 1370pg/ml
no of oocytes retrieved Ganerilix group 7.9±5.1 vs triptorelin group 9.6±6.8
no of embryos obtained Ganerilix group 4.0±3.0 vs triptorelin group 4.7±3.0
no of embryos transferred: not mentioned Implantation rate Ganerilix group 22.9 vs triptorelin group 22.9
clinical preg/cycle Ganerilix group 32.3 vs triptorelin group 37.8
clinical preg/ET Ganerilix group 35.8 vs triptorelin group 41.7
Ongoing pregnancy rate Ganerilix group 31.4 vs triptorelin group 33.9
pregnancies was not mentioned in the table of outcomes and was not clear in the text.
The authors used the estimated difference of ganerilix and buserlin in ongoing pregnancy rate was compared with the margin of -5%.
And for cumulus-oocyte complexes, the estimated treatment difference was compared with the equivalence margin of -3 oocytes.
<table>
<thead>
<tr>
<th>North American</th>
<th>Randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of randomization:</td>
<td>Interactive response voice system (true)</td>
</tr>
<tr>
<td>Multicentre (11 centres, United States and Canada)</td>
<td></td>
</tr>
<tr>
<td>Open-label</td>
<td></td>
</tr>
<tr>
<td>Parallel design</td>
<td></td>
</tr>
<tr>
<td>2:1 randomization ratio</td>
<td></td>
</tr>
<tr>
<td>no power calculation</td>
<td></td>
</tr>
<tr>
<td>stratified randomization</td>
<td></td>
</tr>
<tr>
<td>Number of participants at randomization: 313 (Ganerilix 208/leuprolide 105)</td>
<td></td>
</tr>
<tr>
<td>Number of participants at stimulation:</td>
<td>(Ganerilix 198/leuprolide 99)</td>
</tr>
<tr>
<td>Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI with all causes of infertility</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Ganerilix 33.0 ± 3.4 leuprolide 32.8 ± 4.0</td>
</tr>
<tr>
<td>Duration of infertility: Ganerilix 4.1 ± 3.0 leuprolide 3.8 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>FSH: Ganerilix 7.9 (iu/ml) leuprolide 3.3</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Ganerilix 23.0 ± 3.0 leuprolide 23.0 ± 3.0</td>
</tr>
<tr>
<td>A multiple dose regimen of 0.25 mg of GnRH antagonist (Ganerilix) was administered SC starting from day 6 of rec FSH treatment to 197 participants up to and including day of hCG administration</td>
<td></td>
</tr>
<tr>
<td>Midluteal GnRH analogue (leuprolide 1.0mg sc) to 99 participants of the control group</td>
<td></td>
</tr>
<tr>
<td>Ovarian suppression was confirmed by E2 &gt;50pg/ml / FSH and LH &lt;10IU/L, P &lt;1 ug/ml Then rFSH (Follistim) was started at fixed daily dose of 150 IU for 5 days and the dose was adjusted according to response</td>
<td></td>
</tr>
<tr>
<td>Premature LH surge defined as (LH &gt;10IU/L) and progesterone level &gt;1ng/L</td>
<td></td>
</tr>
<tr>
<td>Ganerilix group vs leuprolide group</td>
<td></td>
</tr>
<tr>
<td>Stimulation length Ganerilix group vs leuprolide group</td>
<td></td>
</tr>
<tr>
<td>recFSH:Ganerilix group iu vs leuprolide group iu</td>
<td></td>
</tr>
<tr>
<td>E2 on hCGGanerilix group pg/ml vs leuprolide group pg/ml</td>
<td></td>
</tr>
<tr>
<td>no of oocytes retrieved</td>
<td>Ganerilix group ± vs leuprolide group ±</td>
</tr>
<tr>
<td>no of embryos obtained</td>
<td>Ganerilix group ± vs leuprolide group ±</td>
</tr>
<tr>
<td>Cancellation Ganerilix group 22 vs triptorelin group 15</td>
<td></td>
</tr>
<tr>
<td>Miscarriage Ganerilix group 10.3 vs triptorelin group 11.4</td>
<td></td>
</tr>
<tr>
<td>Ectopic Ganerilix group 2 vs triptorelin group 0</td>
<td></td>
</tr>
<tr>
<td>OHSS Ganerilix group 4 vs triptorelin group 1</td>
<td></td>
</tr>
<tr>
<td>severe OHSS: only one case Ganerilix group</td>
<td></td>
</tr>
<tr>
<td>Local reaction Ganerilix group 11.9 vs triptorelin group 24.1</td>
<td></td>
</tr>
</tbody>
</table>

