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Effect of pretreatment with combined oral contraceptives on outcomes of assisted reproductive technology for women with polycystic ovary syndrome: a meta-analysis

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Abstract

Objective To evaluate the effect of pretreatment with combined oral contraceptives (COC) on outcomes in women with polycystic ovary syndrome (PCOS) who underwent assisted reproductive technology for subfertility.

Methods Two authors independently searched MEDLINE, EMBASE, and the Cochran Library to identify and review articles published from October 1995 until December 2018 according to selection criteria. Outcomes are expressed as mean difference and odds ratio (OR) in a meta-analysis model.

Results A total of seven studies were included in this meta-analysis: one randomized controlled study and two prospective and four retrospective cohort studies. Meta-analysis showed that the COC pretreatment did not affect rate of clinical pregnancy (OR = 0.93, 95% confidence interval CI 0.65–1.34, $I^2 = 76\%$) or ovarian hyperstimulation syndrome (OR = 0.90, 95% CI 0.57–1.44, $I^2 = 0\%$). However, the rate of miscarriage in the COC group was significantly higher (OR = 1.33, 95% CI 1.02–1.72, $I^2 = 9\%$) and the rate of cumulative live birth was significantly lower compared with the control group (OR = 0.72, 95% CI 0.54–0.98, $I^2 = 55\%$). Subgroup analysis showed higher rates of miscarriage and lower rates of cumulative live birth in studies with a gonadotropin-releasing hormone (GnRH) antagonist protocol (OR = 1.69, 95% CI 1.17–2.44, $I^2 = 0\%$ and OR = 0.38, 95% CI 0.29–0.50, respectively).

Conclusion Pretreatment with COC in women with PCOS before assisted reproductive technology may have an adverse effect on clinical outcomes, especially with a GnRH antagonist protocol.

Keywords Combined oral contraceptives · Assisted reproductive technology · Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS), which is characterized by hyperandrogenism, anovulation, and polycystic ovaries, is a common endocrine disorder that affects 5–20% of women worldwide [1]. Women with PCOS often suffer from infertility due to chronic anovulation. First-line therapy for infertility in women with PCOS is to induce ovulation with clomiphene citrate or aromatase inhibitors [2]. For infertile women without successful pregnancy with ovulation induction, assisted reproductive technology (ART) such as in vitro fertilization and intra-cytoplasmic sperm njection can be used to achieve pregnancy. However, there are several concerns for women with PCOS who undergo ART for infertility. First, the excessive number of follicles in women with PCOS can cause increased risk of ovarian hyperstimulation syndrome (OHSS). Second, excessive follicles are not homogenous in growth, making the rate of mature oocytes after oocyte retrieval lower than expected [3–5]. Third, women with PCOS usually have irregular menstrual cycles, making it challenging to schedule ART for these patients. For these reasons, investigators have suggested pretreatment with combined oral contraceptives (COC) before controlled ovarian stimulation for ART.

Soo Youn Song and Jung Bo Yang contributed equally to this work.

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Pretreatment with COC is not only convenient for cycle scheduling but can also help regulate follicular growth and reduce follicle development [6]. However, researchers have reported conflicting results regarding COC's effects on ART outcomes for patients with PCOS. For instance, some authors reported significantly improved clinical pregnancy rates and lower OHSS rates [6–8], but some failed to find any significant advantage [9–12]. Moreover, some authors found that COC pretreatment had numerous harmful effects [13, 14]. Therefore, the aim of this meta-analysis was to evaluate the effects of pretreatment with COC on clinical outcomes in women with PCOS who underwent ART for infertility.

Materials and methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The protocol of this study was registered on the PROSPERO website in January 2019 (registration number CRD42019119812).

Study selection

Two authors conducted electronic database searches of MEDLINE, Cochrane Library, and EMBASE on December, 2018; we also reviewed ongoing trials and grey literature. We did not restrict articles by publication type, language, or date, and we independently searched, reviewed references, and noted reasons for inclusion or exclusion. We then cross-checked the results and discussed any discrepancies with a third reviewer to draw acceptable conclusions. The terms used for the electronic searches are listed in supplementary Table 1.

We used the following study inclusion criteria: studies with patients who were diagnosed with PCOS; study protocols that used gonadotropin to control ovarian stimulation for ART (in vitro fertilization or intracytoplasmic sperm injection); parallel design studies in which researchers compared outcomes of ART with and without COC pretreatment. The exclusion criteria were studies in which the researchers included women who were not diagnosed with PCOS; did not use controlled ovarian stimulation with gonadotropin; used oral contraceptives other than COC, such as estrogen only or progestin only; included women who underwent timed intercourse or intrauterine insemination; did not evaluate pregnancy outcomes; or did not report the effect of COC alone.

The primary outcome was clinical ART outcomes: rates of clinical pregnancy, miscarriage, cumulative live birth, and OHSS. The secondary outcomes were the characteristics of cycles: cycle cancellation, duration and dose of gonadotropin, endometrial thickness on the day of human chorionic gonadotropin injection, number of retrieved oocytes, rate of fertilization, and implantation.

Assessing study quality

We assessed study quality with different tools for different study designs, using the Cochrane risk-of-bias tool for the randomized controlled trials (RCT) and the Newcastle–Ottawa scale with cohort studies [15]. The Cochrane tool

