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Estrogen Supplementation to Progesterone as Luteal Phase Support in Patients Undergoing In Vitro Fertilization

Systematic Review and Meta-Analysis

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Abstract: Meta-analyses have found conflicting results with respect to the use of progesterone or progesterone plus estrogen as luteal phase support for in vitro fertilization (IVF) protocols involving gonadotropins and/or gonadotropin-releasing hormone analogs. The aim of the present study was to perform an updated meta-analysis on the efficacy of progesterone versus progesterone plus estrogen as luteal phase support.

We searched the MEDLINE, Cochrane Library, and Google Scholar databases (up to March 18, 2014). The search terms were (estrogen OR estradiol OR oestradiol) AND (progesterone) AND (IVF OR in vitro fertilization) AND (randomized OR prospective). We did not limit the form of estrogen and included subjects who contributed more than 1 cycle to a study. The primary outcome was clinical pregnancy rate. Secondary outcomes were ongoing pregnancy rate, fertilization rate, implantation rate, and miscarriage rate.

A total of 11 articles were included in the present analysis, with variable numbers of studies assessing each outcome measure. Results of statistical analyses indicated that progesterone plus estrogen treatment was more likely to result in clinical pregnancy than progesterone alone (pooled odds ratio 1.617, 95% confidence interval 1.059–2.471; $P = 0.026$). No significant difference between the 2 treatment regimens was found for the other outcome measures.

Progesterone plus estrogen for luteal phase support is associated with a higher clinical pregnancy rate than progesterone alone in women undergoing IVF, but other outcomes such as ongoing pregnancy rate, fertilization rate, implantation rate, and miscarriage rate are the same for both treatments.

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Abbreviations: CI = confidence interval, E = estrogen, GnRH = gonadotropin-releasing hormone, IVF = in vitro fertilization, LPS = luteal phase support, OR = odds ratio, P = progesterone.

INTRODUCTION

Most stimulation protocols for assisted reproductive technology result in a defective luteal phase. The mechanisms underlying the insufficient function of the corpus luteum in this context may include supraphysiologic estradiol level, decreased luteinizing hormone level, inhibition of the corpus luteum, and asynchronization of estradiol and progesterone.[1,2] Luteal phase support (LPS) is commonly used in in vitro fertilization (IVF) involving gonadotropin-releasing hormone (GnRH) analogs, and options include human chorionic gonadotropin, progesterone, estradiol, and GnRH agonists, as well as cytokines (eg, granulocyte colony-stimulating factor and lymphocyte immunotherapy).[3] However, there is still controversy in the types of hormones used for LPS, as well as their dosage, duration, and timing.[4]

With respect to the use of progesterone or progesterone plus estrogen as LPS, prior meta-analyses have not included a large number of studies and/or reported conflicting results. Although a 2002 meta-analysis by Pritts and Atwood[5] included 3 studies, of which only one study reported an increase in the implantation rate with the addition of oral estrogen to progesterone. A 2011 Cochrane review[6] (updated from 2004[7]) evaluated 7 studies and found that combining transdermal estrogen and progesterone would improve the clinical pregnancy rate, but the addition of estrogen did not affect other outcomes including ongoing pregnancy, fertilization, implantation, and miscarriage rates. Prior meta-analyses, such as those by Kolibianakis et al[8] (4 studies) and Gelbaya et al[9] (10 studies), found no beneficial effect of a progesterone/estrogen combination on the pregnancy rates, and their findings were further supported by a 2010 meta-analysis performed by Jee et al.[10] The aim of this study was to perform a meta-analysis on the efficacy of progesterone versus progesterone plus estrogen of any form for LPS during IVF.

METHODS

Search Strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] Meta-analyses do not involve patients, and thus do not require institutional review board approval. We searched the MEDLINE, Cochrane Library, and Google Scholar databases up to March 18, 2014. The search terms were

(estrogen OR estradiol OR oestradiol) AND (progesterone) AND (IVF OR in vitro fertilization) AND (randomized OR prospective). Abstracts were reviewed, and reference lists of relevant studies were also searched for relevant studies. This study did not involve human subjects, so informed consent was not required. In addition, no approval was required from an institutional review board.

Inclusion criteria for the meta-analysis were as follows: randomized controlled trial; women undergoing IVF stimulated with gonadotropins and/or GnRH analogs; at least 1 of the treatment arms including the combination of progesterone + estrogen (P + E) for LPS; a control arm including progesterone alone (P) for LPS; and reported outcomes of clinical pregnancy rate, ongoing pregnancy rate, fertilization rate, implantation rate, and/or miscarriage rate. Non-English and non-Chinese publications, case reports, comments, editorials, and letters were excluded.

Study Selection and Data Extraction

Studies were identified via the search strategy by 2 independent reviewers, with a third reviewer being consulted if there was uncertainty regarding eligibility. The following information was extracted from studies that met the inclusion criteria: name of the first author, year of publication, study design, basic information of the subjects (number of patients in each group, age of each group, body mass index of each group, duration of infertility), characteristics of treatment protocols, intervention for each group (type, dosage, timing of initiation, duration of administration), and primary and secondary outcomes (clinical pregnancy rate, ongoing pregnancy rate, fertilization rate, implantation rate, miscarriage rate). Data extraction was also performed by 2 independent reviewers, with a third reviewer being consulted in case of any uncertainty. The Delphi list was used to assess the included studies.[12] Quality assessment was also performed by 2 independent reviewers, with a third reviewer being consulted in cases of uncertainty.

