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Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis

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BACKGROUND: The aim of this systematic review and meta-analysis was to evaluate whether the addition of GnRH agonist for luteal support in ICSI/IVF cycles enhances the probability of live birth.

METHODS: Systematic literature search (MEDLINE, EMBASE, CENTRAL and RCT registries) was conducted to identify relevant randomized controlled trials published as full manuscripts. Meta-analysis of data yielded pooled risk differences (RDs) and 95% confidence intervals (CIs). A random effects model was applied for pooling the studies.

RESULTS: Six relevant RCTs were identified including a total of 2012 patients. The probability of live birth rate (RD: +16%, 95% CI: +10 to +22%) was significantly higher in patients who received GnRH agonist support compared with those who did not. The subgroup analysis according to the type of GnRH analogue used for LH suppression did not change the effect observed (studies in which GnRH agonist was used during ovarian stimulation, RD: +15%, 95% CI: +5 to +23%); (studies in which GnRH antagonist was used during ovarian stimulation, RD: +19%, 95% CI: +11 to +27%).

CONCLUSIONS: The best available evidence suggests that GnRH agonist addition during the luteal phase significantly increases the probability of live birth rates.

Key words: GnRH agonist / luteal support / live birth / ICSI/IVF

Introduction

Ovarian stimulation using either GnRH agonist or GnRH antagonist has been used in IVF in order to achieve multifollicular development. Ovarian stimulation results in supraphysiological steroid levels and is associated with very low LH concentrations during the luteal phase (Tavaniotou et al., 2001). For this reason, several schemes of luteal support have been used to increase the chance of pregnancy (Pritts and Atwood, 2002; Daya and Gunby, 2008), although there is no agreement yet regarding which is the optimal one.

Administration of GnRH agonist has been recently suggested as an alternative for luteal phase supplementation (Tesarik et al., 2004; Pirard et al., 2005, 2006). The exact underlying mechanism is still not clear, although it has been hypothesized that GnRH agonist either supports the corpus luteum function by inducing LH secretion by the pituitary gonadotroph cells or stimulates the endometrium GnRH receptors (Pirard et al., 2006). Tesarik et al. (2004) postulated a direct effect of GnRH agonist on the embryo, evidenced by increased β-HCG secretion.

Currently, available data regarding the beneficial effect of administration of GnRH agonist on the probability of pregnancy exist; however, they are still controversial. The purpose of this systematic review and meta-analysis was to answer the following clinical question: Does the addition of GnRH agonist for luteal support in IVF/ICSI cycles enhance the probability of live birth?

Methods

Literature search

A computerized literature search in MEDLINE, EMBASE, CENTRAL and RCT registries (ClinicalTrials.gov, International Standard Randomized Controlled Trial Number Register and Australian New Zealand Clinical Trials Registry) covering the period up to December 2010 was performed. Additionally, references of retrieved articles were hand-searched. The search strategy aimed at identifying randomized-controlled trials (RCTs) on the basis of the following clinical question: does the addition of GnRH agonist for luteal support in IVF/ICSI cycles enhance the probability of live birth? Search terms used were 'GnRH agonist' combined with 'luteal phase' or 'luteal phase support' and 'in-vitro fertilization' or 'in vitro fertilization' or 'in-vitro fertilisation' or 'in vitro fertilisation' or 'IVF' or 'intracytoplasmic sperm injection' or 'intra-cytoplasmic sperm injection' or 'ICSI'.

Studies were eligible for inclusion in the systematic review and meta-analysis if they were published as full manuscripts and patient allocation in the treatment groups was performed by randomization. No language limitation was applied.

Data extraction

Data extraction was performed independently by two of the authors (D.K. and H.M.F.). The following data were recorded: demographic (citation data, country, study period, number of patients included and selection of cycles), methodological (timing and method of randomization, allocation concealment), procedural (whether financial support was declared or not, type of GnRH analogue and dose used, type and starting dose of gonadotrophin administered for ovarian stimulation, criteria used for triggering final oocyte maturation, type and dose of medication used for triggering final oocyte maturation, timing of oocyte retrieval, type of fertilization, day of embryo transfer, type of luteal support, dose, route of administration, type, timing of initiation, duration of luteal support with GnRH agonist and outcome data (implantation rate, clinical pregnancy rate, ongoing pregnancy, live birth rate, multiple pregnancy rate). Any disagreement between the two reviewers responsible for data extraction was resolved by discussion.

