Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyperstimulation in oocyte donors: a systematic review and meta-analysis

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Objective: To compare GnRH agonists and antagonists in oocyte-donation IVF treatment cycles by a systematic review and meta-analysis of trials.
Design: Systematic review and meta-analysis of randomized clinical trials (RCT). Systematic literature searches were conducted, and all randomized trials that compared GnRH agonists with antagonists in oocyte-donation IVF treatment cycles were included. Study selection, quality appraisal, and data extractions were performed independently and in duplicate.
Setting: Tertiary fertility center.
Patient(s): A total of 1,024 oocyte donors treated in eight RCTs.
Intervention(s): Comparison of GnRH agonists versus antagonists in oocyte-donation IVF treatment.
Main Outcome Measure(s): Ongoing pregnancy, oocytes retrieved, duration of stimulation, gonadotropin consumption, and ovarian hyperstimulation syndrome incidence (OHSS) per randomized oocyte donor.
Result(s): Meta-analysis of these studies showed no significant difference in ongoing pregnancy rate between the GnRH agonists and antagonists (risk ratio [RR] 1.15, 95% confidence interval [CI] 0.97 to 1.36). The duration of stimulation was significantly lower with the GnRH antagonist protocol (weighed mean difference [WMD] −0.90 days, 95% CI −1.61 to −0.20). No significant differences were observed in the number of oocytes retrieved (WMD −0.60, 95% CI −2.26 to +1.07), gonadotropin consumption (WMD −264 IU, 95% CI −682 to +154), or OHSS incidence (RR 0.62, 95% CI 0.18 to 2.15).
Conclusion(s): No significant differences were observed in ongoing pregnancy rate or the number of retrieved oocytes after donor stimulation with GnRH agonist or antagonist protocols. (Fertil Steril® 2011;95:164–9. ©2011 by American Society for Reproductive Medicine.)

Key Words: Oocyte donation, GnRH antagonist, GnRH agonist, COH, meta-analysis, in vitro fertilization

Gonadotropin-releasing hormone antagonists have appeared on the market since the early 1990s, and over the years have proved to be an effective alternative to GnRH agonists to prevent LH surges during controlled ovarian hyperstimulation (COH) in IVF patients. GnRH antagonists represent a more physiologic mechanism of LH suppression and provided the basis for the development of innovative stimulation protocols (1). They also proved to be beneficial in specific patient groups, such as women with polycystic ovary syndrome (2) and poor responders (2, 3), and in minimal-stimulation or natural-cycle IVF treatment protocols (4).

Although an initial meta-analysis (5) evaluating the influence of the type of GnRH analogue used on cycle outcome in IVF patients found that several outcomes (shorter duration of stimulation, reduced gonadotropin consumption, and reduced ovarian hyperstimulation syndrome incidence [OHSS] incidence) were clearly in favor of the GnRH antagonists, drawbacks were highlighted. Most importantly, a significant reduction in pregnancy rates was observed, which had a negative influence on the acceptance and diffusion of GnRH antagonists. Subsequent updated meta-analyses (6, 7) were performed in the general IVF population and had excluded trials that included oocyte donors.

GnRH antagonist protocols were also rapidly applied in the context of oocyte donation, where they provided benefits of treatment simplification and donor convenience. Moreover, several recent retrospective studies (8–10) and randomized clinical trials (RCTs) (11–13) performed in oocyte donors showed a significantly reduced OHSS incidence when a GnRH agonist was used for inducing final oocyte maturation instead of hCG. Because triggering of ovulation with GnRH agonists is only feasible in GnRH antagonist–based protocols, the choice of the most adequate GnRH analogue for donor stimulation protocols is a clinically important question. To date, no meta-analysis existed evaluating

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the effectiveness of different GnRH analogues in oocyte donation, with individual studies yielding inconsistent and conflicting results. Therefore we conducted a systematic review and meta-analysis of studies comparing the GnRH agonist– versus antagonist–based protocols for COH in the context of oocyte-donation IVF treatment.