Statistical Analysis

Data are presented as mean ± standard deviation or number (%). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for both primary outcome (clinical pregnancy rate) and secondary outcomes of subjects treated with P + E compared with P. Heterogeneity among the studies was assessed using the Cochran Q and the I^2 statistics. Either a Q statistic with $P < 0.10$[13] or an I^2 statistic $>50\%$[14] indicates that heterogeneity exists among the studies, and in this case a random-effects model (DerSimonian–Laird method)[15] of analysis was used; otherwise, a fixed-effects model (Mantel–Haenszel method) was used. Sensitivity analysis was performed using the leave-1-out approach. A 1-sided Egger test was performed and funnel

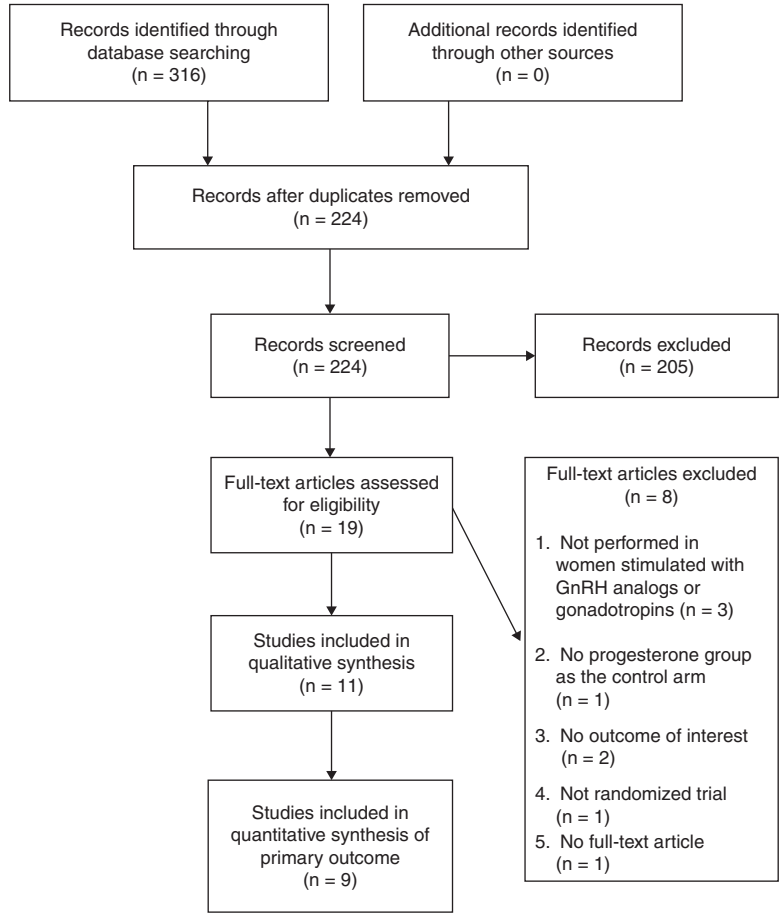


FIGURE 1. Flow diagram of study selection. GnRH = gonadotropin-releasing hormone.

TABLE 1. Delphi Quality Assessment for the Included Studies

	Moini et al[18]	Var et al[17]	Elgindy et al[19]	Serna et al[20]	Engmann et al[21]	Ceyhan et al[22]	Drakakis et al[23]	Fatemi et al[24]	Gorkemli et al[25]	Farhi et al[26]	Lewin et al[27]
1. Treatment allocation											
(a) Was a method of randomization performed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
(b) Was the treatment allocation concealed?	D	Y	D	Y	Y	D	D	N	D	D	D
2. Were the groups similar at baseline regarding the most important prognostic indicators?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	D
3. Were the eligibility criteria specified?	Y	Y	Y	Y	Y	Y	Y	Y	D	Y	Y
4. Was the outcome assessor blinded?	D	D	N	D	N	N	D	D	D	D	D
5. Was the care provider blinded?	D	D	N	D	N	N	D	D	D	D	D
6. Was the patient blinded?	D	D	N	D	N	N	D	D	D	D	D
7. Were point estimates and measures of variability presented for the primary outcome measures?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Did the analysis include an intention-to-treat analysis?	D	D	D	Y	Y	D	D	D	D	D	D

D = do not know, N = no, Y = yes.

TABLE 2. Basic Data of the Subjects in the Included Studies

	Number of Patients		Age of Patients, y		BMI, kg/m^2		Duration of Infertility, y	
	P	P + E	P	P + E	P	P + E	P	P + E
Moini et al[18]	51	47	30.0 ± 0.6	30.3 ± 0.6	NA	NA	6.0 ± 0.6	7.8 ± 1.4
Var et al[17]	97	96	30.0 ± 3.9	31.4 ± 4.9	32.1 ± 40.9	25.8 ± 5.7	9.2 ± 3.9	9.0 ± 5.0
Elgindy et al[19]	90	180*	28.7 ± 5.4	29.2 ± 4.2*	26.8 ± 1.4	26.3 ± 2.2*	5.6 ± 1.9	5.7 ± 2.0*
Serna et al[20]	91	79	34.9 ± 0.9	33.5 ± 0.7	NA	NA	NA	NA
Engmann et al[21]	82	84	35.7 ± 4.1	34.9 ± 4.2	25.6 ± 5.4	25.3 ± 4.5	2.5 ± 2.2	2.3 ± 1.4
Ceyhan et al[22]	29	30	30.9 ± 3.5	31.4 ± 2.6	22.5 ± 1.3	22.9 ± 1.3	NA	NA
Drakakis et al[23]	38	39	35.8 ± 5.3	35.4 ± 3.3	NA	NA	5.6 ± 3.9	5.0 ± 3.2
Fatemi et al[24]	100	101	32.1 ± 3.7	32.0 ± 3.6	22.7 ± 2.8	22.0 ± 2.8	NA	NA
Gorkemli et al[25]	74	70	30.8 ± 5.3	30.8 ± 6.1	NA	NA	9.6 ± 5.7	9.8 ± 6.4
Farhi et al[26]	149	129	33.2 ± 6.0	32.1 ± 6.2	NA	NA	4.0 ± 2.3	4.1 ± 3.9
Lewin et al[27]	50	50	32.7 ± 3.9	33.1 ± 3.6	NA	NA	NA	NA

Data reported as number or mean ± standard deviation. BMI = body mass index, E = estrogen, NA = not available, P = progesterone.
* Data pooled from 2 groups: E = oral estradiol and vaginal estradiol.