Outcomes

The main outcome measure was the probability of live birth. Secondary outcome measures included clinical pregnancy and multiple pregnancy rates.

Quantitative data synthesis

The dichotomous data results for each of the studies eligible for meta-analysis were expressed as a risk difference (RD) with 95% confidence intervals (CIs). These results were combined for meta-analysis using the DerSimonian and Laird method using the random effect model. All results were combined for meta-analysis with Revman Software (Version 5 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Study-to-study variation was assessed by using the I^2 statistic.

Subgroup analyses were planned a priori, and focused on the type of GnRH analogue used for suppression of premature LH surge, on the type of GnRH agonist used for luteal support and on the type of luteal support scheme used for comparison with the GnRH agonist luteal supplementation. Statistical significance was set at a P level of 0.05.

Results

The initial literature search yielded 196 studies (Supplementary data, Fig. S1). Screening of the titles of these studies resulted in 38 publications that could provide information relevant to the question of interest. Evaluation of the abstracts of these studies reduced the eligible trials to six, the manuscripts of which were retrieved and evaluated in detail. Where necessary, an attempt was made to contact the authors in order to retrieve missing information regarding the study design. In total, all six studies were considered eligible and are included in the present systematic review and meta-analysis (Fujii et al., 2001; Tesarik et al., 2006; Isikoglu et al., 2007; Ata et al., 2008; Isik et al., 2009; Razieh et al., 2009).

The study by Ata and Urman (2010) was excluded by the current systematic review and meta-analysis since it was not published as a full manuscript but in the form of a letter.

Systematic review

Characteristics of the eligible studies are listed in Table I. The long agonist protocol was used in four studies to inhibit the premature LH surge (Fujii et al., 2001; Isikoglu et al., 2007; Ata et al., 2008; Razieh et al., 2009), GnRH antagonists were used in one study (Isik et al., 2009), while in the study by Tesarik et al. (2006) patients were treated either by GnRH agonist or antagonist. In that study, two separate randomizations were performed depending on the type of GnRH analogue used for LH suppression and for this reason the study was considered as two separate studies for the current

Table I Characteristics of the RCTs included in the meta-analysis.

Study/ Journal/ Number of centres	Study period	Randomization method/allocation concealment	GnRH analogue/ protocol	Gonadotrophin type/starting dose-adjustment	hCG	Criteria of hCG administration	OR	Fertilization	Embryo transfer day	Embryo transfer policy	LPS	LPS with GnRH agonist in the study group
Fujii et al. (2001)/Hum Reprod/ Single centre	February 1997– March 1999	Patient's identification number/not reported	Busereline/ long agonist	Pure FSH/225– 150 IU after 2 days	5000 IU uhCG	Mean follicular diameter 18 mm	34–36 h	IVF/ICSI	Days 2 or 3	<4 embryos	Dydrogesterone 10 mg/day for 14 days starting on the day of embryo transfer and 2500 IU IM hCG on the day of embryo transfer	GnRH agonist during the luteal phase until 14 days after OR
Tesarik et al. (2006)/Hum Reprod/ Single centre	September 2003– September 2005	Computer-generated randomization list/ sealed envelopes	Tesarik a Triptorelin/ long agonist Tesarik b Ganirelix or Cetrorelix acetate/ antagonist fixed Day 5	rFSH or HMG/not reported-according to E₂ and LH levels	250 g rhCG	At least three follicles ≥18 mm	Not reported	ICSI	Day 3	1–3 embryos	400 mg progesterone and 4 g E₂ daily from day of OR for 17 days Additionally 250 μg rhCG on the day of embryo transfer	Single dose triptorelin 6 days after ICSI
Isikoglu et al. (2007)/ Journal of Reprod Med/ Single centre	Not reported	Computer-generated randomization list/not reported	Leuprolide acetate/long agonist	HMG/ 150–450 IU according to the ovarian reserve	10 000 IU uhCG	At least two follicles >17 mm	35 h	ICSI	Day 2	>4 embryos	Progesterone 50 g/ d IM	GnRH agonist during the luteal phase until 14 days after OR
Ata et al. (2008)/Hum Reprod/ Single centre	September 2006–July 2007	Computer-generated randomization list/ sealed envelopes	Triptorelin/ long agonist	rFSH /150–300 IU according to E₂ levels and follicular development	10 000 IU uhCG	Leading follicle 20 mm accompanied by ≥2 follicles >16 mm	36 h	ICSI	Day 3	1–3 embryos	Progesterone	Single dose Triptorelin 6 days after ICSI
Razieh et al. (2009)/ Taiwan J Obstet Gynecol/ Single centre	Not reported	Randomization table/ sealed envelopes	Busereline/ long agonist	rFSH/ 150–225 IU Not reported	10 000 IU uhCG	At least two follicles ≥18 mm	34–36 h	ICSI	Days 2 or 3	2 or 3 embryos	Progesterone 800 mg/day	Single dose Triptorelin 6 days after ICSI
Isik et al.(2009)/ RBM online/ Single centre	January 2005– September 2005	Computer-generated random table/not reported	Ganirelix or Cetrorelix acetate/ antagonist flexible	rFSH or HMG/not reported according to the patients response	10 000 IU uhCG or 250 μg rhCG	At least three follicles ≥17 mm	35 h	ICSI	Day 3	1–5 embryos	Progesterone 600 mg/day for 17 days and 2500 IU IM hCG on the day of embryo transfer additionally 1500 IU hCG on Day 8 after ICSI	Single dose 0.5 mg Leuprolide acetate 6 days after ICSI

IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; OR, oocyte retrieval; ET, embryo transfer; hCG, human chorionic gonadotrophin; uhCG, urinary human chorionic gonadotrophin; rhCG, recombinant human chorionic gonadotrophin; GnRH, gonadotrophin-releasing hormone; rFSH, recombinant follicle-stimulating hormone; HMG, human menopausal gonadotrophin; IM, intramuscularly; LPS, luteal phase support.

meta-analysis (Tesarik et al., 2006 GnRH agonist; Tesarik et al., 2006 GnRH antagonist).

All the studies were single-centre trials and were published between 2001 and 2009.

The size of the studies ranged from 162 to 570 patients (median 366), whereas a total of 2012 patients were analysed (GnRH agonist group n = 1008).

In the majority of the studies, randomization of patients was performed by computer-generated randomization list (Tesarik et al., 2006; Isikoglu et al., 2007; Ata et al., 2008; Isik et al., 2009).Treatment allocation was concealed in two studies, while in the remaining studies concealment of allocation was either not performed or no relevant information was given (Table I). Financial support was declared only in the study by Razieh et al. (2009). Three out of the six studies reported a power analysis aiming to detect differences in the probability of pregnancy achievement (Tesarik et al., 2006; Ata et al., 2008; Isik et al., 2009).

Regarding the long agonist protocol, suppression of LH surge was performed by triptoreline (Tesarik et al., 2006; Ata et al., 2008), busereline (Fujii et al., 2001; Razieh et al., 2009) and leuprolide acetate (Isikoglu et al., 2007). Ganirelix or cetrorelix acetate was used in the two studies in which the antagonist protocol was applied (Tesarik et al., 2006; Isik et al., 2009). In the majority of the studies, ovarian stimulation was performed with recombinant gonadotrophins (Tesarik et al., 2006; Ata et al., 2008; Isik et al., 2009; Razieh et al., 2009).

In all studies, the criteria used for triggering final oocyte maturation were based on follicular development. Urinary hCG (uhCG) was used to trigger final oocyte maturation in three studies [10 000 IU in three studies (Isikoglu et al., 2007; Ata et al., 2008; Razieh et al., 2009) and 5000 IU in one study (Fujii et al., 2001)]. For the same purpose,

250 μg of recombinant hCG (rhCG) was administered in one study (Tesarik et al., 2006), while in the study of Isik et al. (2009) either uhCG or rhCG was used.

Oocyte retrieval was performed 34–36 following hCG administration, in the majority of the studies fertilization was performed by ICSI (Tesarik et al., 2006; Isikoglu et al., 2007, Ata et al., 2008; Isik et al., 2009; Razieh et al., 2009), while embryo transfers were performed at the cleavage stage.

Type, dose, route of administration, as well as timing of initiation and duration of luteal support varied between the eligible studies (Table I). GnRH agonist as luteal support was administered as single dose 6 days after ICSI in four studies (Tesarik et al., 2006; Ata et al., 2008; Isik et al., 2009; Razieh et al., 2009), while in two studies the GnRH agonist was continuously administered until 14 days after oocyte retrieval (Fujii et al., 2001; Isikoglu et al., 2007).

