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Is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in *in vitro* fertilization? A systematic review and meta-analysis

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The role of progesterone elevation on in vitro fertilization (IVF) outcome has remained a debatable issue for several years. The aim of this systematic review and meta-analysis was to evaluate whether progesterone elevation on the day of human chorionic gonadotrophin (hCG) administration is associated with the probability of pregnancy. Eligible studies were considered those in which patients did not participate more than once. A literature search in MEDLINE, EMBASE and CENTRAL identified 12 eligible studies, 10 of which were retrospective. The majority ($n = 10$) of these studies did not detect a statistically significant association between progesterone elevation and the probability of pregnancy. Meta-analysis was performed only for the studies ($n = 5$) that provided data on clinical pregnancy per patient reaching hCG administration for final oocyte maturation. No statistically significant association between progesterone elevation and the probability of clinical pregnancy was detected (Odds ratio: 0.75, 95% confidence interval 0.53–1.06; $P = 0.10$). This finding persisted in the sensitivity analyses performed, which excluded the studies that did not report clearly that measurement of progesterone did not affect patients' management and those that did not report definition of clinical pregnancy. In addition, subgroup analyses were conducted on the basis of type of gonadotrophin-releasing hormone GnRH analogue used and on the value of serum threshold used to classify patients in those with or without progesterone elevation. These analyses, however, did not materially change the results obtained. In conclusion, the best available evidence does not support an association between progesterone elevation on the day of hCG administration and the probability of clinical pregnancy in women undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF.

Key words: hCG/ovarian stimulation/pregnancy/progesterone

Introduction

The introduction of gonadotrophin-releasing hormone (GnRH) analogues for pituitary suppression in in vitro fertilization (IVF) significantly decreased the incidence of premature luteinizing hormone (LH) surge (Smitz *et al.*, 1992). Despite pituitary down-regulation, however, several researchers have described a phenomenon reported as premature luteinization (Hofmann *et al.*, 1993; Legro *et al.*, 1993; Ubaldi *et al.*, 1996a; Bosch *et al.*, 2003). This refers to a rise in serum progesterone levels on the day of human chorionic gonadotrophin (hCG) administration for final oocyte maturation above a threshold level, which is usually arbitrarily defined. Its incidence varies, ranging between 5 and 30% in IVF patients (Edelstein *et al.*, 1990; Schoolcraft *et al.*, 1991; Silverberg *et al.*, 1991; Fanchin *et al.*, 1993; Givens *et al.*, 1994; Ubaldi *et al.*, 1995).

At present, there is no consensus on whether progesterone elevation on the day of hCG administration is associated with the achievement of pregnancy. Several studies have denied the presence of such an association (Edelstein *et al.*, 1990; Silverberg *et al.*, 1991; Antoine *et al.*, 1992; Check *et al.*, 1994; Givens *et al.*, 1994; Bustillo *et al.*, 1995; Levy *et al.*, 1995; Ubaldi *et al.*, 1995; Abuzeid and Sasy, 1996; Huang *et al.*, 1996; Miller *et al.*, 1996; Moffit *et al.*, 1997; Doldi *et al.*, 1999; Lindheim *et al.*, 1999; Urman *et al.*, 1999; Martinez *et al.*, 2004), whereas others have confirmed the presence of a negative association (the probability of pregnancy decreases significantly when serum progesterone on the day of

hCG administration for final oocyte maturation rises above a threshold level) (Schoolcraft *et al.*, 1991; Check *et al.*, 1993a; Fanchin *et al.*, 1993, 1997a; Harada *et al.*, 1995; Shulman *et al.*, 1996; Bosch *et al.*, 2003).

It should be noted that if a negative association between progesterone elevation on the day of hCG administration and the probability of pregnancy exists, it might be worth examining the possibility of cryopreserving the resulting embryos and their transfer in a subsequent frozen-thawed cycle (Silverberg *et al.*, 1991; Legro *et al.*, 1993; Silverberg *et al.*, 1994) or alternatively, administering hCG at an earlier time in the follicular phase, prior to progesterone elevation (Harada *et al.*, 1996). On the contrary, absence of an association indicates that assessment of serum progesterone on the day of hCG administration might be redundant.

The purpose of this systematic review and meta-analysis was to address the following question: among patients undergoing ovarian stimulation for IVF using GnRH analogues and gonadotrophins, is progesterone elevation on the day of hCG administration associated with the probability of pregnancy?

Materials and methods

Search strategy

For the purpose of this systematic review, a literature search in MEDLINE, EMBASE and CENTRAL electronic databases was performed by two of the authors (C.A.V. and E.M.K. from 10 October 2005 to 31 December 2005 to identify studies which answered the following question: among patients undergoing ovarian stimulation for IVF using GnRH analogues and gonadotrophins, is progesterone elevation on the day of hCG administration associated with the probability of pregnancy? A computerized literature search was performed using the terms 'progesterone' as medical subject heading under 'ovulation induction' or 'hormonal therapy' or 'infertility therapy' and limited to 'human' and 'female'. No language limitations were applied. Additionally, references of retrieved articles were hand-searched.

Selection of studies

In order for the studies to be eligible for this systematic review, the following inclusion criteria were established prior to the literature search: (i) GnRH analogue should have been used for down-regulation and gonadotrophins for ovarian stimulation, (ii) patients should have been classified as showing or not showing progestone elevation on the day of hCG administration for final oocyte maturation, (iii) patients should not have entered the study more than once (number of patients equal to number of cycles performed), (iv) the study should provide data on pregnancy outcome in patients showing or not showing progesterone elevation on the day of hCG administration and (v) the study should have been published in a peer reviewed journal.

In case the pregnancy outcome reported in the studies evaluated was not using as a denominator patients reaching hCG administration for final oocyte maturation, but patients reaching oocyte retrieval or patients in whom embryo transfer (ET) was performed, the authors were contacted and asked to provide the missing information.

All studies identified, which addressed the research question, were initially considered for the present systematic review, regardless of the direction of study (retrospective or prospective), their sample size or the threshold of serum progesterone on the day of hCG administration used to classify the patients as showing or not showing progesterone elevation. Studies that reported that progesterone levels during ovarian stimulation were used to modify patients' management were excluded.