TABLE 3. Treatment Protocols

	GnRH Analog/ Starting Dose	Analog Protocol	Gonadotropin Type/Starting Dose	Gonadotropin Adjustment	Signal for Triggering Final Oocyte Maturation/Dose	Criteria for hCG Administration	Oocyte Retrieval	Fertilization	Embryo Transfer
Moini et al[18]	Buserelin/0.5 cm^3	Long GnRH agonist protocol	hMG (Menopur)/150–225 IU or rFSH (Gonal-f)/150–225 IU		hCG/10,000 IU	3 or more follicles 17 mm in diameter	34–36 h later	IVF/ICSI	48–72 h
Var et al[17]	Lucrin daily	Long GnRH agonist protocol	Gonal-f/225 IU	Fourth day of stimulation and on continuing days according to sonographic findings and circulating E2	Recombinant hCG/250 μg	At least 18 mm in diameter	34–36 h after hCG	ICSI	Day 3
Elgindy et al[19]	Triptorelin/0.1 mg	Long luteal downregulation protocol	FSH and hMG	From Day 6 of stimulation according to sequential transvaginal ultrasonography and serum E2	hCG/10,000 IU	At least 3 follicles 17 mm in diameter	35 h after hCG	ICSI	2 d later
Serna et al[20]	Triptorelin/NA or ganirelix/0.25 mg	Long GnRH agonist/ daily antagonist	rFSH (Gonal-f)/50–225 IU	NA	hCG/NA	Leading follicles 17 mm mean diameter	36 h later	IVF/ICSI	Day 2 or 3
Engmann et al[21]	Long GnRH agonist protocol/ 0.5 mg leuprolide acetate; ganirelix/ Lupron/40 μg	Long luteal-phase GnRH agonist suppression/GnRH antagonist/micro-dose GnRH agonist protocol	rFSH (Gonal-f) alone or in combination with purified urinary hMG/150–450 IU	Monitoring of follicular growth with serial ultrasound and serum E2 measurements	hCG/3300–10,000 IU	2 or 3 leading follicles ≥18 mm in diameter	35 h after hCG	IVF/ICSI	72–76 h
Ceyhan et al[22]	Cetrotide/0.25 mg	Fixed multidose GnRH antagonist protocol	rFSH/300 IU/d	Ovarian response after 6 d of stimulation	hCG/5000–10,000 IU	At least 2 follicles 18–20 mm in diameter	NA	ICSI	Day 3/Day 5
Drakakis et al[23]	Buserelin/100 mg 5 times daily	Long GnRH agonist protocol	rFSH/NA	Serum estradiol and follicular development	hCG/10,000 IU	Mean diameter of at least 2 leading follicles >18 mm and increasing serum estradiol	35–36 h after hCG	IVF/ICSI	NA
Fatemi et al[24]	Ganirelix/0.25 mg	Fixed Day 6	Follitropin-b/200 IU	None until stimulation Day 10	hCG/10,000 IU	As soon as 3 follicles of 17 mm present	36 h after hCG	IVF/ICSI	Day 3
Gorkemli et al[25]	Lucrin/1 mg/mL	Classical long protocol	rFSH or rFSH/hMG/NA	Considering patient age, ovulatory functions, and IVF indications	hCG/10,000 IU	Serial ultrasonographic controls and E2 measurements until 3 follicles 18 mm and serum E2 1500 pg/mL	After 35–37 h	IVF/ICSI	For 2–3 d
Farhi et al[26]	Decapeptyl/3.75 or 0.1 mg	Long or short GnRH-a protocol	FSH/75 IU with hMG (75 IU FSH and 75 IU LH, Pergonal or Menogon)	According to ovarian response, which was monitored by follicular development on ultrasound examination and measurement of E2 and progesterone levels	hCG/10,000 IU	≥3 follicles 18 mm in diameter and serum E2 ≥500 pg/mL	34–36 h after hCG	IVF	48 or 72 h after retrieval
Lewin et al[27]	GnRH-a (Decapeptyl)/ 0.5 mg/d		hMG (Pergonal)/3 ampules/d	According to ovarian response, monitored by serum E2 and number and size of ovarian follicles	hCG/10,000 IU	Leading follicle 20 mm in diameter and serum E2 >500 pg/mL	36 h after hCG	IVF	Maximum of 4 embryos transferred

E2 = estradiol, FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, hCG = human chorionic gonadotropin, hMG = human menopausal gonadotropin, ICSI = intracytoplasmic sperm injection, IVF = in vitro fertilization, LH = luteinizing hormone, NA = not available, rFSH = recombinant follicle-stimulating hormone.