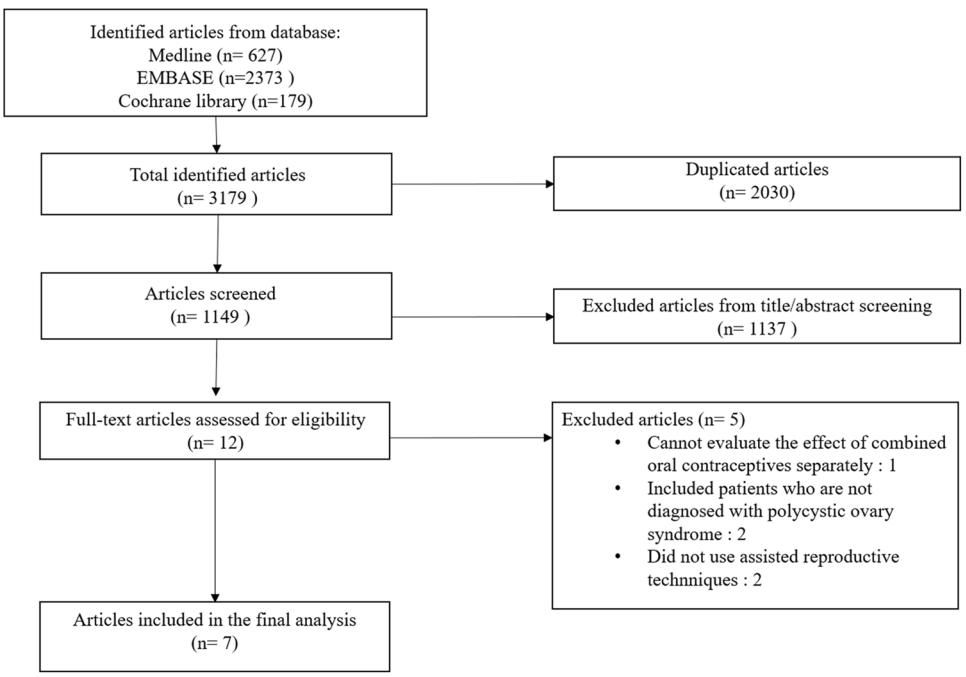

Fig. 1 Flow diagram of study selection

categorizes each of the following types of risk as low, high, or unclear: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential source of bias. For this meta-analysis, we considered studies without a high risk of bias in any category to be of good quality; studies with one high risk or two unclear risks were considered fair quality, and the remainder were considered poor quality.

The Newcastle–Ottawa scale has three domains: selection, comparability, and outcome. Each category in selection receives one star: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study. For comparability, a maximum of two

Table 1 Characteristics of included studies

Study, year	Study type	Participants (*n*)	Age (mean ± SD) or Median [IQR]	COC type, dose	Pituitary suppression	ART	ET	Results
Farhi, 2011	Prospective cohort	COC (16) Control (10)	COC (29.4 ± 3.4) Control (31.4 ± 5.5)	NA	no	IVM and ICSI	Fresh	No differences in clinical or outcome parameters
Wu, 2012	RCT	COC (53) Control (32)	COC (30.71 ± 4.42) Control (30.92 ± 3.5)	EE 35 µg + cyproterone acetate 2 mg	GnRHa long	IVF-ET or ICSI	Fresh	Improvement in percentage of mature oocytes No difference in clinical outcomes
Ozmen, 2014	Retrospective cohort	COC (143) Control (59)	COC (28.0 ± 5.1) Control (27.6 ± 4.3)	EE 30 µg@@ + drospirenone 3 mg	GnRH antagonist	ICSI	Fresh	No beneficial or adverse outcomes with COC treatment
Pan, 2015	Retrospective cohort	COC (208) Control (292)	29.0 ± 2.97	EE 30 µg + gestodene 75 µg	GnRH long Microdose flare GnRH antagonist	IVF-ET or ICSI	Fresh and FET	COC treatment significantly improved the implantation and pregnancy rates
Kalem, 2017	Retrospective cohort	COC (292) Control (376)	29.00[27.00–31.00]	EE 30 µg + gestodene 75 µg	GnRH antagonist	IVF-ET	Fresh	No difference in clinical outcomes
Wei, 2017	Prospective cohort	COC (902) Control (323)	COC (28.0 ± 3.0) Control (28.4 ± 3.0)	EE 30 µg + desogestrel 0.15 mg EE 35 µg + cyproterone acetate 2 mg EE 30 µg + drospirenone 3 mg	GnRH antagonist	IVF-ET	Fresh and FET	COC treatment was associated with lower rate of live birth
Xu, 2018	Retrospective cohort	COC (779) Control (246)	COC [27–31] Control [27–31]	EE 30 µg + desogestrol 0.15 mg EE 35 µg + cyproterone acetae 2 mg EE 30 µg + drospirenone 3 mg	GnRH agonist	IVF-ET	Fresh and FET	COC treatment was not directly responsible for live birth rate reduction

NA not available, *SD* standard deviation, *IQR* interquartile range, *COC* combined oral contraceptives, *ART* assisted reproductive technology, *ET* embryo transfer, *IVM* in vitro maturation, *ICSI* intracytoplasmic sperm injection, *RCT* randomized controlled trial, *GnRHa* gonadotropin-releasing hormone analogue, *IVF-ET* in vitro fertilization and embryo transfer, *EE* ethinyl estradiol, *GnRH* gonadotropin-releasing hormone, *FET* frozen embryo transfer

Table 2 Risk of bias of included randomized controlled study using the Cochrane risk of bias assessment tool

	Wu 2015
Random sequence generation (selection bias)	Unclear risk
Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

stars can be given, and each outcome category can receive one star: outcome assessment, adequacy of length of follow-up, and follow-up of cohorts. We considered studies to be of good quality if we rated them as having more than three stars in the selection domain, one or two stars in comparability, and more than two stars in exposure/outcomes.

Statistical analysis

We performed the statistical analysis with RevMan software (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and calculated dichotomous outcomes with risk ratios or odds ratios (ORs) with 95% confidence intervals (CIs); we calculated continuous outcomes with mean difference or standardized mean difference with 95% CIs. When data were reported with median and range or interquartile range, we calculated mean and standard deviation [16, 17]. For this study, we calculated heterogeneity with I^2 where I^2 above 50% reflected substantial heterogeneity; we used a random-effects model in these cases and otherwise a fixed-effects model. We performed subgroup analysis according to study design and other heterogeneity due to differences in study protocol. We did not use a funnel plot or other tools to assess publication bias because there were few included studies. We carefully discussed the possible effects of publication bias on the outcomes, and we concluded that although we could not exclude publication bias, the results were not skewed in a particular direction. We consulted a statistician for the data analysis.