The authors used the estimated difference of ganerilix and leuprolide in ongoing pregnancy rate was compared with the margin of -5%. And for cumulus-oocyte complexes, the estimated treatment difference was compared with the equivalence margin of -3 oocytes.
| Number of participants at OPU: (Ganerilix 186 / leuprolide 95)  
Details on inclusion and exclusion criteria provided  
Intention to treat analysis: was done for efficacy analysis and all-subjects treated analysis for safety analysis  
Supported by pharmaceutical company  
Center adjusted analysis: not mentioned | Luteal phase support was done according to the center routine practice | group ±  
no of embryos transferred:  
Implantation rate Ganerilix group vs leuprolide group  
clinical preg/cycle Ganerilix group vs leuprolide group  
clinical preg/ET Ganerilix group vs leuprolide group  
Ongoing pregnancy rate Ganerilix group vs leuprolide group  
Cancellation Ganerilix group vs leuprolide group  
Miscarriage Ganerilix group vs leuprolide group  
Ectopic Ganerilix group vs leuprolide group  
OHSS Ganerilix group 4 vs leuprolide group 1  
severe OHSS: Ganerilix 3 cases  
leuprolide 2  
Local reaction Ganerilix group 11.9 vs leuprolide group 24.1 | | | Olivennes 2000  
Randomized controlled trial  
Method of randomization: unclear  
Multicenter (9 centers)  
Location: France  
Open-label | Infertile couples undergoing ovarian stimulation for IVF-ET with or without ICSI  
A single dose of 3 mg of GnRH antagonist (Cetrorelix) was administered SC to 115 participants  
On day 7 of hMG  
Premature LH surge defined as (LH >10IU/L) and progesterone level>1ng/L  
Stimulation length no. of hMG ampoules | When triggering of ovulation was not done within 4 days of administration of the 3mg dose of Cetrorelix, a daily injection of 0.25mg was given to 11 cases | |
<table>
<thead>
<tr>
<th>Parallel design</th>
<th>with no more than three previous IVF-ET attempts with all causes of infertility (except polycystic ovary and moderate or severe endometriosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants at randomization</td>
<td>169 (Cetrorex 126 / Decapeptyl 43)</td>
</tr>
<tr>
<td>Number of participants at stimulation</td>
<td>154 (Cetrorex 115 / Decapeptyl 39)</td>
</tr>
<tr>
<td>Number of participants at OPU</td>
<td>149 (Cetrorex 113 / Decapeptyl 36)</td>
</tr>
<tr>
<td>Details on inclusion and exclusion criteria provided</td>
<td>Intention to treat analysis: not done</td>
</tr>
<tr>
<td>Center adjusted analysis was done</td>
<td>Supported by pharmaceutical company</td>
</tr>
<tr>
<td></td>
<td>Center adjusted analysis was done for all outcomes except miscarriage, ectopic and ovarian hyperstimulation syndrome</td>
</tr>
<tr>
<td></td>
<td>midluteal GnRH analogue (Decapeptyl 3.75)</td>
</tr>
<tr>
<td></td>
<td>Ovarian suppression was confirmed by E2 &gt;50pg/ml / FSH and LH &lt;10IU/L, P &lt;1 ug/ml</td>
</tr>
<tr>
<td></td>
<td>Then hMG (menogon) was started at 2 or 3 ampoules for 4 days and the dose was adjusted according to response</td>
</tr>
<tr>
<td></td>
<td>Luteal phase support using daily vaginal progesterone</td>
</tr>
<tr>
<td></td>
<td>ICSI was done in 12 cases in the Cetrorex group and 5 patients in the Decapeptyl group.</td>
</tr>
<tr>
<td></td>
<td>E2 on hCG</td>
</tr>
<tr>
<td></td>
<td>no of oocytes retrieved</td>
</tr>
<tr>
<td></td>
<td>no of embryos obtained</td>
</tr>
<tr>
<td></td>
<td>no of embryos transferred</td>
</tr>
<tr>
<td></td>
<td>clinical prog/OPU</td>
</tr>
<tr>
<td></td>
<td>clinical prog/ET</td>
</tr>
<tr>
<td></td>
<td>Miscarriage</td>
</tr>
<tr>
<td></td>
<td>Ectopic</td>
</tr>
<tr>
<td></td>
<td>OHSS</td>
</tr>
<tr>
<td></td>
<td>moderate or severe OHSS</td>
</tr>
<tr>
<td></td>
<td>Clinical pregnancy was defined as fetal heart beat on ultrasonography</td>
</tr>
<tr>
<td></td>
<td>Ongoing pregnancy was defined as pregnancy ongoing after 12 weeks of amenorrhoea</td>
</tr>
<tr>
<td></td>
<td>until hCG administration.</td>
</tr>
<tr>
<td></td>
<td>Implantation rate was not mentioned as an outcome variable</td>
</tr>
<tr>
<td></td>
<td>Incidence of multiple pregnancies was not mentioned in the table of outcomes and was not clear in the text.</td>
</tr>
<tr>
<td></td>
<td>Tolerability was not mentioned in the table of outcomes but stated in the text regarding the Cetrorex group only. No mention of itching or redness in the decapteyl group.</td>
</tr>
<tr>
<td></td>
<td>Although power calculation was not done, the authors were concerned with the response to Cetrorex so they assumed 107 patients will be enough number to obtain 95% response rate with a CI width of 5%</td>
</tr>
</tbody>
</table>
Review: Gonadotrophin-releasing hormone antagonists for assisted conception
Comparison: 02 Premature LH surge
Outcome: 01 Premature LH surge