Meta-analysis

Primary outcome measure

Live birth rate. The probability of live birth rate was significantly higher in patients who received GnRH analogue for luteal support compared with those who did not (RD: +16%, 95% CI: +11 to +22%; $I^2 =$ 17%). Five studies offered data for this outcome measure (Fig. 1). Subgroup analysis according to the type of GnRH analogue used for LH suppression did not change the direction or the magnitude of the effect observed (studies in which GnRH agonist was used, RD: 14%, 95% CI: +5 to +23%; $I^2 = 47\%$); (studies in which GnRH antagonist was used, RD: 19%, 95% CI: +11 to +27%; $I^2 = 0\%$).

Secondary outcome measures

Clinical pregnancy rate. The probability of clinical pregnancy was significantly higher in patients who received GnRH analogue for luteal
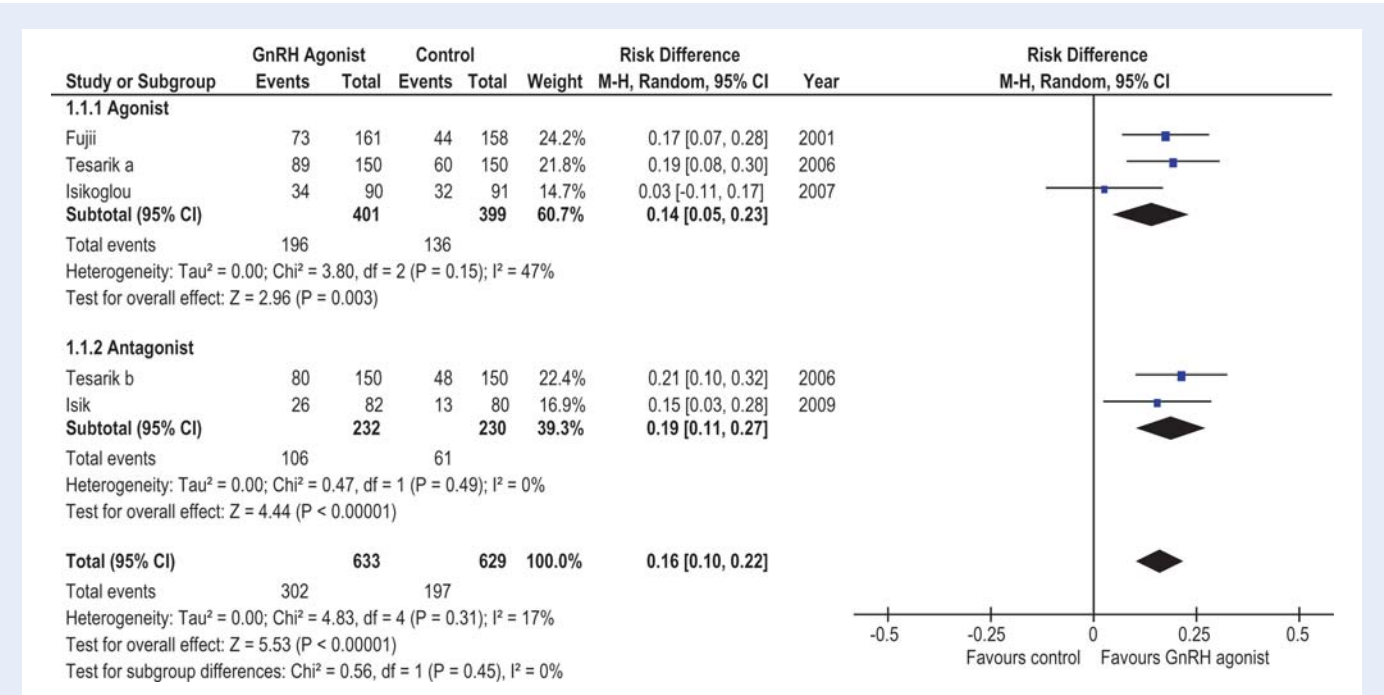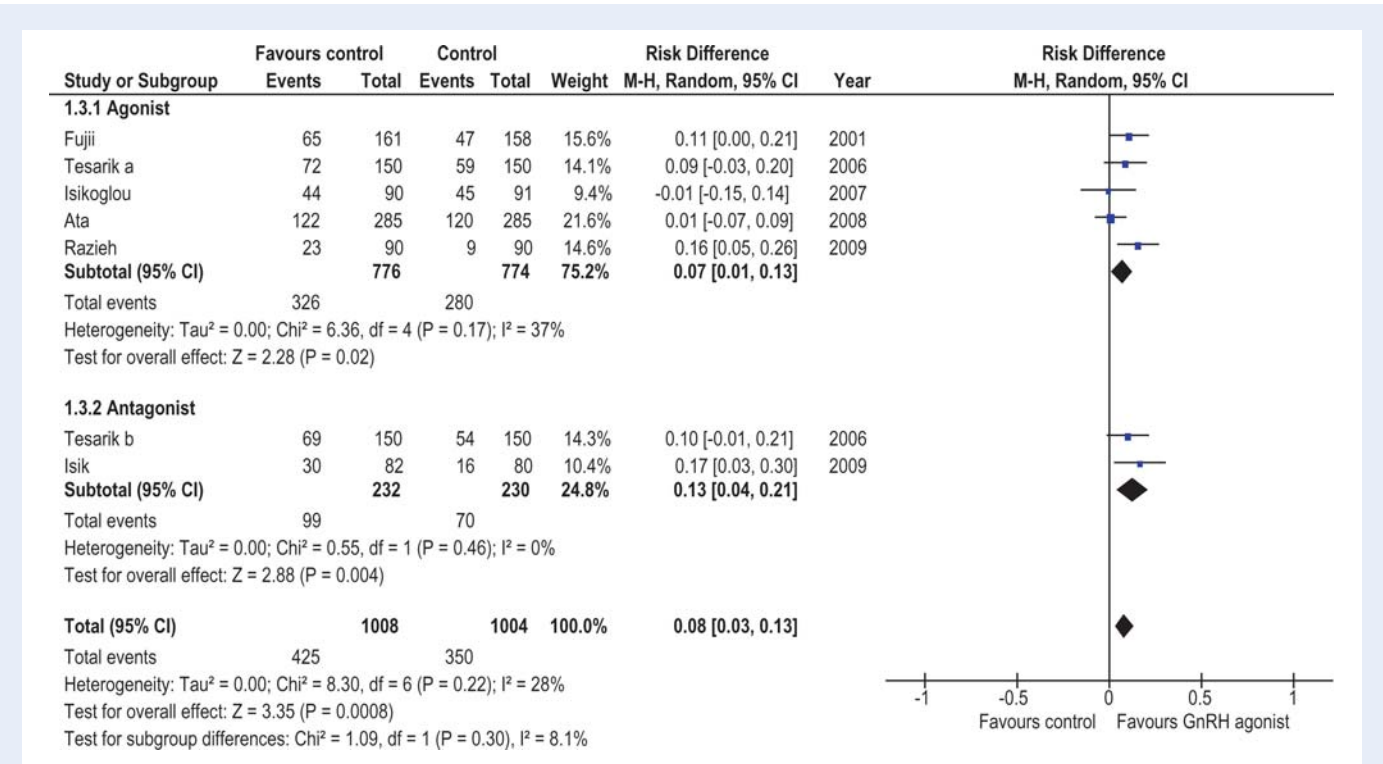