MATERIALS AND METHODS

Literature searches were performed via Medline, Embase, Scopus, the Cochrane Library, and the National Research Register for relevant studies. The search also included Institute for Scientific Information conference proceedings as well as databases for registration of ongoing and archived controlled trials (International Standard Randomised Controlled Trial Number and Metaregister of Controlled Trials). Additionally, references of retrieved articles and meeting proceedings of the American Society for Reproductive Medicine (2001–2009) and the European Society for Human Reproduction and Embryology (2001–2009) were hand searched. The literature search covered the period through December 2009. A combination of Medical Subject Headings and text words were used to generate two subsets of citations, one including studies involving GnRH analogues ("gonadotropin releasing hormone/GnRH analogue/agonist/antagonist/inhibitor") and the other studies related to oocyte donation ("oocyte/egg donor/donation"). These two subsets were combined using "AND" to generate a set of citations relevant to the research question. We also made enquiries about unpublished studies from researchers investigating in this field. No language restrictions were placed in any of the searches. Institutional Review Board approval was not required for the present study, owing to its retrospective nature including already published studies and the fact that data were managed in a way which excluded the subjects' identification.

Study Selection

Studies were selected if the target population was women undergoing oocyte-donation IVF treatment and the interventions were GnRH agonist– versus antagonist–based protocols for COH. The primary outcome was recipient ongoing pregnancy rate per randomized donor. Secondary outcome measures were number of retrieved oocytes, duration of stimulation, total gonadotropin consumption, and OHSS incidence per randomized oocyte donor. Studies were selected in a two-stage process. First, two reviewers (D.B. and S.K.S.) scrutinized the titles and abstracts from the electronic searches independently, and full manuscripts of all citations that definitely or possibly met the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of the full manuscripts. Assessment of the manuscripts was performed independently by two reviewers (D.B. and S.K.S.), and any disagreement about inclusion were resolved by consensus after consultation with a third reviewer (A.C.).

Data Extraction

The selected studies were assessed for methodologic quality by using the components of study design that are related to internal validity (Center for Reviews and Dissemination, 2001). The information on the method of randomization, allocation concealment, blinding, intention-to-treat analysis, and follow-up rates was sought by examining the full text articles and by contacting the authors if clarification was needed. The following data were also recorded from each of the studies: demographic (author, type of study, country of origin, period of enrollment), procedural (number of patients included, inclusion and exclusion criteria for patients populations, type of COH protocol, type of gonadotropin administered, criteria for triggering final oocyte maturation, the type and dose of triggering agent, type of fertilization, type of protocol used for recipient preparation) and outcome data (ongoing pregnancy rate, number of retrieved oocytes, duration of stimulation, gonadotropin consumption, incidence of OHSS in oocyte donors).

Statistical Analysis

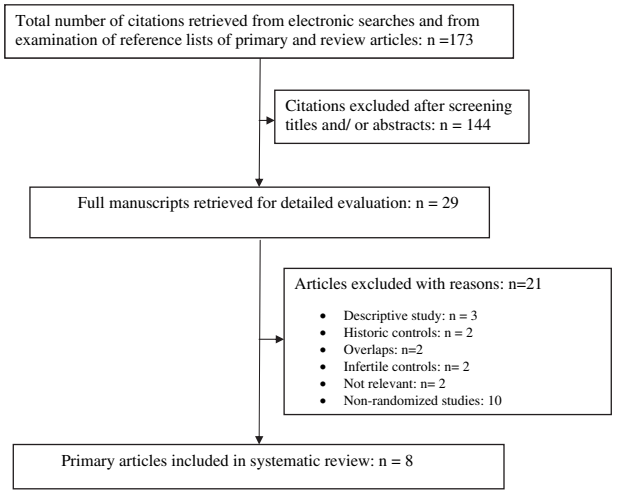
From each study, binary data were extracted in 2×2 tables and the results were pooled and expressed as risk ratio (RR) with 95% confidence interval (CI) by using fixed-effects models if significant heterogeneity was absent. Ongoing pregnancies were meta-analyzed for studies in which one donor donated eggs to one recipient only; the reason for this approach is that studies that contain multiple recipients from one donor have multiple nonindependent outcome data which invalidate the assumptions made in standard meta-analytical approaches. Weighed mean difference (WMD) was calculated for continuous variables using means and standard deviations from individual studies. Heterogeneity of treatment effects was evaluated graphically using forest plot and statistically using chi-square heterogeneity test and the I^2 statistic. Exploration of clinical heterogeneity was conducted using variation in features of the study population, intervention, and study quality. All statistical analysis was performed with RevMan 5.0 software (14). To assess for publication bias, a funnel plot analysis was performed (15).