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRH antagonist n/N</th>
<th>GnRH agonist n/N</th>
<th>Peto OR 95% CI</th>
<th>Weight %</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albano 2000</td>
<td>3/198</td>
<td>1/95</td>
<td>16.59</td>
<td>1.41 [0.17, 11.55]</td>
<td></td>
</tr>
<tr>
<td>Euro Orgalutran 2000</td>
<td>13/463</td>
<td>3/237</td>
<td>67.08</td>
<td>1.99 [0.70, 5.68]</td>
<td></td>
</tr>
<tr>
<td>Olivennes 2000</td>
<td>0/126</td>
<td>1/43</td>
<td>3.63</td>
<td>0.02 [0.00, 1.77]</td>
<td></td>
</tr>
<tr>
<td>Euro-Mild East 2001</td>
<td>1/226</td>
<td>0/111</td>
<td>4.44</td>
<td>4.50 [0.24, 85.63]</td>
<td></td>
</tr>
<tr>
<td>North American 2001</td>
<td>2/198</td>
<td>0/99</td>
<td>8.47</td>
<td>1.76 [0.75, 4.16]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1211</td>
<td>586</td>
<td>100.00</td>
<td>1.76 [0.75, 4.16]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 19 (GnRH antagonist), 5 (GnRH agonist)
Test for heterogeneity: $\chi^2 = 4.51, df = 4 (P = 0.34), I^2 = 11.3\%$
Test for overall effect: $Z = 1.30 (P = 0.19)$

Figure 1: comparison between GnRH agonist and antagonist (Premature LH surge )
### Table: Comparison between Gonadotropin-releasing hormone agonist and antagonist (number of oocytes retrieved)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>WMD (fixed)</th>
<th>Weight</th>
<th>VMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albano 2000</td>
<td>198</td>
<td>8.00 (4.90)</td>
<td>95</td>
<td>10.60 (6.60)</td>
<td>16.80</td>
</tr>
<tr>
<td>Euro OrgaUtran 2000</td>
<td>463</td>
<td>9.10 (5.40)</td>
<td>237</td>
<td>10.40 (5.80)</td>
<td>47.54</td>
</tr>
<tr>
<td>Olivennes 2000</td>
<td>126</td>
<td>9.20 (5.10)</td>
<td>43</td>
<td>12.60 (7.40)</td>
<td>6.58</td>
</tr>
<tr>
<td>Euro-Méd East 2001</td>
<td>226</td>
<td>7.30 (5.10)</td>
<td>111</td>
<td>9.60 (5.80)</td>
<td>18.32</td>
</tr>
<tr>
<td>North American 2001</td>
<td>198</td>
<td>11.60 (6.70)</td>
<td>99</td>
<td>14.10 (8.20)</td>
<td>10.75</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1211</td>
<td>9.50 (5.70)</td>
<td>686</td>
<td>10.60 (7.10)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 4.56$, df = 4 ($P = 0.39$, $P = 12.8\%$)
Test for overall effect: $I = 5.96$ ($P < 0.0001$)

---

**Figure 2:** comparison between GnRH agonist and antagonist (number of oocytes retrieved)
03.03 Clinical pregnancy / woman

Review: Gonadotrophin-releasing hormone antagonists for assisted conception
Comparison: 03 Pregnancy outcome
Outcome: 03 Clinical pregnancy / woman