Figure 1 Forest plot live birth.

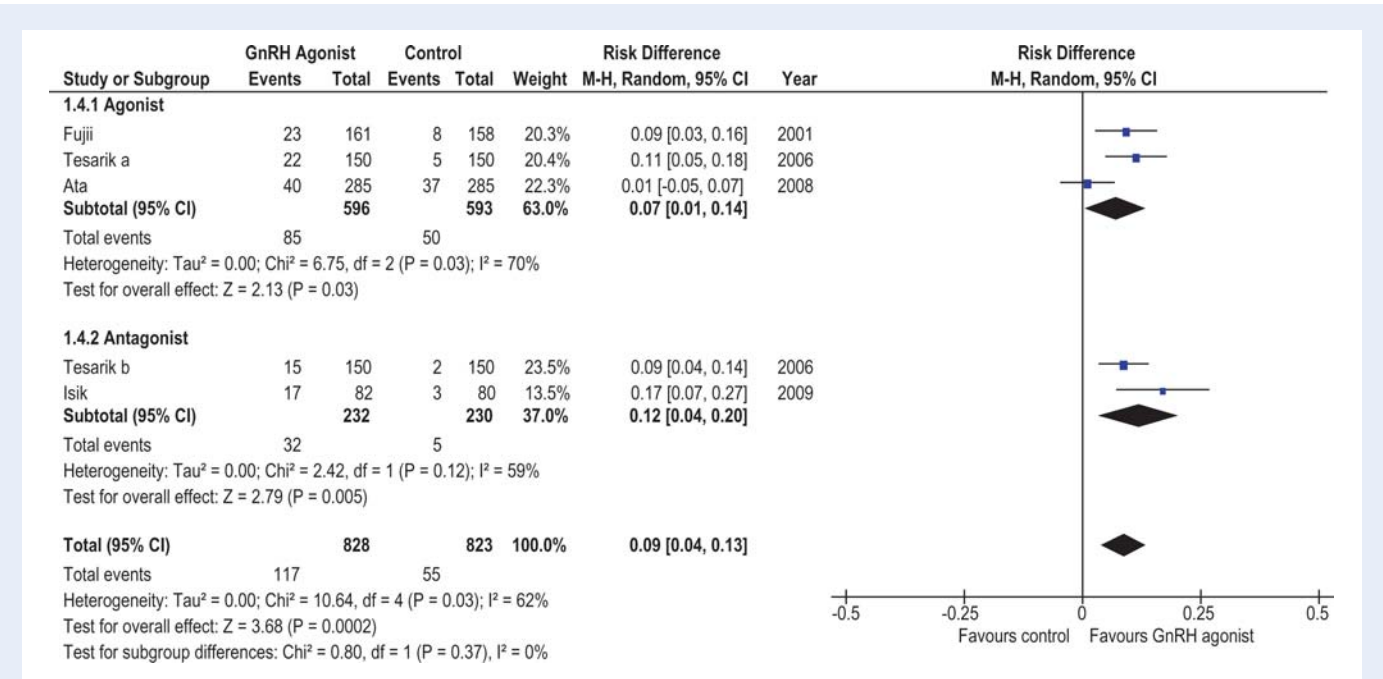**Figure 2** Forest plot clinical pregnancy.

Figure 3 Forest plot multiple pregnancy.

support compared with those who did not (RD:8%, 95% CI: +3 to +13%; $I^2 = 28\%$) (Fig. 2). All seven eligible studies offered data for this outcome. Repeating the analysis with the excluded study (Ata and Urman, 2010) the RD was not materially changed from the original results: (RD:7%, 95% CI: +1 to +13%; $I^2 = 49\%$).

Multiple pregnancy rate. The probability of multiple pregnancy was significantly higher in patients who received GnRH analogue for luteal support compared with those who did not (RD: 9%, 95% CI: +4 to +13%; $I^2 = 62\%$). Five studies provided data regarding multiple pregnancy rate (Fig. 3).

Discussion

The present systematic review summarizes data from six RCTs that evaluate the effectiveness of GnRH agonist addition for luteal support in ICSI/IVF-embryo transfer cycles and included 2012 patients. Meta-analysis of these data showed that live birth rate was significantly higher (+16%), when the GnRH agonist was added to the luteal support scheme. The same was true for clinical pregnancy rate and multiple pregnancy rate, which were higher with the addition of GnRH agonist during the luteal phase.

A subgroup analysis performed according to the type of GnRH analogue used for endogenous LH suppression confirmed the beneficial effect of GnRH agonist addition. Administration of GnRH agonist during the luteal phase is expected to improve the probability of pregnancy in ovarian stimulation cycles using either GnRH agonist or GnRH antagonist for prevention of premature LH surge.

It should be noted that the current systematic review is based on the analysis of manuscripts published in full and not of abstracts presented in congresses. During the process of a systematic review studies published only as abstracts can also be included together with manuscripts published in full. Exclusion of abstracts might lead to the omission of potentially important information, since many studies are not finally published in full. If the abstract publication probability is associated with the magnitude and the direction of the outcome reported in the abstract, then this might lead to the so-called publication bias.