TABLE 4. Progesterone and Estradiol Interventions

	Type		Dose		Timing of Initiation		Duration of Administration	
	Progesterone	**Estradiol**	**Progesterone**	**Estradiol**	**Progesterone**	**Estradiol**	**Progesterone**	**Estradiol**
Moini et al[18]	Vaginal administration of P supplementation	E2 valerate; oral	400 mg twice a day	2 mg orally	Day after oocyte retrieval		Until 10th week if positive chemical pregnancy test	NA
Var et al[17]	Vaginal gel P (Crinone 8%)	E2 (Estrofem); oral	90 mg	2 mg orally twice daily	Day of oocyte pickup	Day of oocyte pickup	Until day of pregnancy test	Until day of the pregnancy test
Elgindy et al[19]	IM injection of P (Gestone)	E2 valerate (Cyclo-Progynova); oral or vaginal	100 mg	2 mg either orally or vaginally 3 times daily	ET day	ET day	Until negative pregnancy test or positive fetal heartbeat documented by transvaginal ultrasound	Lasting for the entire luteal phase, orally in group B (P/oral E2 group) and vaginally—upper third—in group C (P/vaginal E2 group)
Serna et al[20]	Vaginal P (Progeffik 200)	Estraderm Matrix 100; transdermal	200 mg/12 h	100 μg/d	Night after oocyte pickup	Beginning on the day of ET	10th week of pregnancy	10th gestational week
Engmann et al[21]	P in oil daily IM	E2; vaginal	50 mg	2 mg vaginally twice daily	Evening after oocyte retrieval	ET day	Continued until negative pregnancy test or positive fetal heartbeat documented by transvaginal ultrasound	Until positive fetal heartbeat on ultrasound or negative pregnancy test
Ceyhan et al[22]	Vaginal natural micronized P (Progestan 100 mg)	Estraderm TTS 100; transdermal	600 mg	100 mg/d E2 release, twice weekly	Day of oocyte retrieval	Day of oocyte retrieval	Until eighth week of gestation, provided pregnancy was achieved	After diagnosis of clinical pregnancy until 8 wk of gestation
Drakakis et al[23]	1 capsule of Utrogestan1 (P; 100 μg)	Cyclacur (2 mg E2 valerate + 0.5 mg norgestrel) and Dermestril patch 50 mg (estradiol hemihydrate); oral and transdermal	Three times per day orally and 2 capsules of Utrogestan 3 times per day vaginally	Cyclacur (3 times daily for 15 d) + Derme-Dermestril 50 mg every 4 d	Day before embryo transfer	Day of oocyte retrieval	Measurement of β-hCG serum level	NA
Fatemi et al[24]	Vaginal P (Utrogestan)	E2 valerate (Progynova); oral	200 mg, 3/d	2 mg orally twice daily	Day after oocyte retrieval	Day after oocyte retrieval	Until 7 wk of gestation, if pregnancy achieved	Until 7 wk of gestation, if pregnancy achieved
Gorkemli et al[25]	Vaginal P (Progestan 100 mg)	E2 (Estraderm TTS 100); transdermal	600 mg	100 μg/d	Night of oocyte retrieval	Night of oocyte retrieval	14–15 d, regarding day of embryo transfer (second or third day)	14–15 d, regarding day of embryo transfer (second or third day)
Farhi et al[26]	P (Geston)	E2 (Estrophem); oral	150 mg/d and 50-mg vaginal tablets twice per day	2 mg orally twice daily	Day after oocyte retrieval	Day 7 after ET	Vaginal ultrasound examination at 6 wk to detect pregnancy sac and fetal heartbeat in conception cycle	Vaginal ultrasound examination at 6 wk to detect pregnancy sac and fetal heartbeat in conception cycle
Lewin et al[27]	IM injection of P (Geston)	E2 (Estrofem); oral	50 mg/d	2 mg/d	ET day	ET day	20 d	20 d

E2 = estradiol, ET = embryo transfer, hCG = human chorionic gonadotropin, IM = intramuscular, NA = not available, P = progesterone.

TABLE 5. Summary of Primary and Secondary Outcomes

	Clinical Pregnancy Rate, %		Ongoing Pregnancy Rate, %		Fertilization Rate, %		Implantation Rate, %		Miscarriage Rate, %	
	P	P+E	P	P+E	P	P+E	P	P+E	P	P+E
Moini et al[18]	19/51 (37.3)	23/47 (48.9)	NA	NA	NA	NA	NA	NA	NA	NA
Var et al[17]	21/97 (21.6)	39/96 (40.6)	NA	NA	NA	NA	7.9% ± 15.4%*	16.7% ± 22.7%*	8/21 (38.0)	5/39 (12.8)
Elgindy et al[19]	27/90 (30.0)	74/180 (41.1)†	NA	NA	68.0 ± 6.3	69.7 ± 12.9†	NA	NA	6/27 (22.2)	2/74 (2.7)†
Sema et al[20]	NA	NA	33/79 (41.8)	NA	NA	NA	51/146 (34.9)	41/142 (28.9)	6/40 (15.0)	5/38 (13.2)
Engmann et al[21]	52/82 (63.4)	42/84 (50.0)	46/82 (56.1)	40/84 (47.6)	79.6 ± 15.8	75.3 ± 15.7	64/203 (31.5)	56/210 (26.7)	8/59 (13.6)	5/59 (8.5)
Ceyhan et al[22]	13/29 (44.8)	13/30 (43.3)	10/29 (34.4)	11/30 (36.6)	NA	NA	NA	NA	NA	NA
Drakakis et al[23]	5/38 (13.2)	13/39 (33.3)	NA	NA	71.7	76.2	6/150 (4.0)	18/176 (10.2)	1/6 (16.7)	4/18 (22.2)
Fatemi et al[24]	NA	NA	26/100 (26.0)	30/101 (29.7)	NA	NA	34/90 (37.8)	39/92 (42.4)	8/34 (23.4)	9/39 (23.1)
Gorkemli et al[25]	14/148 (9.5)	44/140 (31.4)	14/148 (9.5)	34/140 (24.3)	NA	NA	NA	NA	6/148 (4.1)	10/140 (6.8)
Farhi et al[26]	35/149 (23.4)	46/136 (33.8)	NA	NA	72.3 ± 41.0	67.0 ± 20.0	53/553 (9.6)	70/500 (14.0)	6/35 (17.1)	5/46 (10.8)
Lewin et al[27]	14/50 (28)	13/50 (26)	NA	NA	NA	NA	NA	NA	NA	NA

* Data are presented as count (percentage) or mean ± standard deviation. E = estrogen, NA = not available, P = progesterone.
† Data pooled from 2 groups: E = oral estradiol and vaginal estradiol.

plots were created to evaluate publication bias.[16] A P value <0.05 was considered statistically significant. Homogeneity tests, pooled estimates, and sensitivity analyses were performed using the Comprehensive Meta-Analysis Version 2.0 (Biostat, Englewood, NJ).

RESULTS

The initial search identified 315 articles (Figure 1). We identified abstracts with full-text articles, and performed manual search of relevant reference lists but did not identify additional articles. A total of 296 articles were excluded, and 19 were subjected to full-text review. Eight more articles were excluded for the following reasons: not performed in women stimulated with gonadotropins and/or GnRH analogs (n = 3), having no outcome of interest (n = 2), no progesterone-alone group (n = 1), not a randomized controlled trial (n = 1), and having no retrievable article (n = 1) (Supplemental). Thus, 11 articles[17–27] were included in the meta-analysis.