Studies identified

Literature search was conducted for the time interval between 1984, when the first study describing the use of agonists in IVF appeared in the literature (Porter *et al.*, 1984), and 2005. This electronic search resulted in the retrieval of 1114 publications. Subsequently, the titles of these manuscripts were examined to exclude irrelevant studies, resulting in 104 potentially eligible publications. The abstracts of these studies were examined and, eventually, 45 manuscripts that could provide data to answer the research question were identified (Fig. 1). The full text of these studies was examined thoroughly, resulting in the exclusion of 33 publications (Supplementary material, Table I). Specifically, studies were excluded because: (i) they did not properly address the research question ($n = 6$), (ii) they did not use GnRH analogues for pituitary suppression ($n = 2$), (iii) they included patients more than once ($n = 18$), (iv) they were letters to journals or reviews ($n = 6$) and (v) measurement of serum progesterone during ovarian stimulation affected patients' management ($n = 1$). The references of all the studies in which the full text was retrieved were hand-searched. However, no additional studies that could provide data to answer the research question were found. Eventually, 12 studies associating progesterone elevation on the day of hCG administration with pregnancy achievement were identified (Table 1).

Data extraction

The following data were recorded from each of the 12 eligible studies: demographic (type of study, citation data, country, study period, number of patients included, number of cycles performed, selection of cycles and indication for treatment), procedural (type of down-regulation and protocol of ovarian stimulation, type of gonadotrophin administered, dose and criteria for hCG administration, time of oocyte

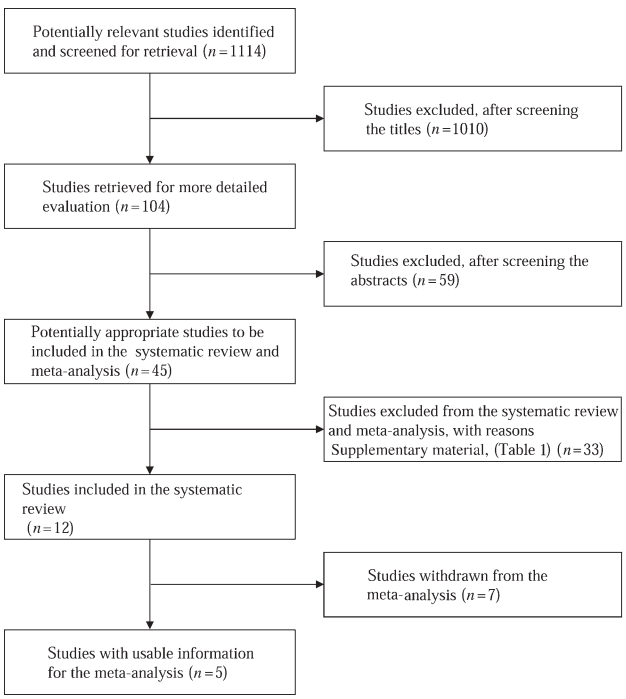

Figure 1: QUOROM statement flow diagram for study selection

Table 1: Demographic data of the studies included in the systematic review

Study number	Authors, year, country of origin, journal	Type of study (power analysis)	Study period	Cycles/pts	Selection of cycles	Pt diagnosis in group with progesterone elevation or not	Authors contacted
1	Edelstein *et al.* (1990), USA, Fertil Steril	Retrospective (n/a)	August 1989–November 1989	101/101	Consecutive cycles (five cycles excluded due to severe male factor)	Reported as not significantly different	No
2	Silverberg *et al.* (1991), USA, J Clin Endocrinol Metab	Retrospective (n/a)	Not reported	115/115	Consecutive cycles	Reported as not significantly different	Yes
3	Check *et al.* (1993a), USA, Eur J Obstet Gynecol Reprod Biol	Unclear (not reported)	Not reported	119/119	Cycles that resulted in ET	Not reported	Yes
4	Check *et al.* (1994)[a], USA, Fertil Steril	Retrospective (n/a)	November 1991–August 1992	138/138	All women undergoing IVF–ET who shared oocytes	Not reported	Yes
5	Shechter *et al.* (1994), Israel, Gynecol Endocrinol	Retrospective (n/a)	Not reported	104/104	Cycles in which at least three embryos were transferred	Not reported	Yes
6	Hofmann *et al.* (1996), USA, Fertil Steril	Retrospective (n/a)	Not reported	133/133	Consecutive cycles that resulted in ET in patients $\leq$39 yrs,with normal day 3 FSH levels and normal CC challenge test	Reported as not significantly different	Yes
7	Miller *et al.* (1996) (Group A)[b], USA, J Assist Reprod Genet	Retrospective (n/a)	Not reported	125/125	Cycles using a combination of GnRH agonist with menotropin and/or follitropin	Not reported	Yes
	Miller *et al.* (1996) (Group B)[b], USA, J Assist Reprod Genet	Retrospective (n/a)	Not reported	168/168	Cycles using a combination of GnRH agonist with menotropin and/or follitropin	Not reported	Yes
8	Ubaldi *et al.* (1996b), Belgium, Hum Rep	Retrospective[c] (n/a)	Not reported	24/24	$<$30 yrs, regular menstrual cycle, basal normal serum FSH and estradiol concentrations, normal pelvic morphology at USS and $<$3 previous IVF/ICSI procedures.	Not reported	Yes
9	Moffit *et al.* (1997), USA, Fertil Steril	Retrospective (n/a)	January 1989–October 1993	333/333	Pts with fresh transfer and at least one transfer of cryopreserved embryos from the same cohort of recruited oocytes	Not reported	Yes
10	Urman *et al.* 1999, Turkey, Fertil Steril	Retrospective (n/a)	Not reported	911/911	Pts undergoing their first cycle for male infertility who had ET	Male infertility	Yes

Continued overleaf

Table 1: *Continued*

Study number	Authors, year, country of origin, journal	Type of study (power analysis)	Study period	Cycles/pts	Selection of cycles	Pt diagnosis in group with progesterone elevation or not	Authors contacted
11	Bosch *et al.* (2003)[d], Spain, Fertil Steril	Prospective (no)	Not reported	85/85	First IVF-ICSI cycle and normal basal hormonal profile (cycle day 3 FSH level <10 mIU/mL, LH level <10 mIU/mL and E_2 level <60 pg/mL), no previous adnexal surgery, no endometrioma on ultrasonography and no diagnosis of polycystic ovary syndrome	Not reported	Yes
12	Martinez *et al.* (2004), Spain, Reprod Biomed Online	Retrospective (n/a)	July 2002–January 2003	377/377	Not reported	Not significantly different, reported and analysed	Yes

n/a, not applicable; OHSS, ovarian hyperstimulation syndrome; Pts, patients; yrs, years; CC, clomiphene citrate; USS, ultrasound scan.
[a]Data analysed originate exclusively from the donors group and not the acceptors.
[b]The study Miller *et al.* (1996) analyses two groups of patients (Groups A and B) based on the type of luteal support. The type of group used in each study has been indicated subsequently in parenthesis.
[c]Pts were prospectively recruited for a different purpose.
[d]Four patients which had their embroys cryopreserved are included. Data on classification of these patients in those with or progesterone elevation were retrieved after communication with the authors.