Results

Figure 1 shows the flow diagram of study selection. Among 3179 studies, we only included a total of seven: one RCT [18], two prospective cohort studies [14, 19], and four retrospective cohort studies [8, 10, 12, 13]; the characteristics of included studies are listed in Table 1. If the outcome of interest was reported by RCT and cohort studies, subgroup analysis was performed. There were 2393 women in the COC group and 1338 in the control group. The authors of the included studies used differing methods to report the women's ages (i.e., mean with SD for each group; mean with SD for all included women; median with range for each group; median with range for all included women; range for each group), so we could not directly compare ages across the studies in this meta-analysis. Types of COC were also heterogeneous among studies: the COC in one study contained 35 μg of ethinyl estradiol and 2 mg of cyproterone acetate; in one it was 30 μg of ethinyl estradiol and 3 mg of drospirenone; in two studies, investigators used 30ug of ethinyl estradiol and 75 μg of gestodene; authors of two studies used all three kinds of COC; and one study did not include COC

Table 3 Quality assessment of included cohort studies using the New castle—Ottawa scale

	Farhi 2011	Ozmen 2014	Pan 2015	Kalem 2017	Wei 2017	Xu 2018
Selection						
Representativeness of exposed cohort	*	*	*	*	*	*
Selection of non-exposed cohort	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*
Outcome not present at the start of the study	*	*	*	*	*	*
Comparability outcome			**			**
Assessment of outcomes	*	*	*	*	*	*
Length of follow-up	*	*	*	*	*	*
Adequacy of follow-up	*	*	*	*	*	*
Total	*******	*******	*********	*******	*******	*********

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain

*Thresholds for converting the NOS rating to Agency for Healthcare Research and Quality—AHRQ—standards (good, fair, and poor)

type. As for the method of pituitary suppression, investigators in two studies used a gonadotropin-releasing hormone (GnRH) agonist protocol and in three studies used a GnRH antagonist protocol. In one study, the protocols varied: GnRH agonist long protocol, microdose GnRH agonist, and GnRH antagonist protocol. Authors of one study did not use pituitary suppression at all. Most researchers used fresh embryo transfer (ET) only, but authors of two studies used frozen-thawed ET as well as fresh ET. Reasons for exclusion after full text review are listed in Supplementary Table 2; Table 2 presents the results of our quality assessment of the RCT, and Table 3 shows the assessments for the cohort studies. Of the seven studies, two cohort studies were of good quality and the other four cohort studies as well as one RCT were of poor qualtiy. The conflicts of interest reported in each study is listed in Supplementary Table 3.

Primary outcomes

Figure 2 shows the forest plot of the clinical pregnancy and cumulative live birth rates. Rate of clinical pregnancy was not altered by treatment with COC (OR = 0.93, 95% CI 0.65–1.34, $I^2 = 76\%$), but the rate of cumulative pregnancy, which was reported by two cohort studies, were higher in COC group compared to control group (OR = 0.72, 95% CI 0.54–0.98, $I^2 = 55\%$). Adverse events are shown in Fig. 3. The rate of OHSS was not different between two groups (OR = 0.90, 95% CI 0.57–1.44, $I^2 = 0\%$). However, pooled analysis showed that the rate of

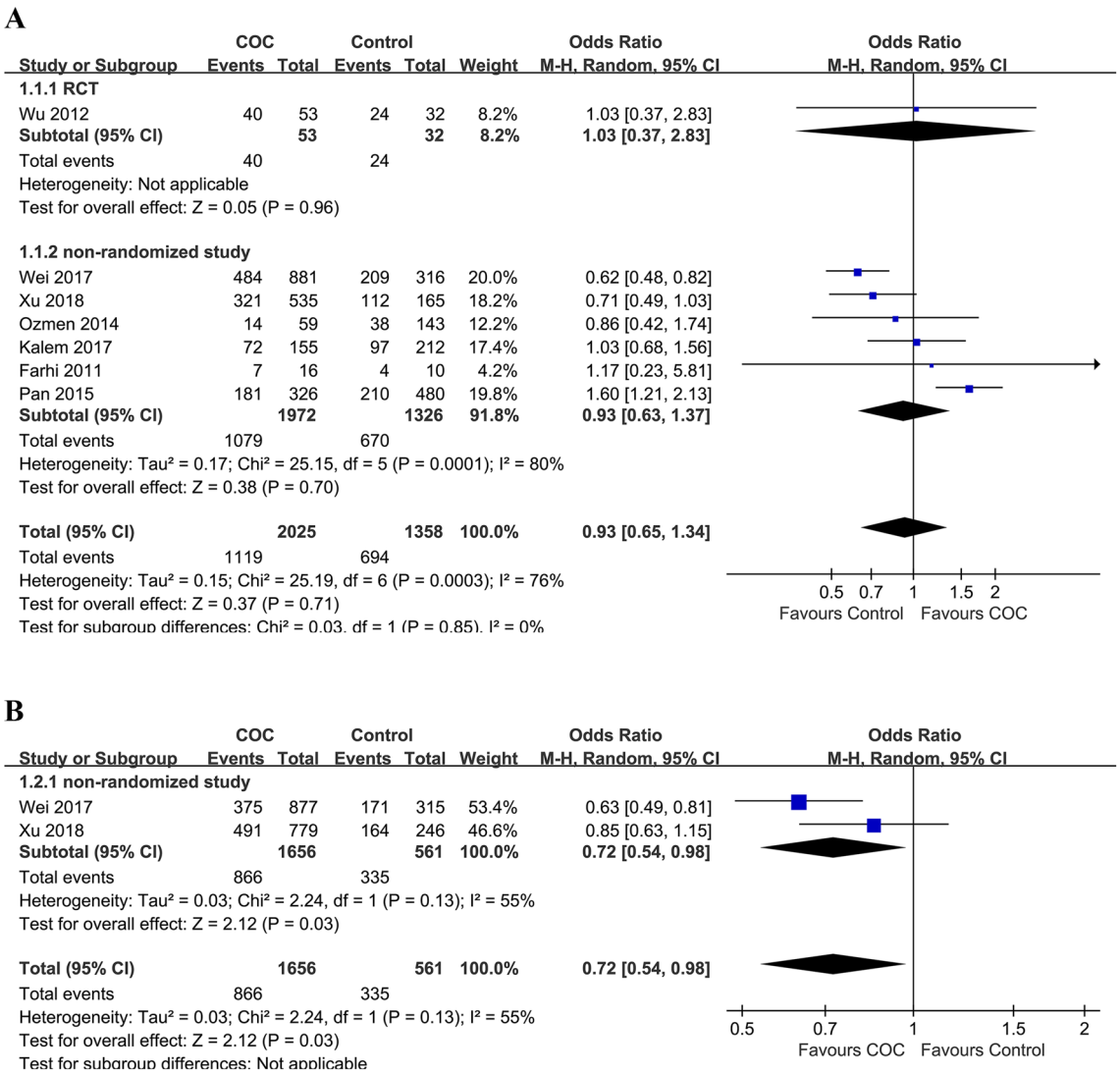

Fig. 2 Effect of combined oral contraceptives on pregnancy (**a**) clinical pregnancy, (**b**) cumulative live birth