Quality Assessment

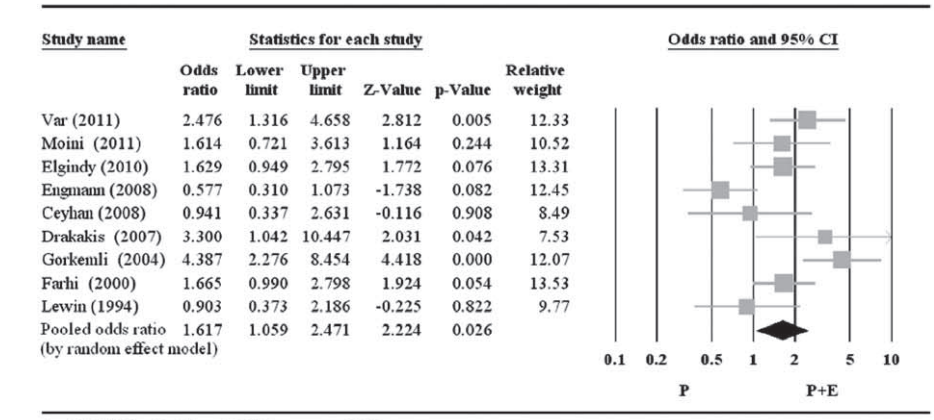
Table 1 shows the results of the Delphi quality assessment. All 11 studies were randomized, with 10 studies meeting specified eligibility criteria, and had similar group characteristics at baseline. However, most of the included studies did not conceal treatment allocation, and did not address whether the analysis was intent-to-treat. None of the studies addressed or performed blinding.

Study and Subject Characteristics

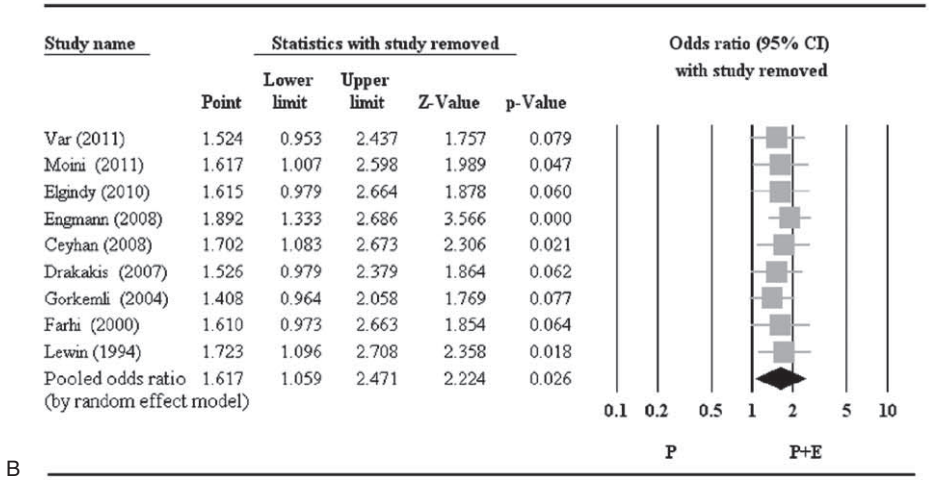
The 11 studies included a total of 1756 subjects. The mean age of subjects ranged from 28.7 ± 5.4 to 35.8 ± 5.3 years; mean body mass index, when reported, ranged from 22.0 ± 2.8 to 32.1 ± 40.9 kg/m^2; and the mean duration of infertility, when reported, ranged from 2.3 ± 1.4 to 9.8 ± 6.4 years (Table 2). Details regarding overall treatment protocols and progesterone and estradiol interventions are summarized in Tables 3 and 4, respectively. Oral estrogen was administered in 7 studies, transdermal estrogen was administered in 4 studies, and vaginal estrogen was administered in 2 studies (1 study included oral or vaginal estrogen,[19] and the other study included oral and transdermal estrogen[23]). Table 5 summarizes the primary and secondary outcomes after intervention (P + E vs P).

Significantly More Clinical Pregnancies With P + E Versus P

Of the 11 studies, 9 studies reported clinical pregnancy rate (Table 5).[17–19,21–23,25–27] P + E was more likely to result in a clinical pregnancy than P alone (pooled OR = 1.617, 95% CI 1.059–2.471; $P = 0.026$) (Figure 2A). A random-effects model was used, as there was heterogeneity among the studies ($Q = 25.45$, $P = 0.001$; $I^2 = 68.57$). Pooled ORs remained >1.0 as each study was removed in turn. In 5 instances, the pooled ORs became nonsignificant after each of those 5 studies was removed, but since their P values were borderline and near the threshold with points in the same direction, influence from any of these 5 studies on the overall pooled OR (without study removal) is negligible (Figure 2B). The funnel plot with the Egger test (Figure 2C) was performed to evaluate publication bias in these studies, and with an estimated intercept of −0.157, and a 1-tailed $P = 0.477$, there is no significant asymmetry or bias (Figure 2C).



A Q = 25.45 (df = 8) with p=0.001, I-square = 68.57



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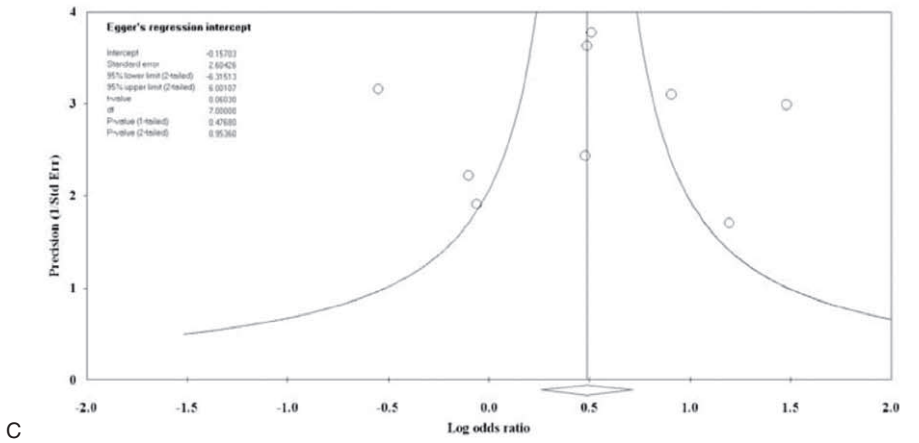

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FIGURE 2. Meta-analysis (A), sensitivity analysis (B), and funnel plot (C) for odds ratio of clinical pregnancy. CI = confidence interval.