retrieval, type of fertilization, day of ET, number of embryos transferred, type of luteal support administered, serum progesterone threshold level used for classification of patients in those showing and those not showing progesterone elevation and type of assay used for the measurement of progesterone on the day of hCG) and outcome data [pregnancy achievement, duration and total dose of follicle-stimulating hormone (FSH) required for ovarian stimulation, serum estradiol (E_2) levels on the day of hCG administration, number of cumulus–oocyte complexes (COCs) retrieved and fertilization rates]. Any disagreement was resolved unanimously by discussion.

Outcomes

The main outcome measures chosen for meta-analysis were clinical pregnancy (defined as the detection of fetal heart by ultrasound at 6–8 weeks of gestation), ongoing pregnancy (defined as the confirmation of viable pregnancy beyond 12 weeks of gestation) and live birth/delivery per patient reaching hCG administration for final oocyte maturation. In case the studies did not report data regarding one or more of the above outcome measures, the authors were contacted and asked to provide the missing information. Secondary outcome measures included duration and total dose of FSH required for ovarian stimulation, serum E_2 levels on the day of hCG administration, number of COCs retrieved and fertilization rates.

Quantitative data synthesis

The dichotomous data results for each of the studies eligible for meta-analysis were expressed as an odds ratio (OR) with 95% confidence intervals (CI). These results were combined for meta-analysis using the Mantel/Haenszel model, when using the fixed effects method, and the DerSimonian and Laird model, when using the random effects method.

When the outcome of interest was of a continuous nature, the differences were pooled across the studies, which provided information on this outcome parameter, resulting in a weighted mean difference (WMD) with 95% CI. The inverse variance method and the DerSimonian and Laird method were used, respectively, when the fixed or random effects method was applied.

All results were combined for meta-analysis with Revman Software (The Cochrane Collaboration, 2000). Study-to-study variation was assessed by using the χ^2-statistic (the hypothesis tested was that the studies are all drawn from the same population, i.e. from a population with the same effect size). Moreover, due to the fact that the χ^2 test is considered to have low power to detect inconsistency across studies, when the studies have a small sample size or are limited in number, a *P*-value of 0.10 was used to determine statistical significance (Dickersin and Berlin, 1992). A fixed effects model was used, where no heterogeneity was present, whereas in the presence of significant heterogeneity, a random effects model was applied. A funnel plot analysis and Egger's test were performed to detect the presence of publication bias.

Subgroup analyses were performed depending, on (i) the serum progesterone level used as a threshold by each study to classify patients as showing or not showing progesterone elevation on the day of hCG administration and (ii) the type of GnRH analogue used for down-regulation.

Sensitivity analyses were carried out to check the stability of the results obtained by excluding (i) the studies that did not report clearly that the measurement of progesterone during ovarian stimulation did not affect patients' management and (ii) the studies that did not provide the definition of the pregnancy outcome examined.

Results

Twelve studies fulfilled the inclusion criteria for the systematic review (see Table 1). A total of 2733 patients were reviewed (GnRH antagonists: $n = 109$, GnRH agonists: $n = 2624$).

Systematic review

Characteristics of the eligible studies are listed in Tables 1 and 2. All included studies were published between 1990 and 2004. The majority of the studies were published in Fertility Sterility ($n = 6$) and Human Reproduction ($n = 2$). Ten studies were retrospective in design, one study was prospective and in one study it was unclear whether a retrospective or prospective design was followed. The size of the studies ranged from 24 to 911 patients, and the median number of patients included was 125.

For ovarian stimulation, a combination of urinary and recombinant gonadotrophins was used in two studies, in nine studies this was achieved with urinary gonadotrophins, whereas in one study ovarian stimulation was performed with recombinant gonadotrophins. Criteria for triggering final oocyte maturation varied markedly across studies and were based on follicular data ($n = 2$), on a combination of follicular data and E_2 levels ($n = 8$), whereas in two studies these criteria were not reported. In the majority of the studies ($n = 10$), the medication used for triggering final oocyte maturation was urinary hCG (10 000 IU), whereas in two studies this was not reported. Oocyte retrieval was performed 34–37 h after hCG administration in 10 studies, whereas 2 studies did not provide any details about the timing of oocyte retrieval (Supplementary material, Table II).

To inhibit premature LH surge, the long luteal agonist protocol was used in eight studies, in two studies this was performed using both the long luteal and the short agonist protocol in the same study, whereas in two studies a fixed day-6 antagonist protocol was applied. In the agonist group of studies, nafarelin, triptorelin, leuprolide acetate and buserelin were employed in various protocols, whereas cetrorelix was the analogue used in the antagonist group. Details about the GnRH analogue protocols used in the studies analysed are presented in Supplementary material, Table II.

For the measurement of serum progesterone on the day of hCG administration, all the studies used commercially available immunoassay kits. The inter-assay coefficient of variance (CV) ranged between 3.9 and 34%, whereas the intra-assay CV ranged between 2.9 and 11.9%. In one study, the inter- or intra-assay CV was not reported (Table 2).

Fertilization methods included IVF ($n = 7$), intracytoplasmic sperm injection (ICSI) ($n = 2$) and IVF/ICSI ($n = 3$). ETs were performed in the majority of studies ($n = 8$) on day 2 or 3 after oocyte retrieval, in one study on day 1, whereas in three studies the day of ET was not reported. Luteal support varied between studies as well as within a study (Miller *et al.*, 1996). Four studies did not provide details about the type of luteal support used (Supplementary material, Table II).