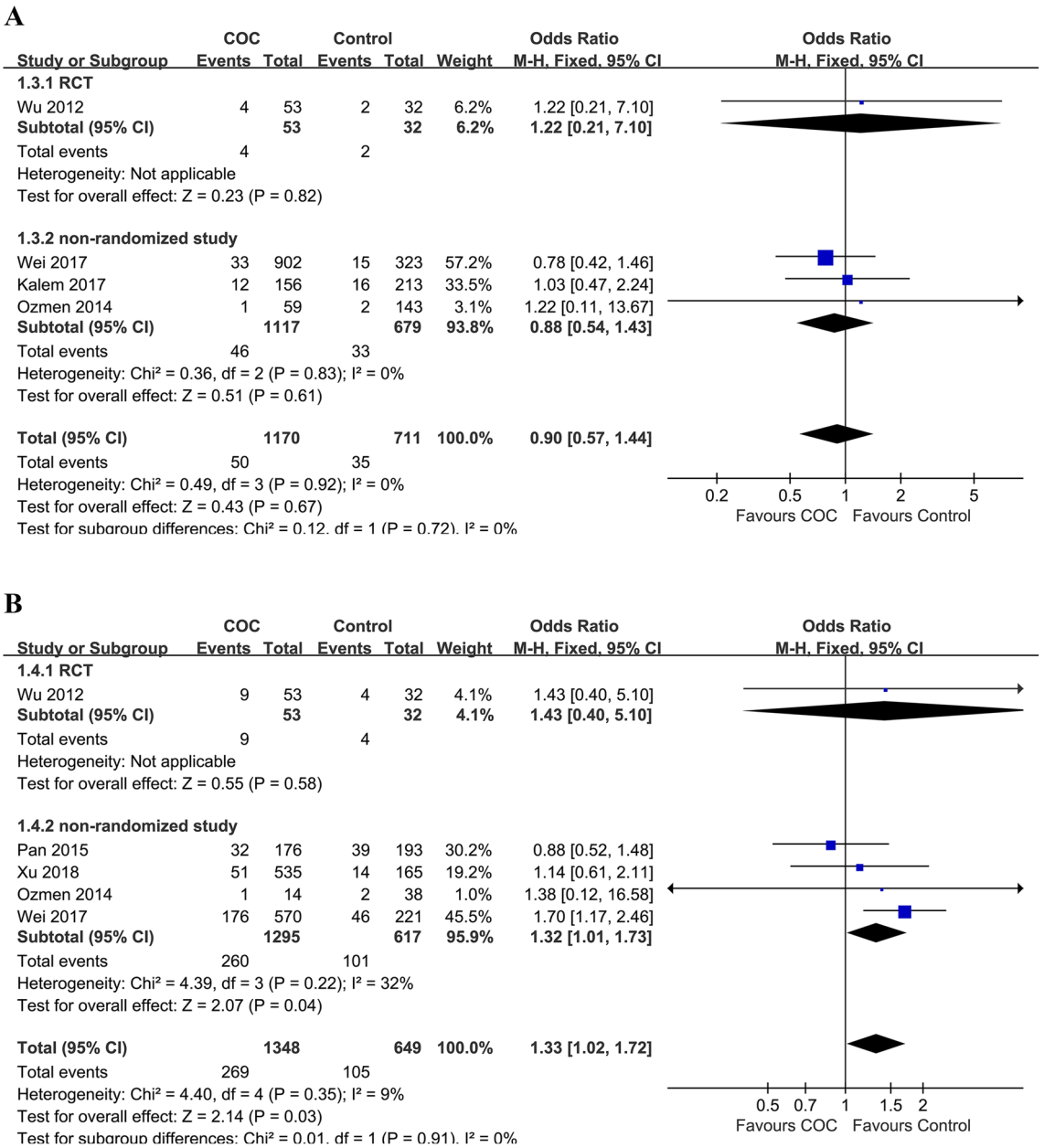

Fig. 3 Effect of combined oral contraceptives on adverse outcomes (**a**) ovarian hyperstimulation syndrome, **b** miscarriage

miscarriage was significantly higher in COC group compared to control group (OR = 1.33, 95% CI 1.02–1.72, $I^2 = 9\%$). This difference was significant in analysis of cohort studies (OR = 1.32, 95% CI 1.01–1.73, $I^2 = 32\%$), but not significant in one randomized study (OR = 1.43, 95% CI 0.40–5.10).

Secondary outcomes

Figure 4 shows the rate of cycle cancellation was not different between two groups (OR = 0.59, 95% CI 0.29–1.22, $I^2 = 0\%$). Duration and total dose of gonadotropin are shown in Fig. 5. Neither duration nor total dose of gonadotropin was altered by the use of COC (OR = 0.03, 95% CI − 0.70 to 0.76, $I^2 = 86\%$; OR = − 35.42, 95% CI − 97.18 to 26.34, $I^2 = 66\%$, respectively). As shown in Figs. 6 and 7, endometrium on the day of the human chorionic gonadotrophin injection was significantly thinner in the COC group (MD = − 1.06, 95% CI − 1.39 to − 0.73, $I^2 = 72\%$), and there were fewer retrieved oocytes in the COC group (MD = − 0.67, 95% CI − 0.99 to − 0.35, $I^2 = 17\%$). Fewer retrieved oocytes were significant in analysis of cohort