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRH antagonist</th>
<th>GnRH agonist</th>
<th>Peto Odds Ratio</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albano 2000</td>
<td>42/198</td>
<td>22/95</td>
<td>14.3</td>
<td>100.0</td>
<td>0.79 [0.49, 1.41]</td>
</tr>
<tr>
<td>European-Orgakuran</td>
<td>101/463</td>
<td>67/237</td>
<td>37.3</td>
<td>100.0</td>
<td>0.70 [0.40, 1.11]</td>
</tr>
<tr>
<td>European-Middle East</td>
<td>73/226</td>
<td>40/111</td>
<td>21.7</td>
<td>100.0</td>
<td>0.85 [0.52, 1.37]</td>
</tr>
<tr>
<td>North American 2001</td>
<td>66/198</td>
<td>36/99</td>
<td>19.5</td>
<td>100.0</td>
<td>0.67 [0.43, 1.05]</td>
</tr>
<tr>
<td>Olivennes 2000</td>
<td>24/124</td>
<td>11/43</td>
<td>7.2</td>
<td>100.0</td>
<td>0.75 [0.33, 1.73]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1211</td>
<td>585</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 308 (GnRH antagonist), 176 (GnRH agonist)
Test for heterogeneity: Chi-square = 0.01 df = 8 p = 0.99
Test for overall effect: Z = 2.02 p = 0.04

Figure 3: comparison between GnRH angonist and antagonist (clinical pregnancy rate)

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRH antagonist</th>
<th>GnRH agonist</th>
<th>Peto OR</th>
<th>Weight</th>
<th>Peto OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albano 2000</td>
<td>42/166</td>
<td>22/72</td>
<td>14.85</td>
<td>0.77</td>
<td>[0.41, 1.42]</td>
</tr>
<tr>
<td>Euro Orgakuran 2001</td>
<td>101/399</td>
<td>67/208</td>
<td>41.07</td>
<td>0.71</td>
<td>[0.49, 1.03]</td>
</tr>
<tr>
<td>Olivennes 2000</td>
<td>0/1</td>
<td>0/1</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euro-Midd East 2001</td>
<td>73/204</td>
<td>40/94</td>
<td>22.77</td>
<td>0.75</td>
<td>[0.45, 1.24]</td>
</tr>
<tr>
<td>North American 2001</td>
<td>66/178</td>
<td>36/91</td>
<td>21.31</td>
<td>0.90</td>
<td>[0.54, 1.51]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>949</td>
<td>466</td>
<td>100.00</td>
<td>0.76</td>
<td>[0.60, 0.97]</td>
</tr>
</tbody>
</table>

Total events: 292 (GnRH antagonist), 165 (GnRH agonist)
Test for heterogeneity: Chi² = 0.54, df = 3 (p = 0.91), P = 0.91
Test for overall effect: Z = 2.19 (p = 0.03)

Figure 4: comparison between GnRH angonist and antagonist (pregnancy /ET)

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Review: Gonadotrophin-releasing hormone antagonists for assisted conception
Comparison: 03 Pregnancy outcome
Outcome: 06 Miscarriage

Study or sub-category | GnRH antagonist n/N | GnRH agonist n/N | Peto OR 95% CI | Weight | Peto OR 95% CI
--- | --- | --- | --- | --- | ---
Aibano 2000 | 7/42 | 2/22 | 21.08 [1.85, 8.08] | 0.34 | 34.89 [0.75, 1.76]
Euro Orgalutran 2000 | 7/101 | 6/67 | 14.70 [1.08, 2.78] | 0.47 | 15.61 [1.09, 2.34]
Olivennes 2000 | 4/25 | 3/11 | 13.20 [5.00, 32.49] | 0.77 | 100.00 [1.03, 2.04]
Euro-Mid East 2001 | 3/73 | 0/36 | 0.00 | 0.24 | 0.75 [0.24, 2.39]
North American 2001 | 5/66 | 0/36 | 0.00 | 0.24 | 0.75 [0.24, 2.39]

Total (95% CI) 308 | 176 | 100.00 | 1.03 [0.52, 2.04]

Test for heterogeneity: Ch² = 5.02, df = 4 (P = 0.29), I² = 20.2%
Test for overall effect: Z = 0.09 (P = 0.93)

Figure 5: comparison between GnRH agonist and antagonist (Miscarriage rate)

Review: Gonadotrophin-releasing hormone antagonists for assisted conception
Comparison: 04 Ovarian hyperstimulation
Outcome: 02 Severe OHSS