The threshold of serum progesterone on the day of hCG administration, used to classify patients as showing or not showing

Table 2: Serum threshold used to classify patients into patients with or without progesterone (P) elevation and type of assay used for P measurement in the studies included in the systematic review

Study Number	Authors and year	Threshold (ng/mL)	Reason for choosing threshold	Assay for progesterone	Inter/Intra-assay CV (%)	Did assessment of progesterone affect patients' management?
1	Edelstein *et al.* (1990)	0.9	Arbitrary	Commercially available RIA kit (Pantex, Santa Monica, CA, USA)	34/not reported	No
2	Silverberg *et al.* (1991)	0.9	ROC curve analysis	^{125}I RIA kit (Diagnostic Products Corporation, Los Angeles, CA, USA)	11.8/8.9	No
3	Check *et al.* (1993a)	1.0	Arbitrary	Commercial RIA kit (Amersham-Amerlex, Arlington Hights, IL, USA)	9.1/11.9	Not reported
4	Check *et al.* (1994)	1.0	Arbitrary	Amerlex-M RIA (Amersham Inc., Arlington Heights, IL, USA)	Not reported/not reported	Not reported
5	Shechter *et al.* (1994)	1.0	Arbitrary	Solid phase RIA (Coat-a Count; Diagnostic Products Corporation, Los Angeles, CA, USA)	10/6.4	Not reported
6	Hofmann *et al.* (1996)	0.9	Arbitrary	RIA kit (Diagnostic Products Corporation, Los Angeles, CA, USA)	6.4/4.7	Not reported
7	Miller *et al.* (1996) (Group A)[a]	0.9	Arbitrary	Commercially available RIA kit (Diagnostic Products Corporation, Los Angeles, CA, USA)	6.2/5.0	No
	Miller *et al.* (1996) (Group B)[a]	0.9	Arbitrary	Commercially available RIA kit (Diagnostic Products Corporation, Los Angeles, CA, USA)	6.2/5.0	No
8	Ubaldi *et al.* (1996b)	Low progesterone: ≤ 0.9 and high progesterone: >1.1	Arbitrary	Commercially available RIA	6/4	Not reported
9	Moffitt *et al.* (1997)	0.9	Arbitrary	RIA Coat-a Count (Diagnostic Products Corporation, Los Angeles, CA, USA)	13.1/10	No
10	Urman *et al.* (1999)	0.9	ROC curve analysis	Solid phase, ligand-labelled competitive chemiluminescent immunoassay (Immulite Progesterone; Diagnostic Products Corp., Los Angeles, CA, USA)	7.2/5.8	No
11	Bosch *et al.* (2003)	1.2	ROC curve analysis	Microparticle enzyme Immunoassay Axsym System (Abbott Scientifica, SA, Madrid, Spain)	3.9/9.6	Not reported
12	Martinez *et al.* (2004)	0.9	Arbitrary	Automated immunofluorescent assay (Kryptor Brahms, Saint Ouen, France)	4.7–5.1/2.9–5.8	No

RIA, radioimmunoassay.

[a]The study Miller *et al.* (1996) analyses two groups of patients (Groups A and B) based on the type of luteal support. The type of group used in each study has been indicated subsequently in parenthesis.

Table 3: Pregnancy outcomes examined in the studies included in the systematic review

Study number	Authors and year	Pregnancy outcome examined[a]	Definition	OR (CIs)	Association of progesterone elevation with pregnancy outcome examined
1	Edelstein *et al.* (1990)	Clinical pregnancy per hCG	Not reported	1.09 (0.43–2.79)	No association
		Ongoing pregnancy per hCG	Not reported	1.03 (0.38–2.83)	No association
2	Silverberg *et al.* (1991)	Clinical pregnancy per hCG	FH by USS at 7 wks of gestation	0.16 (0.01–2.86)	No association
3	Check *et al.* (1993a)	Live birth per oocyte retrieval	Live birth	0.18 (0.06–0.51)	Negative association
4	Check *et al.* (1994)	Live birth per oocyte retrieval	Viable infant at delivery	0.46 (0.15–1.43)	No association
5	Shechter *et al.* (1994)	Clinical pregnancy per ET	Sac at USS	1.22 (0.47–3.16)	No association
6	Hofmann *et al.* (1996)	Ongoing pregnancy per ET	>20 wks/delivered	1.48 (0.69–3.19)	No association
7	Miller *et al.* (1996) (Group A)[b]	Clinical pregnancy per ET	FH by USS at 7 wks of gestation	0.44 (0.16–1.18)	No association
	Miller *et al.* (1996) (Group B)[b]	Clinical pregnancy per ET	FH by USS at 7 wks of gestation	1.03 (0.53–2.00)	No association
8	Ubaldi *et al.* (1996b)	Clinical pregnancy per hCG	FH by USS at 7 wks of gestation	1.87 (0.24–14.65)	No association
9	Moffitt *et al.* 1997	Clinical pregnancy per ET	Not reported	1.16 (0.59–2.28)	No association
		Ongoing pregnancy per ET	>20 wks	1.65 (0.84–3.25)	No association
10	Urman *et al.* (1999)	Clinical pregnancy per ET	FH by USS at 6 wks of gestation	1.42 (1.07–1.88)	Positive association
		Ongoing pregnancy per ET	>12 wks	1.27 (0.94–1.72)	No association
11	Bosch *et al.* (2003)	Clinical pregnancy per hCG	FH by USS at 6–7 wks of gestation	0.27 (0.10–0.72)	Negative association
		Ongoing pregnancy per hCG	>20 wks	0.29 (0.11–0.79)	Negative association
12	Martinez *et al.* (2004)	Clinical pregnancy per hCG	Sac at USS at 6 wks of gestation	0.89 (0.58–1.35)	No association
		Delivery per hCG	Delivery	0.98 (0.62–1.55)	No association

OR, Odds ratio; CI, Confidence Intervals; P, progesterone; FH, fetal heart; wks, weeks; USS, ultrasound scan; hCG, human chorionic gonadotrophin; ET, embryo transfer; OPU, oocyte pick-up.
[a]When the authors reported the pregnancy outcome with more than one denominators (per hCG, and/or per oocyte retrieval and per ET), then the denominator closest to the day of hCG administration is reported in this table.
[b]The study Miller *et al.* (1996) analyses two groups of patients (Groups A and B) based on the type of luteal support. The type of group used in each study has been indicated subsequently in parenthesis.