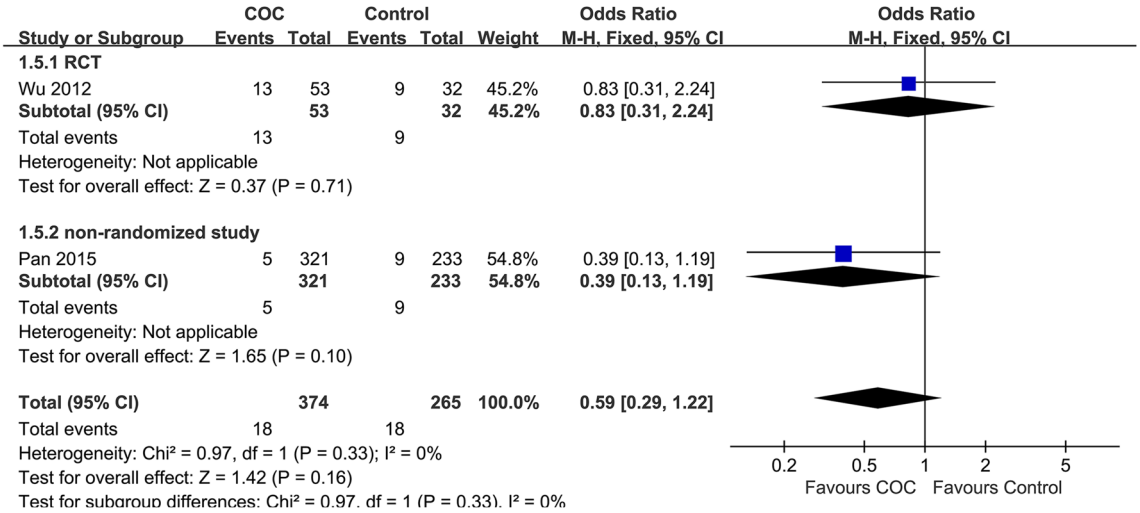

Fig. 4 Effect of combined oral contraceptives on cycle cancellation

studies (OR = − 0.97, 95% CI − 0.97 to − 0.32, $I^2 = 2\%$), but not in analysis of one RCT (OR = − 2.68, 95% CI − 5.52 to 0.16). Figure 8 shows rates of fertilization were similar between the two groups (MD = − 13.07, 95% CI − 37.90 to 11.75, $I^2 = 88\%$). Pooled analysis shows the rate of implantation was significantly higher in the COC group (OR = 1.28, 95% CI 1.08–1.51, $I^2 = 0\%$) as shown in Fig. 9, but the difference was not significant in analysis of one RCT (OR = 0.94, 95% CI 0.39–2.26).

Subgroup analysis

The studies we included in this meta-analysis were heterogeneous in terms of study protocol: method of pituitary suppression; use of vitro maturation of oocytes; use of frozen-thawed ET, and we performed subgroup analysis based on these protocol differences. Table 4 shows the results for the subgroup analysis of the study outcomes. The rates of clinical pregnancy and OHSS were not different between the two groups, although authors reported higher miscarriage rates and lower cumulative live birth rates with GnRH antagonists (OR = 1.69, 95% CI 1.17–2.44, $I^2 = 0\%$ and OR = 0.38, 95% CI 0.29–0.50, respectively). Cumulative live birth was reported in only two studies that included frozen-thawed ET, and the rate was higher in the control than the COC group (OR = 0.72, 95% CI 0.54–0.98, $I^2 = 55\%$). Rates of cycle cancellation, total gonadotropin dose, and number of retrieved oocytes were not significantly different between groups. Studies with GnRH antagonist protocols reported thinner endometrium (MD = − 1.30, 95% CI − 1.55 to − 1.05) and lower fertilization rate (MD = − 57.00, 95% CI − 84.86 to − 29.14) with COC pretreatment. In terms of ET, studies that included frozen-thawed ET reported thinner endometrium, fewer retrieved oocytes, and higher implantation rate (MD = − 1.13, 95% CI − 1.39 to − 0.73, $I^2 = 76\%$; MD = − 0.68, 95% CI − 1.01 to − 0.34, $I^2 = 0\%$ and OR = 1.40, 95% CI 1.14–1.73, respectively).

Discussion

The current study was an evaluation of the effect of COC pretreatment on women with PCOS who underwent ART for infertility, and in the study, COC pretreatment was associated with adverse clinical outcomes such as increased rate of miscarriage and decreased rate of cumulative live birth. These effects were especially significant in studies for which researchers used a GnRH antagonist for pituitary suppression [10, 12, 14]. Similarly, in a recent systematic review that included all women who underwent ART, oral contraceptive pretreatment (COC, progestin, or estrogen) decreased the rates of live birth and ongoing pregnancy with a GnRH antagonist protocol [20]. In the present study, we also found that COC pretreatment before ART in women with PCOS showed risky fertility outcomes with a GnRH antagonist protocol. Due to these adverse effects, care should be taken when using a GnRH antagonist protocol as part of COC pretreatment for women with PCOS. However, this finding should be confirmed in a randomized case–control study with a larger population.

In terms of ET, the lower cumulative live birth rate was more prominent in fresh ET cycles than in frozen-thawed cycles [13, 14]. This effect can be explained by the fact that COC decreases the receptivity of the endometrium in fresh ET cycles; in these cycles, COC treatment can accelerate endometrial maturation advance [21], and remnant effects of COC can aggravate the effect of controlled ovarian stimulation on asynchrony between endometrium and embryo [14],