No Significant Difference in Ongoing Pregnancy Rate for P + E Versus P

A total of 5 of the 11 studies reported ongoing pregnancy rate (Table 5).[20–22,24,25] There was no significant difference between P + E and P treatments with respect to ongoing pregnancy rates (pooled OR = 1.232, 95% CI 0.743–2.044; $P = 0.419$) (Figure 3A). A random-effects model was used, as there was heterogeneity among the studies ($Q = 10.679$, $P = 0.030$; $I^2 = 62.54$). All pooled ORs remained nonsignificant after each study was removed in turn, indicating no obvious influence of any individual study on the pooled estimate (Figure 3B). The Egger test showed an estimated intercept of

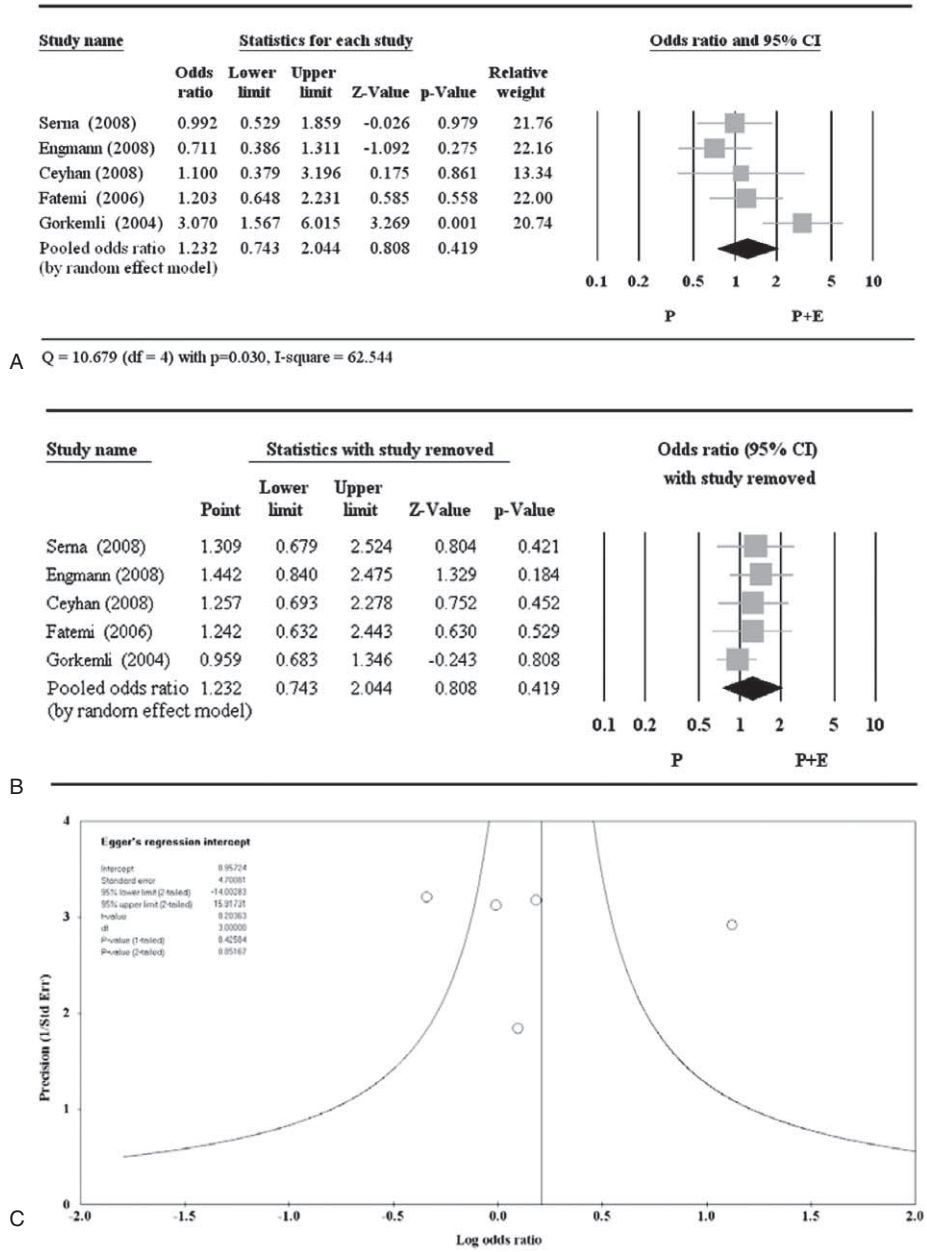

FIGURE 3. Meta-analysis (A), sensitivity analysis (B), and funnel plot (C) for odds ratio of ongoing pregnancy. CI = confidence interval.

0.957, with a 1-tailed $P = 0.426$, indicating no significant asymmetry or bias (Figure 3C).

No Significant Difference in Fertilization Rate for P + E Versus P

Of the 11 studies, only 4 reported fertilization rate (Table 5).[19,21,23,26] But among those 4 studies, the study by Drakakis et al[23] did not report standard deviation, and therefore was not included in the analysis. There was no significant difference between P + E and P with respect to the fertilization rate (pooled difference in means −1.912, 95% CI −6.807 to 2.983; $P = 0.444$) (Figure 4A). A random-effects model was used, as there was heterogeneity among the studies ($Q = 6.197$, $P = 0.045$; $I^2 = 67.72$). Of the 3 included studies, pooled OR was significant when the study by Elgindy et al[19] was removed but the overall pooled OR was nonsignificant, indicating influence of that particular study on the overall pooled estimate (Figure 4B). Nevertheless, point estimate of the study by Elgindy et al was in the same direction as that of the other 2 studies. The Egger test was not performed because more than 5 studies are needed to observe publication bias.