RESULTS

The process of literature identification and selection is summarized in Figure 1. Out of the 173 citations identified, 29 were selected during the initial screening, and on examination of manuscripts, eight studies (16–23) including a total of 1,024 randomized oocyte donors satisfied the selection criteria for the review. The quality of the included trials was generally good, showing evidence of adequate randomization method and allocation concealment in six of the eight studies. The study populations uniformly included young (18–35 years) oocyte donors with regular menstrual cycles, normal body mass index (BMI; 18–29 kg/m^2), and basal hormonal values (FSH <10 UI/mL). In seven RCTs the GnRH agonist long regimen was compared with the GnRH antagonist regimen, whereas in one trial it was compared with the short flare-up GnRH agonist regimen. Three different analogues (leuprorelin, triptorelin, buserelin) were used in the agonist arm, and both available GnRH antagonists (ganirelix and cetrotide) were used in the antagonist arm. Recombinant FSH was used for ovarian stimulation in the majority of trials (7/8). The treatment characteristics of the included studies are presented in Table 1. Funnel plot analysis for the outcome of ongoing pregnancy showed that publication and related biases were unlikely.

FIGURE 1

Study selection process for systematic review of GnRH agonists versus antagonists in oocyte-donation cycles.



Bodri. GnRH analogues in oocyte donor cycles. Fertil Steril 2011.

TABLE 1

Characteristics of randomized controlled trials comparing GnRH agonists versus antagonists in oocyte donation cycles.

Study	Donors (allocation), recipients	Hormonal pretreatment	GnRH agonist protocol/ gonadotropin type	GnRH antagonist protocol/ gonadotropin type	Criteria for triggering final oocyte maturation	Triggering final oocyte maturation	Type of fertilization	Donor-recipient ratio	Recipient preparation
Shamma et al., 2003 (17)	29 donors (17 agonist, 12 antagonist), 62 recipients	OCP	Depot Leuprorelin 3.75 mg (midluteal phase)/rFSH/3–5 ampoules/day + 1 ampoule hMG (if baseline LH <0.5)	Ganirelix by two follicles 12–14 mm (0.25 mg/d)/rFSH 3–5 ampoules + 1 ampoule hMG (if baseline LH <0.5)	At least two follicles 18–20 mm	10,000 hCG	ICSI	1:2–3	Oral E_2 6 mg/d, E_2 patch 0.1 mg/d, P IM 100 mg/d
Lan, 2004 (20)	222 donors (124 agonist, 98 antagonist), 222 recipients	OCP (Marvelon)	Buserelin 0.5 mg/d and reduced to 0.2 mg/d after down-regulation (midluteal phase) /Follitropin-β 100–300 IU/day	Ganirelix by a follicle >14 mm (0.25 mg/d)/ Follitropin-β 100–300 IU	At least two follicles ≥17 mm	5,000 hCG	IVF/ICSI	1:1	Oral E_2 valerate 4mg/d, micronized vaginal P 600 mg/d
Prapas et al., 2005 (23)	98 donors participating with 148 cycles (75 agonist, 73 antagonist), 148 recipients	Oral contraceptive (Gynofen)	Triptorelin 0.1 mg/d (midluteal phase) /Follitropin-β 300 IU/d	Ganirelixfixed on day 8 (0.25 mg/d) /Follitropin-β 300 IU	At least three follicles ≥17 mm	10,000 hCG	ICSI	1:1	Oral E_2 valerate 6 mg/d, micronized vaginal P 600 mg/d
Simón et al., 2005 (16)	42 donors (14 agonist, 14 standard-dose antagonist, and 14 high-dose antagonist), 51 recipients	Not mentioned	Buserelin 0.6 mg/d (21st–24th cycle day)/Follitropin-β 150 IU/d	Ganirelix fixed on day 6 (0.25 mg/d for the standard-dose group and 2.0 mg/d for the high-dose group) /Follitropin-β 150 IU	At least three follicles ≥17 mm	10,000 hCG	IVF/ICSI	1:1.6	Oral E_2 valerate 6mg/d, micronized vaginal P 800mg/d
Shamma et al., 2006 (18)	58 donors (27 agonist, 31 antagonist), 107 recipients	OCP	Depot Lupron 0.125 mg (luteal phase)/rFSH 3–5 ampoules/d	Cetrorelix by a follicle >14 mm (0.25 mg/d)/rFSH 3–5 ampoules	At least four follicles 18–20 mm	250 μg r-hCG	ICSI	1:1.8	Oral E_2 6 mg/day, E_2 patch 0.1 mg/d, P IM 100 mg/d
Bodri et al., 2006 (19)	118 donors (60 agonist, 58 antagonist), 166 recipients	None	Triptorelin 0.1 mg/ d (cycle day 2)/ Follitropin-α 187.5 IU/d	Cetrorelix fixed on day 6 (0.25 mg/d)/Follitropin-α 225 IU	At least three follicles ≥18 mm	250 μg r-hCG	ICSI	1:1.5 overall, 66 had 1:1 donor-recipient ratio	Oral E_2 valerate 6mg/d, micronized vaginal P 800mg/d
Martínez et al., 2008 (21)	323 donors (160 agonist, 163 antagonist), 273 recipients	Vaginal contraceptive (Nuvaring)	Depot Leuprorelin 3.75 mg (cycle day 20–22)/hMG 2–3 ampoules/d	Ganirelix fixed on day 6 (0.25 mg/d)/Follitropin-β 150–200 IU	At least three follicles ≥20 mm	10,000 hCG	IVF/ICSI	1:1	Oral E_2 valerate 6mg/d, micronized vaginal P 600mg/d