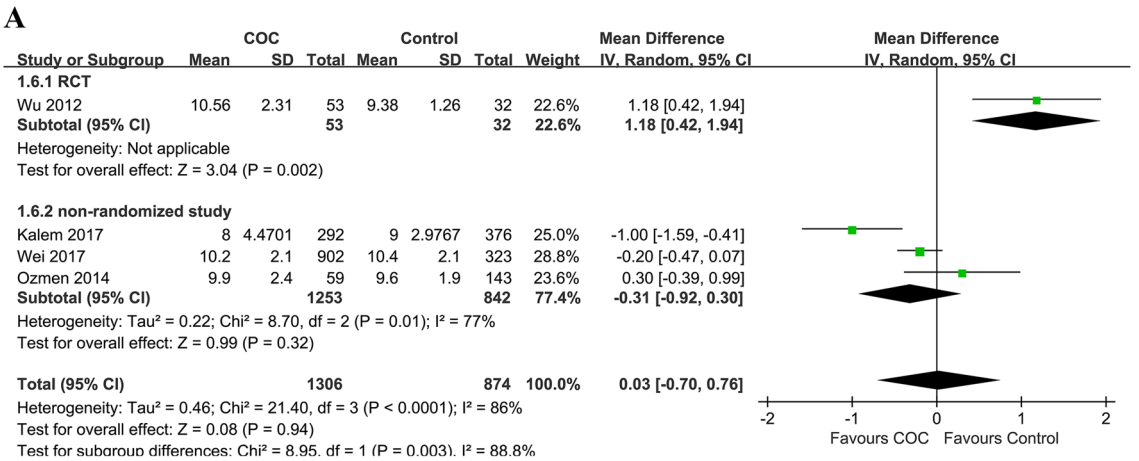

Fig. 5 Effect of combined oral contraceptives on the use of gonadotropin (**a**) duration of gonadotropin use, (**b**) total dose of gonadotropin

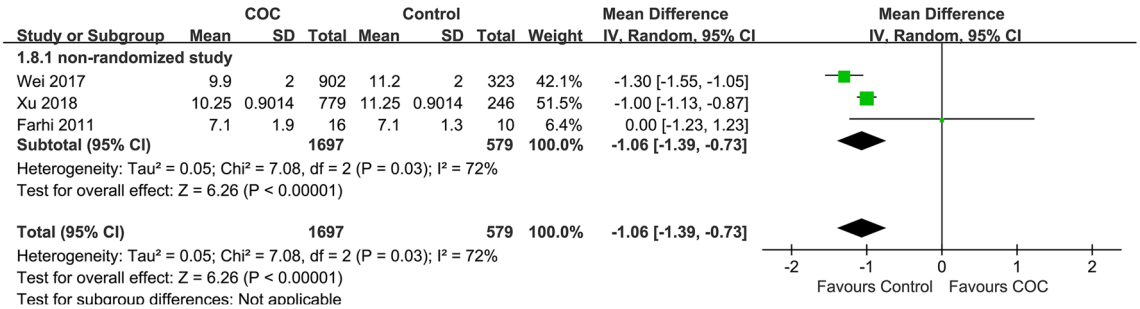

Fig. 6 Effect of combined oral contraceptives on endometrial thickness on the day of human chorionic gonadotropin injection

leading to decreased embryonic implantation rate and other adverse pregnancy outcomes. However, in frozen-thawed ET cycles, the effect of COC may be too low to cause adverse effect on endometrial receptivity [14]. Because recent studies have revealed that frozen-thawed ET is not inferior to fresh in terms of pregnancy outcomes [22], frozen-thawed ET might be a better option for women with PCOS who undergo ART with COC.

Rate of implantation was significantly higher in the COC group than in the control group in this meta-analysis. In particular, Pan et al. reported a markedly higher implantation rate in their COC group [8]. This result is consistent with findings by Damario et al., who reported higher