No Significant Difference in Implantation Rate for P + E Versus P

A total of 6 of the 11 studies reported implantation rate (Table 5).[17,20,21,23,24,26] However, the study by Var et al[17] used a

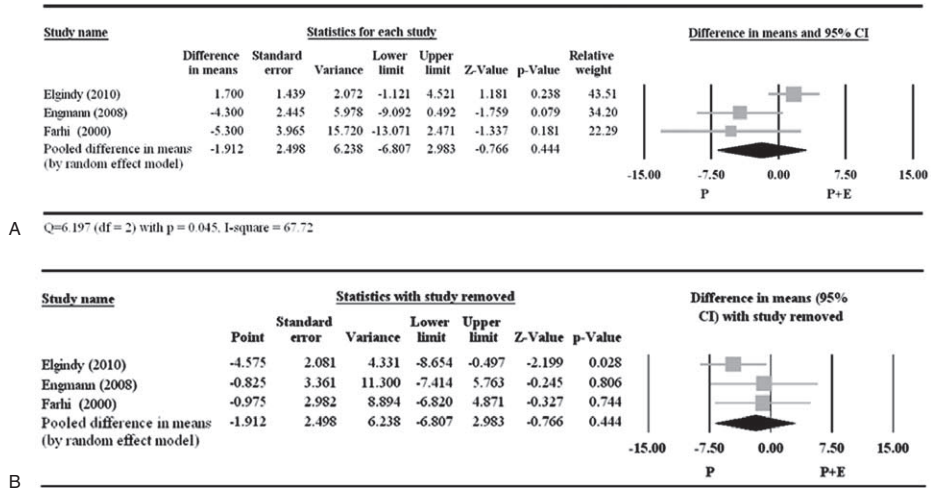

FIGURE 4. Meta-analysis (A) and sensitivity analysis (B) for the difference in fertilization rate between the 2 treatment groups. The study by Drakakis et al[23] did not report standard deviation and was excluded from the meta-analysis. CI = confidence interval.

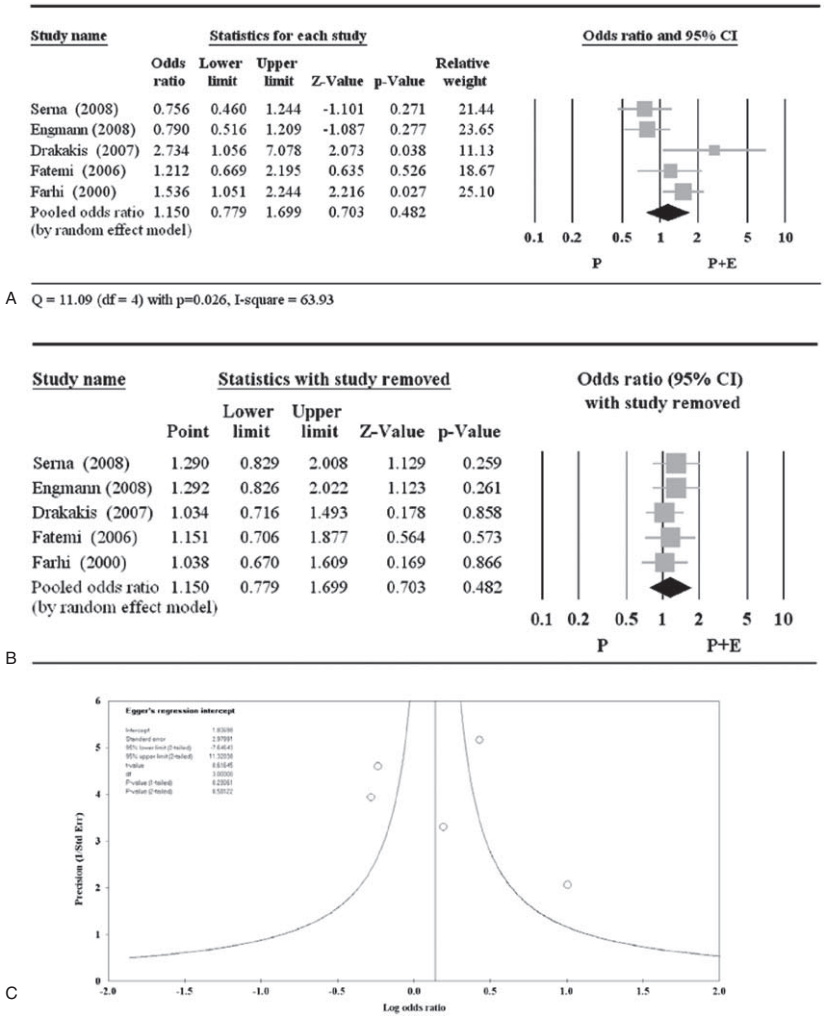

FIGURE 5. Meta-analysis (A), sensitivity analysis (B), and funnel plot (C) for the odds ratio of implantation. The study by Var et al[17] used a different definition of implantation rate and was excluded from the meta-analysis. CI = confidence interval.