Bodri. GnRH analogues in oocyte donor cycles. Fertil Steril 2011.

TABLE 1

Continued.

Study	Donors (allocation), recipients	Hormonal pretreatment	GnRH agonist protocol/ gonadotropin type	GnRH antagonist protocol/ gonadotropin type	Criteria for triggering final oocyte maturation	Triggering final oocyte maturation	Type of fertilization	Donor-recipient ratio	Recipient preparation
Martínez et al., 2008 (22)	84 donors (40 agonist, 44 antagonist), 61 recipients	OCP in the GnRH antagonist group (Microdiol)	0.5 ampoule depot Leuprorelin 3.75 mg (cycle day 20–22)/hMG/ Follitropin-β 150–200 IU/d	Cetrorelix by a follicle >14 mm (3 mg + 0.25 mg/ d after 4 days)/ Follitropin-β 150–200 IU	At least three follicles ≥20 mm	10,000 hCG in the agonist group/hCG or GnRH agonist in the antagonist group	IVF/ICSI	1:1	Oral E_2 valerate 6mg/d, micronized vaginal P 600mg/d

Note: ICSI = intracytoplasmic sperm injection; IM = intramuscular; IVF = in vitro fertilization; OCP = oral contraceptive pill; rFSH = recombinant FSH.

Bodri. GnRH analogues in oocyte donor cycles. Fertil Steril 2011.

Primary Outcome: Ongoing Pregnancy Rate

Six of the eight studies reported recipient ongoing pregnancy rate as an outcome. However, the donor recipient ration was 1:1 in only five of the eight studies (Table 1). Pooling of results from those five studies showed no significant difference in recipient ongoing pregnancy rate per randomized donor after COH with GnRH agonist– or antagonist–based protocols: RR 1.15 (95% CI 0.97 to 1.36; P=.12; heterogeneity P=.80; I^2 0%, fixed effects model; Fig. 2).

Secondary Outcomes

Oocytes retrieved Meta-analysis of seven of the eight studies that reported the number of oocytes retrieved as an outcome showed no significant difference in the number of retrieved oocytes after COH with the GnRH agonist or antagonist protocols: WMD −0.60 (95% C: −2.26 to 1.07; P=.48; heterogeneity P=.002; I^2 71%, random effects model; Fig. 3).

Duration of stimulation Five of the eight studies reported the duration of stimulation with gonadotropins as an outcome. Meta-analysis of those five studies showed that the duration of stimulation was significantly lower after COH with the GnRH antagonist protocol compared with the agonist protocol: WMD −0.90 days (95% CI −1.61 to −0.20 days; P=.001; heterogeneity P<.00001; I^2 91%, random effects model).