However, neither approach (inclusion of only manuscripts published in full or full manuscripts plus abstracts) is without drawbacks. The inclusion of abstracts means that in many cases, information required to critically evaluate a potentially eligible study is missing. This is true even for manuscripts published in full. Practically, not all authors of abstracts reply to the questions asked by the authors of a meta-analysis and thus only a proportion of abstracts are included in the final estimate. In addition, in many cases information required by the reviewers is no longer available from the authors of an abstract at the time of the review, posing significant difficulties in evaluating the eligibility of the study. Nevertheless, existing evidence suggests that although there is a considerable publication deficit in reproductive medicine for RCTs, there is no concomitant publication bias (Evers, 2000).

It should be noted that, in the eligible studies, GnRH agonist addition during the luteal phase was not always carried out by using the same protocol. Moreover, luteal support in the control arms of the studies analysed was not always the same (Table I). Due to the small number of eligible studies, however, a meaningful subgroup analysis for the above sources of heterogeneity was not possible. Nevertheless, clinical heterogeneity was not accompanied by statistical heterogeneity for the primary outcome measure.

The beneficial effect of GnRH agonist addition during the luteal phase in IVF/ICSI cycles on the probability of pregnancy has also been shown in the oocyte donation model (Tesarik et al., 2004). Significantly higher ($P < 0.05$) implantation (36.9 versus 25.1%) and live birth rates (31.1 versus 21.5%) were observed in oocytes recipients who, in addition to estradiol (E_2) and progesterone, were treated with GnRH agonist 6 days after ICSI compared with recipients who received E_2 and progesterone only for luteal support.

The mechanism of the beneficial effect of luteal phase GnRH agonist administration might be explained by a direct effect of GnRH agonist on the embryo and/or on the endometrium.

Raga et al. (1999) demonstrated that both GnRH and its receptor are expressed at the mRNA level in vitro in cultured mouse embryos during the preimplantation development period (morula to hatching blastocyst stages). Moreover, they showed the presence of an immunoreactive GnRH in the cytotrophoblast of prehatched blastocyst and in the placental cytotrophoblast.

In addition, it has been suggested that GnRH might play an important role in the control of hCG synthesis and secretion in the placenta and in the preimplantation embryos. This is due to the fact that GnRH receptors are located not only in the trophectoderm, but also in the inner cell mass of the mouse blastocyst (Raga et al., 1999). Data to support an important role of GnRH agonist addition during the luteal phase regarding steroidogenesis and hCG synthesis have been offered by the study of Tesarik et al. (2006). In that study, it was shown that serum concentrations of E_2 and progesterone on Day 15 after ICSI were higher in the group to which GnRH agonist was added in the luteal support scheme. Moreover, in the same study, a higher serum β-HCG concentration 15 days after ICSI was observed in pregnant patients in whom GnRH agonist was added in the luteal support scheme.

On the other hand, a direct effect of GnRH agonist on endometrium cannot be excluded, since GnRH receptors are expressed in human endometrium (Reshef et al., 1990), both in endometrial stromal and epithelial cells (Raga et al., 1998).

The LH released during agonist administration may have biological effects that exogenous hCG does not provide. This effect might be seen in to the corpus luteum and progesterone secretion, or endometrium and even embryos.

Regardless of the effect of GnRH agonist addition during the luteal phase on the probability of pregnancy, it should be noted that such an intervention raises safety concerns, since a direct effect of GnRH agonist on early embryonic development cannot be excluded (Raga et al., 1999). Currently, available data suggest that inadvertent administration of a GnRH agonist during a conception cycle is not accompanied by an increased risk of birth defects (Ron-El et al., 1990; Smitz et al., 1991; Golan et al., 1992; Wilshire et al. 1993; Young et al., 1993; Elefant et al., 1995; Gartner et al., 1997; Chardonnens et al., 1998). However, a long-term follow up of nine children born after GnRH agonist administration during a conception cycle raised concerns about their neurodevelopmental status (Lahat et al., 1998; Papanikolaou et al., 2005).

In conclusion, on the basis of the currently best available evidence, it appears that GnRH agonist addition during luteal phase significantly increases the probability of live birth; however, more data focusing particularly on the safety of the method for the children born are necessary.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

Authors' roles

D.K. conceived and designed the study, selected the articles and retrieved the data, drafted the manuscript. E.M.K. analysed, interpreted the data and revised the manuscript. H.M.F. conceived and designed the study, selected the articles and retrieved the data. T.B.T. analysed and interpreted the data. P.D. revised the manuscript. B.C.T. revised the manuscript. All the authors approved the final version of the manuscript.

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Conflict of interest

None declared.

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