Study or sub-category | GnRH antagonist n/N | GnRH agonist n/N | Peto OR 95% CI | Weight | Peto OR 95% CI
--- | --- | --- | --- | --- | ---
Aibano 2000 | 2/198 | 5/95 | 37.41 [0.03, 0.80] | 0.16 | 37.41 [0.03, 0.80]
Euro Orgalutran 2000 | 2/486 | 0/244 | 11.07 [0.24, 85.12] | 4.50 | 11.07 [0.24, 85.12]
Olivennes 2000 | 2/126 | 2/43 | 18.56 [0.03, 2.59] | 0.27 | 18.56 [0.03, 2.59]
Euro-Mid East 2001 | 1/236 | 0/119 | 5.55 [0.07, 286.04] | 4.50 | 5.55 [0.07, 286.04]
North American 2001 | 3/208 | 2/105 | 27.41 [0.12, 4.83] | 0.75 | 0.75 [0.12, 4.83]

Total (95% CI) 1254 | 606 | 100.00 | 0.47 [0.18, 1.25]

Test for heterogeneity: Ch² = 5.57, df = 4 (P = 0.29), I² = 28.2%
Test for overall effect: Z = 1.51 (P = 0.13)

Figure 6: comparison between GnRH agonist and antagonist (severe OHSS )

138
Review: Gonadotrophin-releasing hormone antagonists for assisted conception
Comparison: 01 Ovarian stimulation
Outcome: 03 Stimulation length

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment N</th>
<th>Mean(SD)</th>
<th>Control N</th>
<th>Mean(SD)</th>
<th>VMD (fixed) 95% CI</th>
<th>Weight</th>
<th>VMD (fixed) 95% CI</th>
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<td>Albano 2000</td>
<td>198</td>
<td>10.60(2.30)</td>
<td>96</td>
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<td>□</td>
<td>44.97</td>
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<tr>
<td>Euro-Orgalutran 2000</td>
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<tr>
<td>Total (95% CI)</td>
<td>1111</td>
<td>685</td>
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<td></td>
<td>□</td>
<td>100.00</td>
<td>-1.12 [-1.45, -0.80]</td>
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Test for heterogeneity: CH² = 5.33, df = 4 (P = 0.26), I² = 24.9%
Test for overall effect: Z = 6.78 (P < 0.00001)

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<td>Favours treatment</td>
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Figure 7: comparison between GnRH agonist and antagonist (stimulation length)
Update of the meta-analysis

The first version of this Cochrane review aimed at determining the efficacy of the GnRH antagonist regimen and the standard long GnRHa protocol in patients undergoing controlled ovarian hyperstimulation for assisted reproduction techniques (ART). Since its release in 2001, many studies have been conducted addressing the same topic. We found it necessary to update the best available evidence comparing GnRH antagonist vs. long agonist protocol.

In this update amendment, twenty-seven RCTs were identified to meet our inclusion criteria (original review included five only). Clinical pregnancy rate was significantly lower in the antagonist group. (OR = 0.84, 95% CI = 0.72 - 0.97). The ongoing pregnancy/ live-birth rate showed the same significant lower pregnancy in the antagonist group (P = 0.03; O.R = 0.82, 95% CI = 0.69 - 0.98).

However, there was statistically significant reduction in incidence of severe OHSS with antagonist protocol. The relative risk ratio was (P = 0.01; R.R. = 0.61, 95% CI = 0.42 - 0.89). In addition, interventions to prevent OHSS (e.g. coasting, cycle cancellation) were administered more frequently in the agonist group (P = 0.03; O.R = 0.44, 95% CI = 0.21 - 0.93).

Thus, GnRH antagonist protocol is a short and simple protocol with good clinical outcome with significant reduction in incidence of severe ovarian hyperstimulation syndrome and amount of gonadotrophins but with lower pregnancy rate compared to the GnRH agonist long protocol.
Review: Gonadotrophin-releasing hormone antagonists for assisted conception (March 2011)
Comparison: 01 Pregnancy outcome
Outcome: 02 Clinical pregnancy rate

<table>
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<tr>
<th>Study or sub-category</th>
<th>GnRH antagonist n/N</th>
<th>GnRH agonist n/N</th>
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<th>Weight %</th>
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Total (95% CI) 2554/1804 = 0.83 [0.72, 0.95]
Total events: 668 (GnRH antagonist), 553 (GnRH agonist)
Test for heterogeneity: Chi² = 18.03, df = 26 (P = 0.57), P = 0%
Test for overall effect: Z = 2.62 (P = 0.009)
References