Gonadotropin consumption Data from one study (19) where different gonadotropin starting doses were used were excluded from analysis. Meta-analysis of the remaining four studies that reported data on gonadotropin consumption showed no significant difference after COH with the GnRH agonist versus antagonist protocols: WMD −264 IU (95% CI −682 to 154 IU; P=.22; heterogeneity P<.00001; I^2 95%, random effects model.)

OHSS incidence Meta-analysis of four of the eight studies that reported data on OHSS incidence showed no significant difference after COH with the GnRH agonist versus antagonist protocols: RR 0.61 (95% CI 0.18 to 2.15; P=.45; heterogeneity P=.45; I^2 0%, fixed effects model).

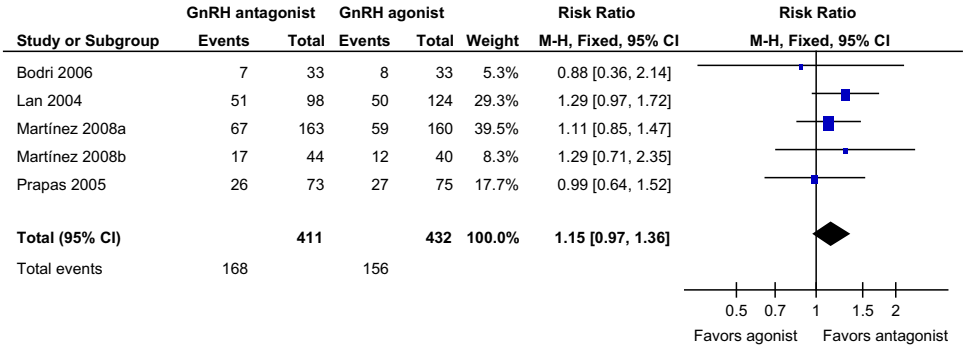
DISCUSSION

The present systematic review and meta-analysis analyzed data from eight RCTs on the use of GnRH agonists versus antagonists in COH of oocyte donors. The findings suggest that there are no statistically significant differences in ovarian response or recipient ongoing pregnancy rates with the use of either GnRH agonist or antagonist protocols.

Comparing our findings with other meta-analyses performed in general IVF population (6, 7), a similar trend was observed in the duration of stimulation and gonadotropin consumption. On the other hand, the difference in the number of retrieved oocytes was less important (0.60 vs. 1.07–1.19 fewer oocytes with antagonist protocols) and ongoing pregnancy rates were not negatively affected (RR 1.16 vs. odds ratio 0.82–0.86). This could be related to the smaller number of trials included, but it could also suggest real differences between donor and nondonor IVF. The oocyte donation model allows studying oocyte quality and embryo implantation potential separately from possible endometrial effects of different stimulation protocols. In this context, it is interesting to notice that pregnancy rates do not seem to be negatively affected after oocyte donation compared with IVF patients, which might suggest a negative endometrial effect related to the GnRH antagonist.

FIGURE 2

Risk ratio for recipient ongoing pregnancy rate per randomized donor (studies with 1:1 donor-recipient ratio). Heterogeneity: $\chi^2 = 1.64$; df = 4 ($P = .80$); $I^2 = 0$. Test for overall effect: Z = 1.57 ($P = .12$).



Bodri. GnRH analogues in oocyte donor cycles. Fertil Steril 2011.