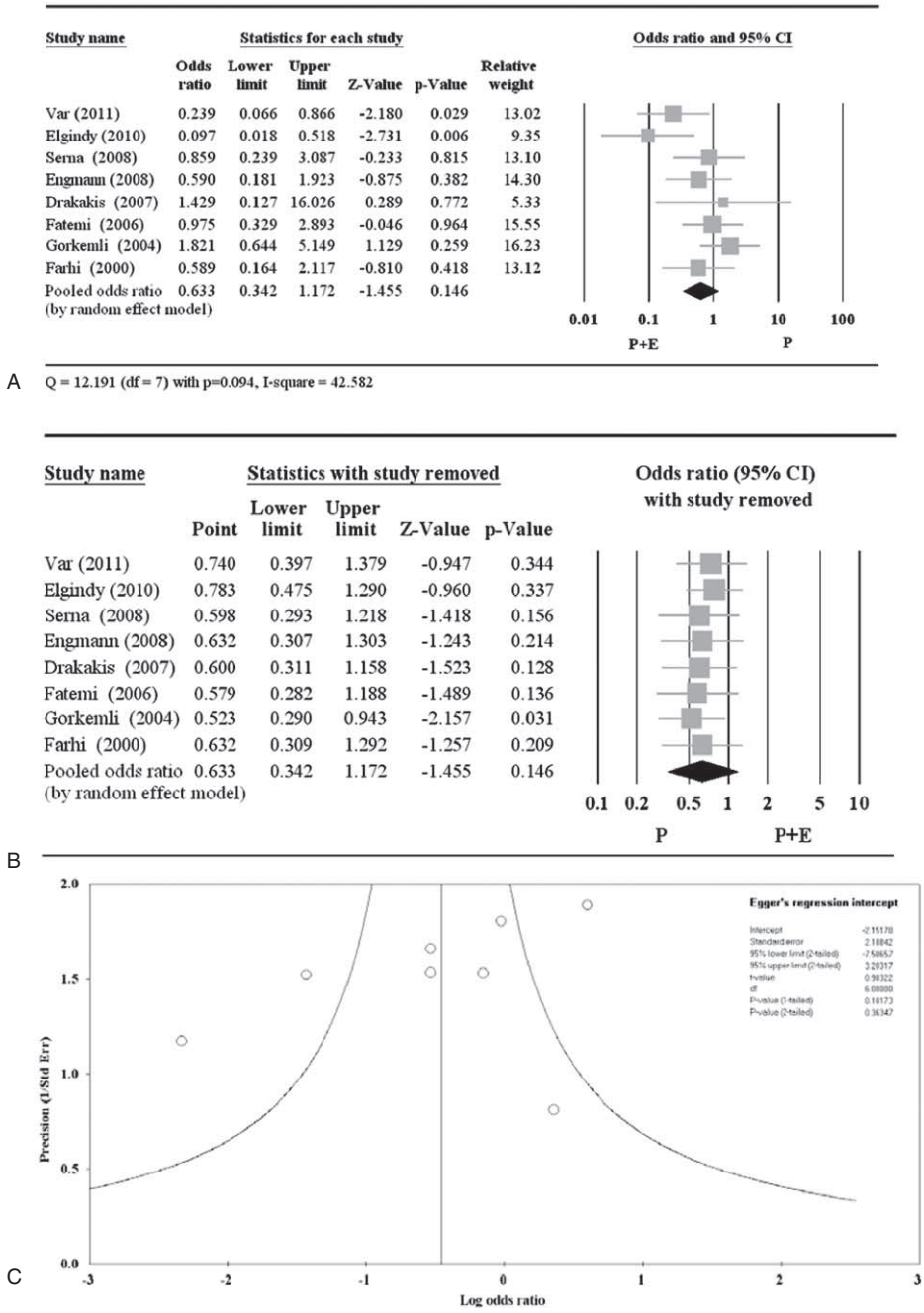

FIGURE 6. Meta-analysis (A), sensitivity analysis (B), and funnel plot (C) for the odds ratio of miscarriage. CI = confidence interval.

different definition of implantation rate compared with the other studies, and therefore was excluded from meta-analysis with respect to this parameter. There was no significant difference between P + E and P with respect to implantation rate (pooled OR 1.150, 95% CI 0.779–1.699; $P = 0.482$) (Figure 5A). A random-effects model was used, as there was heterogeneity among the studies ($Q = 11.09$, $P = 0.026$; $I^2 = 63.93$). All pooled ORs remained >1.0, and were nonsignificant when each study was removed in turn, indicating no obvious influence of any individual study on the pooled estimate (Figure 5B). The Egger test had an estimated intercept of 1.837, with a 1-tailed $P = 0.291$, indicating no significant asymmetry or bias (Figure 5C).

No Significant Difference in Miscarriage Rate for P + E Versus P

A total of 8 of the 11 studies reported miscarriage rate data (Table 5).[17,19,20,21,23–26] There was no significant difference between P + E and P treatments with respect to miscarriage rate (pooled OR 0.633, 95% CI 0.342–1.172; $P = 0.146$) (Figure 6A). A random-effects model was used, as there was

heterogeneity among the studies ($Q = 12.191$, $P = 0.094$; $I^2 = 42.58$). With exception of the study by Gorkemli et al,[25] all other pooled ORs remained <1.0 and were nonsignificant when each study was removed in turn, indicating no obvious influence on the overall pooled estimate from any of those remaining 7 studies (Figure 6B). The study by Gorkemli et al (point estimate 0.523, $P = 0.031$) might influence the pooled estimate but was not removed since its point estimate is in the same direction as the overall pooled OR. The Egger test showed an estimated intercept of −2.15, with a 1-tailed $P = 0.182$, indicating no significant asymmetry or bias (Figure 6C).

DISCUSSION

The aim of the present study was to perform a meta-analysis examining the efficacy of progesterone plus estrogen versus progesterone alone as LPS during IVF. A search of the literature identified 11 articles. A risk of bias was present given that none of the articles addressed or performed blinding.

A meta-analysis of the 11 articles (1756 subjects with variable numbers of articles/subjects analyzed for each outcome measure) showed a significant benefit for progesterone plus estrogen compared with that for progesterone alone only for the primary outcome of clinical pregnancy. No significant difference was found between the 2 treatment groups for any of the secondary outcomes including the ongoing pregnancy rate, fertilization rate, implantation rate, and miscarriage rate. These results support findings of the 2011 Cochrane review (9 articles; 1571 subjects, also with variable numbers of articles/subjects analyzed for each outcome measure).[9] But in that analysis, the significant benefit of progesterone plus estrogen over progesterone alone was based on a subgroup analysis of transdermal estrogen (and transdermal and oral estrogen in 1 study), while our analysis included estrogen supplementation in oral, vaginal, and transdermal forms. Our analysis also included a new article by Moini et al[18] and the 2 articles that were excluded from the 2011 Cochrane review.[17,26]

Potential limitations of this study include the limited sample size (1756 subjects), the inclusion of different forms and dosages of estrogen supplementation, and the inclusion of subjects who contributed more than 1 cycle to a study. Furthermore, while the live birth rate may be the more appropriate outcome, no trial has yet reported this outcome, so our meta-analysis is limited by the design of included studies and appears less than optimal. Nonetheless, the use of estrogen as a supplement to progesterone in LPS does not appear to be significantly beneficial. Additional large randomized controlled trials are necessary to clarify the role of estrogen supplementation in addition to progesterone for LPS in IVF, and to definitively show any beneficial effect of estrogen with respect to outcome measures other than clinical pregnancy. Other than estrogen forms and dosages, factors such as subject age[28] or GnRH agonist protocol[29] may be relevant and warrant further investigation. The adoption of standardized terminology in assisted reproductive technology[30] will also be helpful in future studies.

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