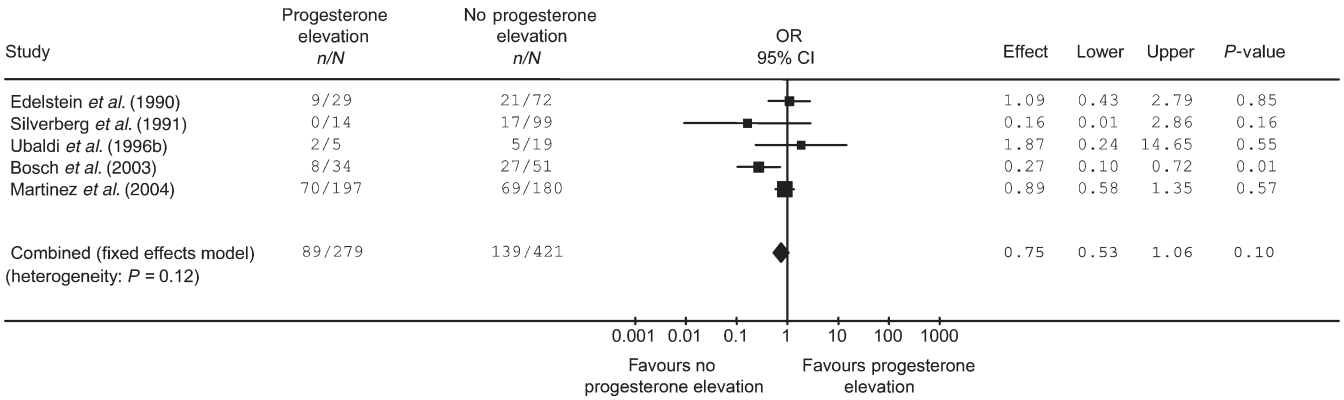

Figure 2: OR of clinical pregnancy rate per patient reaching hCG administration for final oocyte maturation

progesterone elevation varied among studies. For this purpose, eight studies used 0.9 ng/mL, three studies used 1.0 ng/mL and one study used 1.2 ng/mL. In the majority of the studies ($n = 9$) analysed, this threshold was selected arbitrarily, whereas in three studies, receiver operator characteristics (ROC) curve analysis was used (Table 2).

Two studies (Check *et al.*, 1993a; Bosch *et al.*, 2003) detected a negative association between elevation of progesterone on the day of hCG administration and the pregnancy outcomes examined. On the contrary, Urman *et al.* (1999) reported a significantly higher probability of clinical, but not ongoing, pregnancy in patients with progesterone elevation. The remaining studies ($n = 9$) did not find any association between the elevation of progesterone on the day of hCG administration and the pregnancy outcomes analysed (Table 3).

Meta-analysis

Clinical pregnancy rate

The probability of clinical pregnancy did not differ significantly between patients with and those without progesterone elevation on the day of hCG administration (OR: 0.75, 95% CI: 0.53–1.06; $P = 0.10$; heterogeneity: $P = 0.12$; fixed effects model) (Fig. 2). Clinical pregnancy rate was lower, but not significantly so, in the group with progesterone elevation [rate difference (RD): −10%, (95% CI: −22%–+2%; $P = 0.11$; heterogeneity: $P = 0.04$; random effects model] (Fig. 3). A funnel plot of the included studies is shown in Supplementary material, Figure 1. No publication bias was detected in the studies analysed (Egger's test: $P = 0.60$). The exclusion of the study that did not provide definition for clinical pregnancy (Edelstein *et al.*, 1990) led to similar results (OR: 0.59, 95% CI: 0.24–1.43; $P = 0.24$; heterogeneity: $P = 0.08$, random effects model) (Supplementary material, Figure 2). Finally, these results did not change substantially, by excluding the studies that did not report clearly that the measurement of progesterone during ovarian stimulation did not affect patients' management (OR: 0.86, 95% CI: 0.59–1.25; $P = 0.44$; heterogeneity: $P = 0.46$; fixed effects model) (Supplementary material, Figure 3).

Subgroup analyses regarding the probability of clinical pregnancy were conducted on the basis of serum progesterone threshold, used to classify patients in those showing and those not showing progesterone elevation and in addition, on the type of analogue used for down–regulation. When only the studies that used 0.9 ng/mL as a threshold for the classification of patients in those without progesterone elevation were analysed ($n = 4$), the probability of clinical pregnancy between patients with and those without progesterone elevation on the day of hCG administration remained not significantly different (OR: 0.88, 95% CI: 0.61–1.28; $P = 0.51$; heterogeneity: $P = 0.56$; fixed effects model) (Fig. 4). The subgroup analysis based on the type of GnRH analogue used for down-regulation did not materially change the original results. In the agonist group of studies ($n = 3$), the probability of

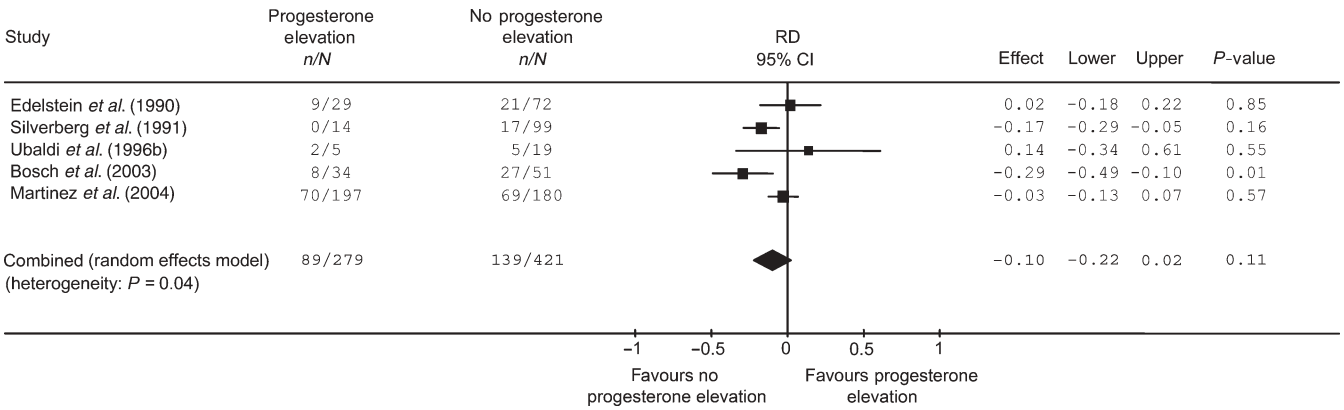

Figure 3: Rate difference (RD) for clinical pregnancy per patient reaching hCG administration for final oocyte maturation