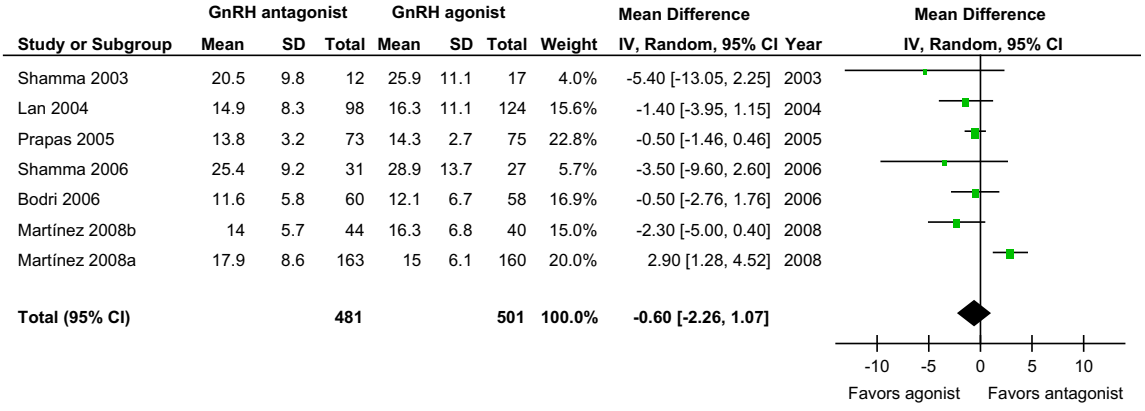
The incidence of OHSS was not significantly different between the two treatment groups, but this might be related to the fact that the aggregated sample size was too small to detect any significant difference. Furthermore it must be pointed out that hCG was used exclusively for inducing the final oocyte maturation in all trials except in the most recent one where GnRH agonist was partially used in the antagonist arm. It has been suggested that the choice of the triggering agent is directly related to the reduction in OHSS incidence in the antagonist arm (24). Recent trials (8–10) demonstrated extensively the elimination of the syndrome in oocyte donors after GnRH agonist triggering. Moreover recent RCTs (11–13) also showed similar outcome in terms of oocyte maturation, fertilization rates, and recipient pregnancy rates after substituting hCG with a GnRH agonist for inducing final oocyte maturation in GnRH antagonist protocols. Therefore, owing to their increased safety potential, GnRH antagonist–based protocols coupled with GnRH agonist triggering could be advocated as a first choice treatment regimen for donor stimulation (25, 26).

In the RCTs included and analyzed in the present review, recipients were not formally randomized, owing to the fact that a thorough donor-recipient phenotype matching—which is an inherent part of all oocyte donation programs—prevents random donor attribution. Nonetheless, it is unlikely that this would introduce significant bias, because the matching procedure is not influenced by the type of stimulation protocol received by the donor. This is supported by the fact that in the majority of the included trials, recipients were similar regarding baseline characteristics such as age, BMI, and indication for oocyte donation.

In this review, it was demonstrated that donor and recipient outcome were not significantly different according to the type of GnRH analogue used in donor stimulation. The validity of this finding depends on the methodologic rigor of the review and the component primary studies. A prospective protocol was used, and a concerted effort was made to find all of the evidence. Two independent reviewers assessed study quality and extracted data, and the agreement between the two reviewers was high.

FIGURE 3

Weighted mean difference for the number of retrieved oocytes. Heterogeneity: $\tau^2 = 2.91$; $\chi^2 = 20.49$; df = 6 ($P = .002$); $I^2 = 71\%$. Test for overall effect: Z = 0.70 ($P = .48$).



Bodri. GnRH analogues in oocyte donor cycles. Fertil Steril 2011.

One major problem usually encountered when synthesizing the evidence in meta-analysis is clinical and methodologic heterogeneity between the studies. In our review, the methodologic quality of the included RCTs was good and recipient follow-up complete. The donor population was also uniform, owing to generally accepted criteria for inclusion in an oocyte-donation program. Some clinical heterogeneity (type of GnRH analogues used) existed between treatment protocols used for donor stimulation, but owing to the limited number of studies identified, it was not feasible to perform a subgroup analysis. It is also important to highlight that this review was only sufficiently powered to detect an ~9% difference in recipient ongoing pregnancy rates between groups.

In conclusion, currently available evidence suggests a similar effectiveness of GnRH antagonists and agonists in the context of oocyte donation. Owing to its increased safety potential, the GnRH antagonist protocol combined with GnRH agonist triggering could be advocated as the treatment of first choice for oocyte donors.