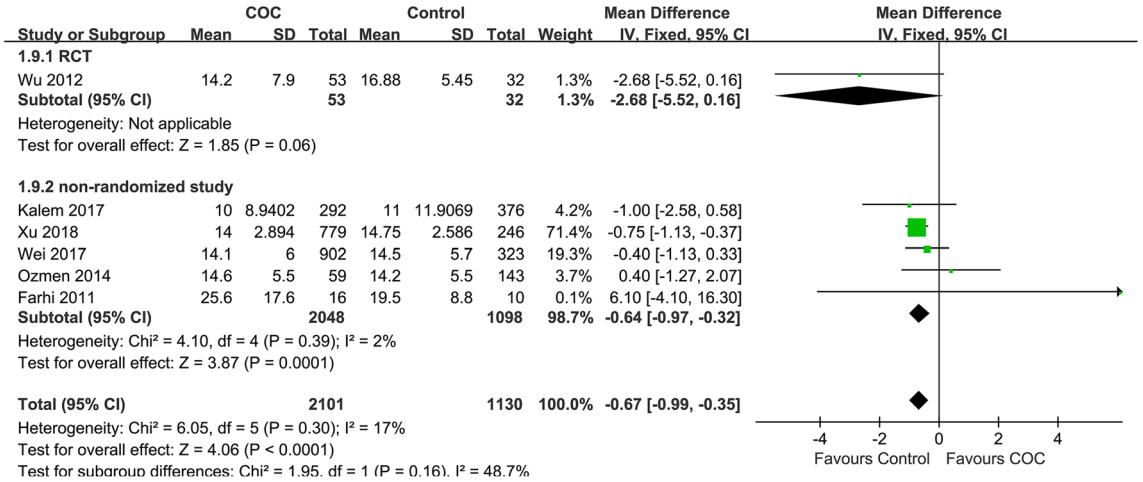

Fig. 7 Effect of combined oral contraceptives on number of retrieved oocytes

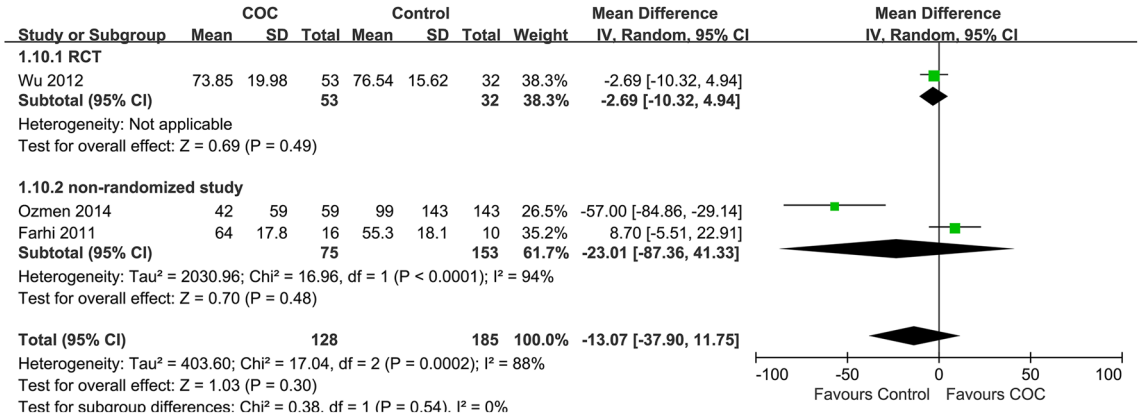

Fig. 8 Effect of combined oral contraceptives on the rate of fertilization

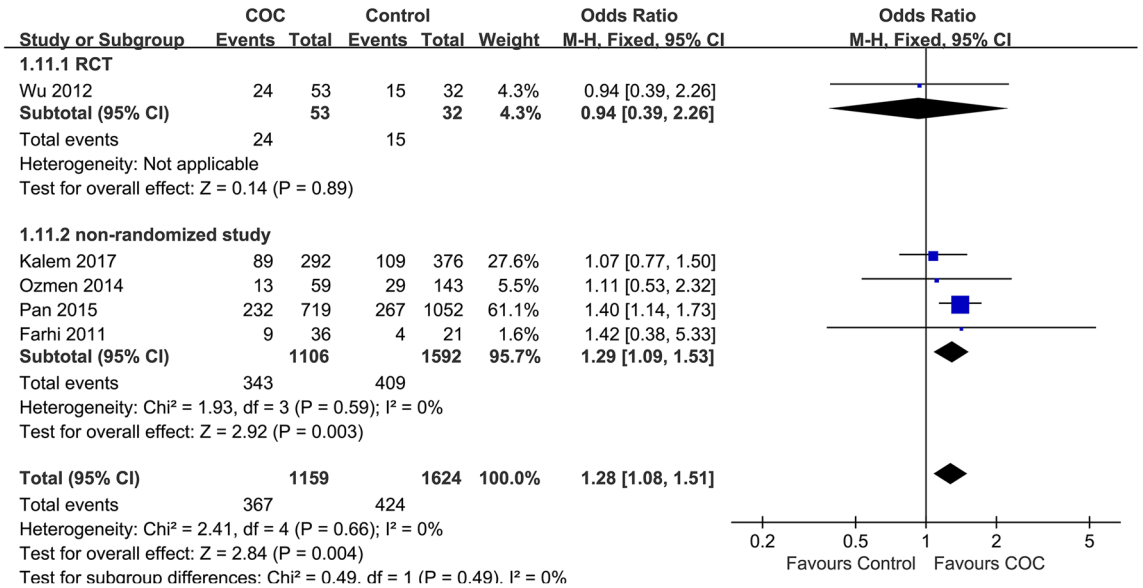

Fig. 9 Effect of combined oral contraceptives on implantation

Table 4 Subgroup analysis of outcomes according to study design, pituitary suppression, in vitro maturation or frozen embryo transfer

Outcomes	Factor	No of studies	Odds ratio[a] or mean difference[b] (95% CI)	I^2 (%)	Model used
Clinical pregnancy	All	7	0.93 [0.65, 1.34][a]	76%	RE
	Pituitary suppression				
	GnRHa	2	0.74 [0.52, 1.05][a]	0%	FE
	GnRH antagonist	3	0.79 [0.55, 1.12][a]	52%	RE
	In vitro maturation				
	Yes	1	1.17 [0.23, 5.81][a]	NA	NA
	No	6	0.92 [0.63, 1.35][a]	80%	RE
	Embryo transfer				
	Fresh only	5	0.85 [0.67, 1.09][a]	0%	FE
	Fresh and FET	2	1.00 [0.40, 2.52][a]	96%	RE
Miscarriage	All	5	1.33 [1.02, 1.72][a,*]	9%	FE
	Pituitary suppression				
	GnRHa	2	1.19 [0.68, 2.07] [a]	0%	FE
	GnRH antagonist	2	1.69 [1.17, 2.44][a,*]	0%	FE
	In vitro maturation				
	No	5	1.33 [1.02, 1.72][a,*]	9%	FE
	Embryo transfer				
	Fresh only	3	1.20 [0.69, 2.06][a]	0%	FE
	Fresh and FET	2	1.25 [0.66, 2.39][a]	76%	RE
Cumulative live birth	All	2	0.72 [0.54, 0.98][a]	55%	RE
	Pituitary suppression				
	GnRHa	1	0.85 [0.63, 1.15][a]	NA	NA
	GnRH antagonist	1	0.38 [0.29, 0.50][a,*]	NA	NA
	In vitro maturation				
	No	2	0.72 [0.54, 0.98][a]	55%	RE
	Embryo transfer				
	Fresh and FET	2	0.72 [0.54, 0.98][a,*]	55%	RE
OHSS	All	4	0.90 [0.57, 1.44][a]	0%	FE
	Pituitary suppression				
	GnRHa	1	1.22 [0.21, 7.10][a]	NA	NA
	GnRH antagonist	3	0.88 [0.54, 1.43][a]	0%	FE
	In vitro maturation				
	No	4	0.90 [0.57, 1.44][a]	0%	FE
	Embryo transfer				
	Fresh only	3	1.07 [0.54, 2.11][a]	0%	FE
	Fresh and FET	1	0.78 [0.42, 1.46][a]	NA	NA
Cycle cancellation	All	2	0.59 [0.29,1.22][a]	0%	FE
	Pituitary suppression				
	GnRH ant	1	0.87 [0.42, 1.81][a]	NA	NA
	In vitro maturation				
	No	2	0.59 [0.29, 1.22][a]	0%	FE
	Embryo transfer				
	Fresh only	1	0.83 [0.31, 2.24][a]	NA	NA
	Fresh and FET	1	0.39 [0.13, 1.19][a]	NA	NA

Table 4 (continued)