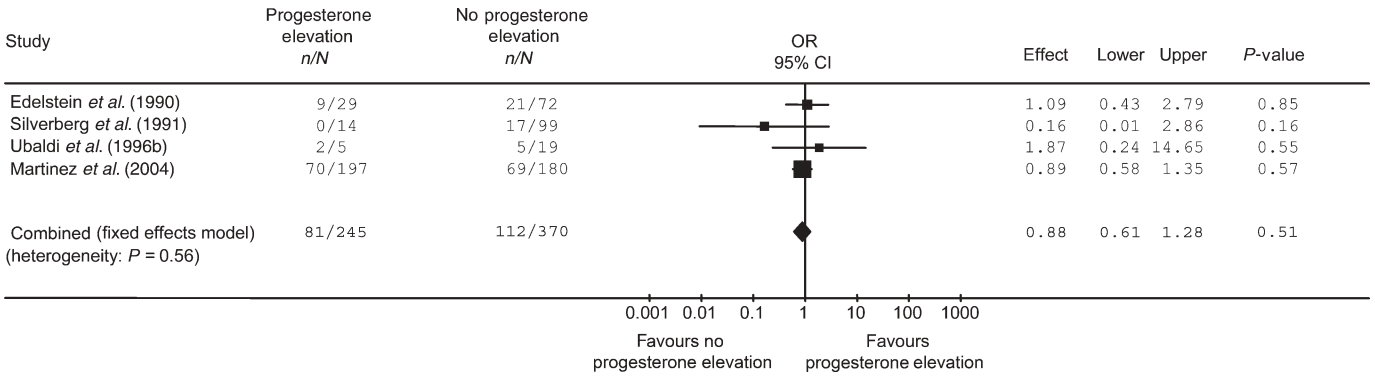

Figure 4: OR of clinical pregnancy rate per patient reaching hCG administration for final oocyte maturation: studies that used 0.9 ng/mL as a threshold for classifying patients as not having progesterone elevation

clinical pregnancy between patients with and those without progesterone elevation on the day of hCG administration was not significantly different (OR: 0.86, 95% CI: 0.59–1.25; $P = 0.44$; heterogeneity: $P = 0.46$; fixed effects model), which was also the case when the two antagonist studies were pooled (OR: 0.57, 95% CI: 0.09–3.56; $P = 0.55$; heterogeneity: $P = 0.10$; random effects model) (Fig. 5).

It should be noted that both female age (Supplementary material, Figure 4) and the number of embryos transferred (Supplementary material, Figure 5) were not significantly different between the groups that did and did not exhibit progesterone elevation on the day of hCG administration (female age: WMD: 0.06 years, 95% CI: −1.25–+1.38, $P = 0.92$; heterogeneity: $P = 0.02$; random effects model; number of embryos transferred: WMD: 0.07 embryos 95% CI: −0.06–+0.19, $P = 0.29$; heterogeneity: $P = 0.68$; fixed effects model).

Ongoing pregnancy rate/live birth rate

Pooling of data for these outcome measures in the studies eligible for meta-analysis was not considered appropriate, due to the fact that these were either not uniformly defined or not reported (Table 3). Ongoing pregnancy rate per patient reaching hCG administration was present in two of the studies included in the current systematic review (Edelstein *et al.*, 1990; Bosch *et al.*, 2003). In the study by Bosch *et al.* (2003), ongoing pregnancy was defined as the confirmation of pregnancy beyond 20 weeks of gestation, whereas in the study by Edelstein *et al.* (1990), ongoing pregnancy was not defined. Live birth rate per patient reaching hCG administration was reported only in one study (Martinez *et al.*, 2004).

Secondary outcomes

FSH requirement

The number of FSH ampoules required was not significantly different between patients with and those without progesterone elevation (WMD: 0.92 ampoules, 95% CI: −1.74–+3.59; $P = 0.50$; heterogeneity: $P = 0.06$; random effects model) (Supplementary material, Figure 6). Four studies offered data for this outcome measure.

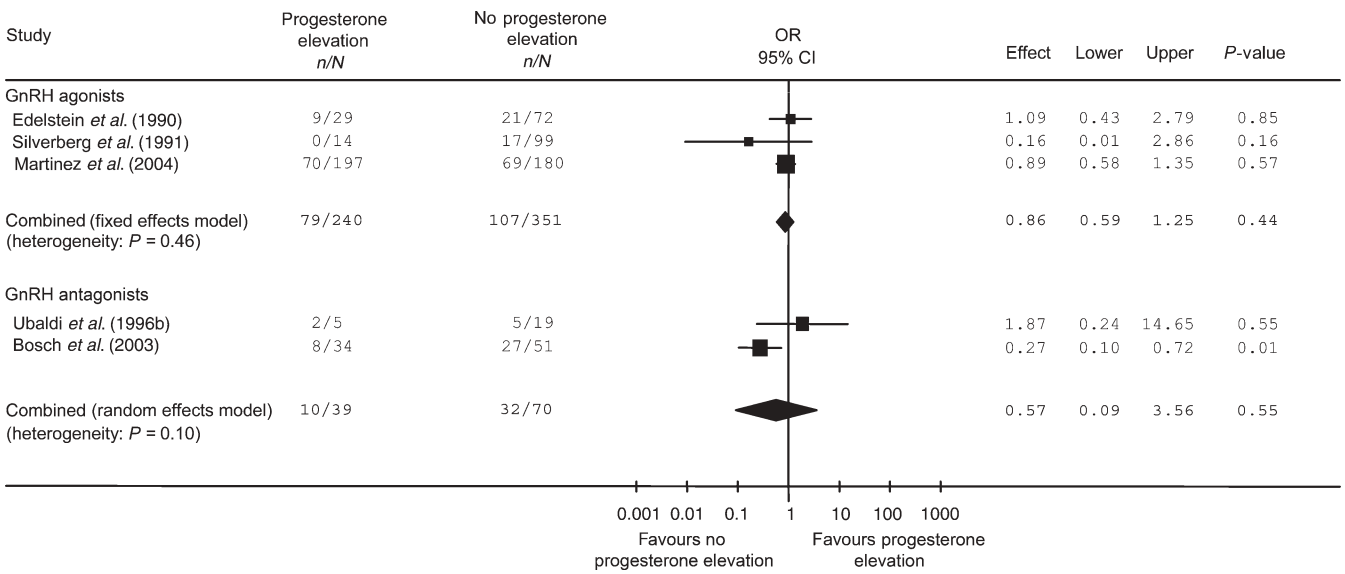

Figure 5: OR of clinical pregnancy rate per patient reaching hCG administration for final oocyte maturation, depending on the type of GnRH analogue used (agonist–antagonist)