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REFERENCES

1. Devroey P, Aboulghar M, Garcia-Velasco J, Griesinger G, Humaidan P, Kolibianakis E, 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.
2. 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.
3. Sunkara SK, Tuthill J, Khairy M, El-Toukhy T, Coomarasamy A, Khalaf Y, et al. Pituitary suppression regimens in poor responders undergoing IVF treatment: a systematic review and meta-analysis. Reprod Biomed Online 2007;15: 539–46.
4. Verberg MF, Macklon NS, Nargund G, Frydman R, Devroey P, Broekmans FJ, et al. Mild ovarian stimulation for IVF. Hum Reprod Update 2009;15: 13–29.
5. Al-Inany H, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. Cochrane Database Syst Rev 2001:CD001750.
6. Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. Cochrane Database Syst Rev 2006;3:CD001750.
7. Kolibianakis EM, Collins J, Tarlatzis BC, Devroey P, Diedrich K, Griesinger G. 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.
8. Bodri D, Guillen JJ, Trullenque M, Schwenn K, Esteve C, Coll O. Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study. Fertil Steril 2009.
9. Hernandez ER, Gomez-Palomares JL, Ricciarelli E. No room for cancellation, coasting, or ovarian hyperstimulation syndrome in oocyte donation cycles. Fertil Steril 2009;91:1358–61.
10. Bodri D, Guillen JJ, Galindo A, Mataro D, Pujol A, Coll O. 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.
11. Galindo A, Bodri D, Guillen JJ, Colodron M, Vernaeve V, Coll O. Triggering with hCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. Gynecol Endocrinol 2009;25:60–6.
12. Melo M, Busso CE, Bellver J, Alama P, Garrido N, Meseguer M, et al. GnRH agonist versus recombinant hCG in an oocyte donation programme: a randomized, prospective, controlled, assessor-blind study. Reprod Biomed Online 2009;19:486–92.
13. Acevedo B, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. Fertil Steril 2006;86:1682–7.
14. Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.
15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
16. Simón C, Oberye J, Bellver J, Vidal C, Bosch E, Horcajadas JA, et al. Similar endometrial development in oocyte donors treated with either high- or standard-dose GnRH antagonist compared to treatment with a GnRH agonist or in natural cycles. Hum Reprod 2005;20:3318–27.
17. Shamma FN, Grossman MP, Abuzeid MI, Al-Hosn L, Ayers WTN, Fakih MH. Comparison of daily ganirelix administration to a long agonist protocol for controlled ovarian hyperstimulation in oocyte donors: the results of a prospective randomized controlled trial [O-98]. Fertil Steril 2003;80 (Suppl 3):S37–8.
18. Shamma F, Sakhel K, Ashraf M, Fakih M, Ayers J, Khan I. Comparison of daily cetrorelix acetate administration to a long leuprolide acetate protocol for controlled ovarian hypersimulation in oocyte donors: the results of a prospective randomized controlled trial [P-33]. Fertil Steril 2006;86(Suppl):S140–1.
19. Bodri D, Vernaeve V, Guillen JJ, Vidal R, Figueras F, Coll O. Comparison between a GnRH antagonist and a GnRH agonist flare-up protocol in oocyte donors: a randomized clinical trial. Hum Reprod 2006;21:2246–51.
20. Lan VTN. Orgalutran in donor cycles. GnRH antagonist in IVF. Beigem, Belgium: ESHRE, 2004.
21. Martinez F, Clua E, Parera N, Rodriguez I, Boada M, Coroleu B. Prospective, randomized, comparative study of leuprorelin + human menopausal gonadotropins versus ganirelix + recombinant follicle-stimulating hormone in oocyte donors and pregnancy rates among the corresponding recipients. Gynecol Endocrinol 2008;24:188–93.
22. Martinez F, Clua E, Parera N, Rodriguez I, Boada M, Coroleu B. Prospective randomized trial comparing triptorelin versus cetrorelix 3 mg treatment in oocyte donors and pregnancy rates among their recipients. Hum Reprod 2008;23(Suppl):1:i4.
23. Prapas N, Prapas Y, Panagiotidis Y, Prapa S, Vanderzwalmen P, Schoysman R, et al. GnRH agonist versus GnRH antagonist in oocyte donation cycles: a prospective randomized study. Hum Reprod 2005;20:1516–20.
24. Bodri D, Guillen JJ, Polo A, Trullenque M, Esteve C, Coll O. Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles. Reprod Biomed Online 2008;17:237–43.
25. Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril 2010;94:389–400.
26. Humaidan P, Papanikolaou EG, Tarlatzis BC. GnRHa to trigger final oocyte maturation: a time to reconsider. Hum Reprod 2009;24:2389–94.