Outcomes	Factor	No of studies	Odds ratio[a] or mean difference[b] (95% CI)	I^2 (%)	Model used
Duration of gonadotropin use	All	4	0.03 [− 0.70, 0.76][a]	86%	RE
	Pituitary suppression				
	GnRHa	1	1.18 [0.42, 1.94][b,*]	NA	NA
	GnRH antagonist	3	− 0.31 [− 0.92, 0.30][b]	77%	RE
	In vitro maturation				
	No	4	0.03 [− 0.70, 0.76][b]	86%	RE
	Embryo transfer				
	Fresh only	3	0.14 [− 1.12, 1.41][b]	90%	RE
	Fresh and FET	1	− 0.20 [− 0.47, 0.07][b]	NA	NA
Total dose of gonadotropin	All	6	− 35.42 [− 97.18, 26.34][b]	66%	RE
	Pituitary suppression				
	GnRHa	2	− 0.75 [− 237.03, 235.53][b]	65%	RE
	GnRH antagonist	3	− 49.25 [− 195.75, 97.26][b]	61%	RE
	In vitro maturation				
	Yes	1	− 13.00 [− 61.67, 35.67][b]	NA	NA
	No	5	− 41.25 [− 128.41, 45.91][b]	62%	RE
	Embryo transfer				
	Fresh only	4	− 21.16 [− 144.04, 101.72][b]	54%	RE
	Fresh and FET	2	− 52.35 [− 133.38, 28.69][b]	69%	RE
Endometrial thickness	All	3	− 1.06 [− 1.39, − 0.73][b,*]	72%	RE
	Pituitary suppression				
	GnRHa	1	− 1.00 [− 1.13, − 0.87][b,*]	NA	NA
	GnRH antagonist	1	− 1.30 [− 1.55, − 1.05][b,*]	NA	NA
	In vitro maturation				
	Yes	1	0.00 [− 1.23, 1.23][b]	NA	NA
	No	2	− 1.13 [− 1.42, − 0.84][b,*]	76%	RE
	Embryo transfer				
	Fresh only	1	0.00 [− 1.23, 1.23][b]	NA	NA
	Fresh and FET	2	− 1.13 [− 1.42, − 0.84][b,*]	76%	RE
Number of retrieved oocytes	All	6	− 0.67 [− 0.99, − 0.35][b,*]	17%	FE
	Pituitary suppression				
	GnRHa	2	− 0.78 [− 1.16, − 0.41][b,*]	42%	FE
	GnRH antagonist	3	− 0.38 [− 1.00, 0.24][b]	0%	FE
	In vitro maturation				
	Yes	1	6.10 [− 4.10, 16.30][b]	NA	NA
	No	5	− 0.67 [− 1.00, − 0.35][b,*]	8%	FE
	Embryo transfer				
	Fresh only	4	− 0.59 [− 1.65, 0.47][b]	44%	FE
	Fresh and FET	2	− 0.68 [− 1.01, − 0.34][b,*]	0%	FE
Fertilization rate	All	3	− 13.07 [− 37.90, 11.75][b]	88%	RE
	Pituitary suppression				
	GnRHa	1	− 2.69 [− 10.32, 4.94][b]	NA	NA
	GnRH antagonist	1	− 57.00 [− 84,86, − 29.14][b,*]	NA	NA
	In vitro maturation				
	Yes	1	8.70 [− 5.51, 22.91] [b]	NA	NA
	No	2	− 28.12 [− 81.24, 24.99][b]	93%	RE
	Embryo transfer				
	Fresh only	3	− 13.07 [− 37.90, 11.75][b]	88%	RE

Table 4 (continued)

Outcomes	Factor	No of studies	Odds ratio[a] or mean difference[b] (95% CI)	I^2 (%)	Model used
Implantation	All	5	1.28 [1.08, 1.51][a,*]	0%	FE
	Pituitary suppression				
	GnRHa	1	0.94 [0.39, 2.26][a]	NA	NA
	GnRH antagonist	2	1.08 [0.80, 1.46][a]	0%	FE
	In vitro maturation				
	Yes	1	1.42 [0.38, 5.33][a]	NA	NA
	No	4	1.27 [1.07, 1.51][a,*]	0%	FE
	Embryo transfer				
	Fresh only	4	1.08 [0.81, 1.43][a]	0%	FE
	Fresh and FET	1	1.40 [1.14, 1.73][a,*]	NA	NA

I^2 was used to determine heterogeneity

CI confidence interval, *NA* not applicable, *FE* fixed effect model, *RE* random effect model, *RCT* randomized controlled trial, *GnRH* gonadotropin-releasing hormone, *FET* frozen EMBRYO transfer, *GnRHa* gonadotropin-releasing hormone analogue

implantation with COC pretreatment combined with GnRH agonist protocol in high responders including women with PCOS [7]. On the other hand, however, other researchers reported that the implantation rates were not significantly different between groups [7]. Decanter et al. also reported a similar implantation rate in women who have ovaries with polycystic appearance [9]. These inconsistent results among studies need to be confirmed with future prospective RCTs with larger populations.

This study has several limitations. First, we only included a few studies, and second, these were heterogeneous not only in study designs but also in ART protocols; COC types, criteria by which the authors diagnosed PCOS, method of pituitary suppression, maturation of oocytes, and ET type were also not uniform among studies. Third, multiple clinical outcomes were used as primary outcomes in this meta-analysis rather than using live birth as single primary outcome. This was because of the importance of multiple clinical outcomes besides live birth, and paucity of data. Although live birth was the most important end point of assisted reproductive technology, clinical pregnancy, miscarriage, and ovarian hyperstimulation syndrome were also crucial clinical events to consider when performing assisted reproductive technology. Moreover, there was a paucity of data on live birth because many clinical studies did not report live birth rate as primary or secondary outcomes [8, 10, 12, 13, 18, 19]. Nevertheless, this is the first meta-analysis to evaluate the efficacy of COC in women with PCOS who undergo ART for infertility. Since PCOS can be a confounding factor, women with PCOS are usually excluded from evaluations of specific drugs' effects on ART outcomes, and thus, there is a lack of data available for evaluating the effects of COC before ART in women with PCOS. Also, this study did not apply any restrictions according to study types, language or time to draw conclusion that is not skewed to one side.

In conclusion, pretreatment with COC in women with PCOS before ART may have adverse effects on clinical outcomes in terms of increased rate of miscarriage and decreased rate of cumulative live birth, especially with GnRH antagonist protocols. Therefore, when planning ART for patients with PCOS, clinicians should be aware of these possible risks.

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Compliance with ethical standards

Conflicts of interest The authors have no financial disclosures to declare and no conflicts of interest to report.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patient anonymity was completely preserved and the unique nature of identifying patients was not included in this manuscript.

Informed consent This study was based on retrospective review of published studies, it was not necessary to obtain informed consent from individual participants.

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