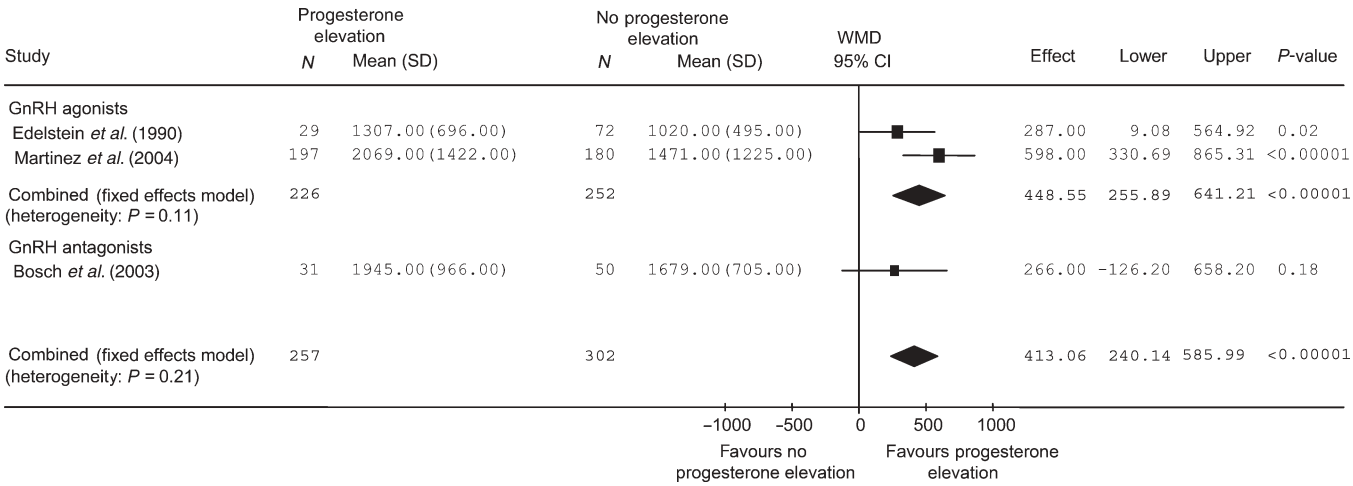

Figure 6: Weighted mean difference (WMD) in serum E2 levels on the day of hCG administration for final oocyte maturation between patients with or without progesterone elevation on the day of hCG administration, depending on the type of GnRH analogue used (agonist–antagonist)

Duration of FSH stimulation

The duration of stimulation did not differ significantly between patients with and those without progesterone elevation (WMD: 0.08 days, 95% CI: −0.57–+0.73; $P = 0.81$; heterogeneity: $P = 0.003$; random effects model) (Supplementary material, Figure 7). Three studies offered data for this outcome measure.

E_2 levels on the day of hCG administration

The E_2 levels (pg/mL) on the day of hCG administration were significantly higher in the group of patients that exhibited progesterone elevation on the day of hCG compared with those who did not (WMD: 413.06 pg/mL, 95% CI: 240.14–585.99; $P < 0.00001$; heterogeneity: $P = 0.21$; fixed effects model) (Fig. 6). Three studies offered data for this outcome measure.

COCs retrieved

No statistically significant difference in the number of COCs retrieved was detected between the patients with and those without progesterone elevation on the day of hCG administration (WMD: 1.87 COCs, 95% CI: −0.07–+3.87; $P = 0.06$; heterogeneity: $P = 0.10$; random effects model) (Supplementary material, Figure 8). Four studies offered data for this outcome measure. However, a subgroup analysis depending on the type of GnRH analogue used showed that in the group of agonist studies significantly more oocytes were retrieved in the progesterone elevation group compared with the group without progesterone elevation (WMD: 2.96 COCs, 95% CI: +1.74–+4.18; $P < 0.00001$; heterogeneity: $P = 0.13$; fixed effects model). This difference was not present when the two antagonist studies were pooled (WMD: 0.00 COCs, 95% CI: −2.98–+2.99; $P = 1.00$; heterogeneity: $P = 0.44$; fixed effects model) (Supplementary material, Figure 9).

Fertilization rates

Fertilization rates were not significantly different between patients with and those without progesterone elevation on the day of hCG administration (WMD: −1.71%, 95% CI: −5.32–+1.90; $P = 0.35$; heterogeneity: $P = 0.78$; fixed effects model) (Supplementary material, Figure 10). Two studies offered data for this outcome measure.

Discussion

The current systematic review suggests that progesterone elevation, on the day of hCG administration for final oocyte maturation, does not appear to be associated with the probability of pregnancy, in women undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF (Table 3).

In the present review, an effort was made to establish firm inclusion criteria, so that reliable conclusions could be drawn. Accordingly, only studies that did not violate the independence assumption were considered eligible. The statistical tests used in the studies analysed, to evaluate the effect of progesterone elevation on the day of hCG administration on the probability of pregnancy, assume that all the observations are made on subjects that are independent from each other (Cochran, 1974; Kruskal, 1988). The inclusion of patients more than once violates the assumption of independence and has been shown to inflate P values (Zimmerman, 1993; Levine and Rockhill, 2006).

Meta-analysis was performed only for the studies that provided data on clinical pregnancy per patient reaching hCG administration for final oocyte maturation (Fig. 2). Studies that reported pregnancy rate per patient reaching oocyte retrieval or per patient having ET performed were not considered for pooling of data. This was due to the fact that the knowledge of the association of progesterone elevation on the day of hCG administration and the probability of clinical pregnancy is important, prior to hCG administration. If an adverse effect of progesterone elevation on the probability of clinical pregnancy was supported by the results of the current meta-analysis, the clinician would still be able to administer earlier hCG, before progesterone elevation occurs (Harada *et al.*, 1996), or to cryopreserve embryos and cancel a fresh transfer (Silverberg *et al.*, 1991, 1994; Legro *et al.*, 1993). The current meta-analysis, however, suggests that an association between progesterone elevation and the probability of clinical pregnancy per patient reaching hCG administration is not present.

The lack of association between progesterone elevation on the day of hCG and clinical pregnancy remained constant in the subgroup analysis performed, based on the type of GnRH analogue used for pituitary suppression (agonist–antagonist) (Fig. 5). In the studies where LH surge was inhibited by GnRH agonists,

exactly the same threshold level of progesterone (0.9 ng/mL) was used to classify patients in those with or without progesterone elevation. Subsequently, in this case, both statistical and clinical heterogeneity is likely to be limited rendering the results obtained more solid. In addition, no association was detected between progesterone elevation and the achievement of clinical pregnancy when the two studies (Ubaldi *et al.*, 1996b; Bosch *et al.*, 2003) in which pituitary suppression was performed by GnRH antagonists were pooled. Significant statistical heterogeneity was present ($P = 0.10$) and although, this might be attributed to the use of a different threshold of progesterone (0.9 ng/mL versus 1.2 ng/mL, respectively), a solid conclusion regarding the source of this heterogeneity could not be drawn, due to the limited number of eligible studies ($n = 2$).

This lack of association was also confirmed in the sensitivity analyses performed by excluding the studies that did not report the definition of clinical pregnancy (Supplementary material, Figure 2) or those that did not report clearly whether the measurement of serum progesterone level influenced the way ovarian stimulation was performed (Supplementary material, Figure 3).

It should be noted that the available studies, which examined the research question, have often chosen arbitrarily the threshold of serum progesterone used to classify patients in those with or without progesterone elevation (Table 2). A subgroup analysis, including only studies that used exactly the same progesterone threshold, did not, however, change the results obtained (Fig. 4).

A more appropriate method to analyse the possible association of serum progesterone on the day of hCG with the probability of pregnancy might be the use of ROC curve analysis, which was performed in three of the studies included in the current systematic review (Silverberg *et al.*, 1991; Urman *et al.*, 1999; Bosch *et al.*, 2003) (Table 2) with contradictory, however, results. This method is able to identify an optimal serum progesterone threshold on the basis of which patients can be classified into pregnant or not pregnant with a certain probability. This threshold characterizes the specific population analysed, the method of progesterone assessment and the protocol of treatment used.

It should be noted that the proportion of patients with progesterone elevation varied widely even among studies (Silverberg *et al.*, 1991; Martinez *et al.*, 2004) in which the same serum progesterone threshold (0.9 ng/mL) and the same type of GnRH analogue (agonist) were used (12.4% versus 52.3%, respectively). This marked variation in the incidence of progesterone elevation has been previously described in the literature (Edelstein *et al.*, 1990; Schoolcraft *et al.*, 1991; Silverberg *et al.*, 1991; Fanchin *et al.*, 1993; Givens *et al.*, 1994; Ubaldi *et al.*, 1995), and although, it might be assumed that it is due to discrepancies in population characteristics and/or treatment protocols among the studies, its explanation is not clear. The effect of this phenomenon on the association of progesterone elevation and the achievement of pregnancy was not possible to be explored in the current meta-analysis due to the limited number of eligible studies.

Considering secondary outcome measures, it appears that no difference is present between patients with and without progesterone elevation regarding the total dose of FSH administered (Supplementary material, Figure 6), the mean duration of stimulation (Supplementary material, Figure 7) and fertilization rates (Supplementary material, Figure 10).

The lack of association between progesterone elevation and fertilization rates, might be indicative of the absence of a detrimental effect of elevated progesterone on the day of hCG administration on oocyte quality, which has also been suggested previously (Hofmann *et al.*, 1993; Legro *et al.*, 1993; Check *et al.*, 1994; Fanchin *et al.*, 1996; Shulman *et al.*, 1996; Moffitt *et al.*, 1997; Bosch *et al.*, 2003; Martinez *et al.*, 2004).

Many researchers in the past have adopted the term 'premature luteinization' for patients with progesterone elevation on the day of hCG administration for final oocyte maturation (Hofmann *et al.*, 1996; Legro *et al.*, 1993; Ubaldi *et al.*, 1996a, b; Bosch *et al.*, 2003). This suggests that the excessive amount of progesterone is produced by granulosa cells that have started the process of luteinization.

However, the fact that a significantly higher mean number of COCs (Supplementary material, Figure 9), accompanied by a higher mean E_2 level on the day of hCG administration (Figure 6), were present in the group of patients with elevated progesterone, when only the agonist studies were pooled, suggests an alternative explanation. It is likely, at least regarding the patients treated with GnRH agonists, that the elevated progesterone might be attributed to an excess number of follicles, each one producing a normal, for the late follicular phase, amount of progesterone. In this way, excess of proliferating granulosa cells leads to an increased progesterone production, independently of LH exposure.

In theory, if the follicles of patients that exhibit progesterone elevation had started the process of luteinization, then it might be expected that the resulting oocytes from those patients would be of lower quality. However, several studies have failed to detect a detrimental effect of progesterone elevation on oocyte and embryo quality (Hofmann *et al.*, 1993; Legro *et al.*, 1993; Check *et al.*, 1994; Fanchin *et al.*, 1996; Shulman *et al.*, 1996; Moffitt *et al.*, 1997; Martinez *et al.*, 2004), which is in line with the results of the present study.

Thus, at least for the studies using GnRH agonists to inhibit LH surge, the use of the term 'premature luteinization' in the presence of normal LH levels might not be appropriate. On the other hand, this might not be the case for the two antagonist studies, since it has been suggested that premature LH surge occurs more frequently in GnRH antagonist when compared with GnRH agonist cycles (Kolibianakis *et al*., 2006). However, the small number of patients analysed in the two eligible studies does not allow for solid conclusions to be drawn.

Despite the sustained interest in the role of progesterone elevation on IVF outcome, reflected on the numerous relevant studies published until today, this systematic review reveals the lack of well-designed prospective studies that could answer the research question asked. In conclusion, the best available evidence does not support an association between progesterone elevation on the day of hCG administration and the probability of clinical pregnancy in women undergoing ovarian stimulation with GnRH analogues and gonadotrophins for IVF.

Supplementary material

Supplementary material is available at *Human Reproduction Update* online.

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