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Research article

Is glucocorticoid use associated with a higher clinical pregnancy rate of *in vitro* fertilization and embryo transfer? A meta-analysis

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ABSTRACT

Background: It has been reported that the use of glucocorticoids may be able to improve clinical pregnancy rates in patients receiving in vitro fertilization and embryo transfer (IVF-ET). The purpose of this study was to investigate the association between glucocorticoid use and clinical pregnancy rate in IVF-ET patients.

Methods: This study has been registered on the International Register of Prospective Systems Evaluation (PROSPERO) (ID: CRD42022375427). A thorough and detailed search of databases including PubMed, Web of Science, Embase, and Cochrane Library was conducted to identify eligible studies up to October 2022. Quality assessment was conducted on the modified Jadad Scoring Scale and Newcastle-Ottawa Scale, and the inter-study heterogeneity was estimated by Q test and I^2 test. Combined hazard ratios with 95% CI were calculated using random effects or fixed effects models based on heterogeneity. Meanwhile, Begg's and Egger's tests were used to detect the existence of publication bias, the leave-one-out method was used for sensitivity analysis and multiple subgroup analyses were conducted.

Results: Seventeen studies involving 3056 IVF-ET cycles were included. We found that glucocorticoid use was associated with a higher IVF-ET pregnancy rate (OR = 1.86, 95% CI = 1.27–2.74, P = 0.002). In the subgroup analysis, studies of different regions and different study types all showed similar results that glucocorticoid is beneficial to improve the clinical pregnancy rate of patients with IVF-ET, and patients with positive autoantibodies and patients receiving IVF-ET multiple times also showed the same results. However, there was no significant change in clinical pregnancy rates in the seven studies with negative autoantibodies and in the seven studies with initial IVF-ET treatment. The results of the 12 medium-acting glucocorticoids and 4 long-

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acting glucocorticoids were also generally consistent with each other. There was no statistical difference in subgroup analysis of whether patients had endometriosis or not.
Conclusion: Appropriate use of glucocorticoids is beneficial for improving the clinical pregnancy rate in women receiving IVF-ET, but this result still needs to be verified by more high-quality and large sample size randomized controlled trials (RCTs).

Abbreviations

IVF-ET	In vitro fertilization and embryo transfer
RCT	Randomized Controlled Trial
uNK	uterine Natural killer
NOS	Newcastle-Ottawa Quality Assessment Scale
CI	Confidence interval
ANA	Antinuclear antibody
ATA	Antithyroid antibodies
ACA	Anticardiolipin antibody
NK	Natural killer
HCG	Human chorionic gonadotropin
FSH	Follicle stimulating hormone

1. Introduction

Infertility is defined as failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse [1,2]. The advent of in vitro fertilization and embryo transfer (IVF-ET) offers hope to families struggling with infertility [3,4]. IVF-ET consists of extracting oocytes from an infertile woman, fertilizing them in vitro, and transferring fertilized eggs into the patient's uterine cavity, which is an assisted reproduction technology [5,6]. Menkin and Rock reported the first human in vitro fertilization procedure using ejaculated sperm and follicles in 1944 and 1948 [5,7,8]. After the success of this type of research in animals in 1930, human IVF-ET trials began [9]. In 1978, the world's first IVF-ET baby was born in the UK [10]. Although IVF-ET technology has been developed for many years, the current clinical pregnancy rate of IVF-ET patients is only 33.8%, according to the European Society of Human Reproduction and Embryology (ESHRE) in 2016 [11].

Clinically used glucocorticoids include long-acting hormones such as dexamethasone, and medium-acting hormones such as prednisone, methylprednisolone, etc [12,13]. Because of their role in reducing inflammatory responses and suppressing immunity, glucocorticoids are very effective in the relief and maintenance of autoimmune diseases such as rheumatoid arthritis, respiratory diseases, glomerular basement membrane diseases, and even some rare diseases such as Kikuchi-Fujimoto disease [14–18]. In addition, the application of glucocorticoids in the field of assisted reproduction has been gradually paid attention to. It has been found that glucocorticoids may act on uterine natural killer (uNK) cells, cytokines, inhibit inflammation and improve the success rate of IVF-ET implantation, and can improve the quality of oocytes by sensitizing the ovary to gonadotrophins and improving the ovarian local microenvironment [13,19]. Zhang et al. concluded that glucocorticoids could effectively improve the clinical pregnancy rate in patients with endometritis receiving IVF-ET [20]. Kolanska et al. also presented similar conclusions, suggesting that glucocorticoids can improve repeated implantation failure and clinical pregnancy rate [21]. However, whether glucocorticoids can improve the clinical pregnancy rate of IVF-ET remains controversial. According to the trials of Zhou et al. and Liu et al. there was no difference in clinical pregnancy rates with glucocorticoids in IVF-ET patients compared to controls [19,22]. IVF-ET is of great significance to the infertile population and its effect on clinical pregnancy rate is controversial, we urgently need to know whether glucocorticoids affect the clinical pregnancy rate of IVF-ET.

This paper focuses on the effect of glucocorticoid use on clinical pregnancy rates in IVF-ET patients, with subgroup analysis by region, study type, whether the patient was autoantibody-positive, whether the patient was receiving IVF-ET for the first time, the type of glucocorticoid, whether the patient had endometriosis and whether the use of glucocorticoids was combined with other medications to draw relatively reliable conclusions. This study has far-reaching significance for the improvement of clinical pregnancy rate of patients receiving IVF-ET, especially patients receiving multiple failed IVF-ET and patients with positive autoantibodies.

2. Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in the current meta-analysis. This study has been signed up on the International Prospective Register of Systematic Reviews (PROSPERO). The number of registration ID was CRD42022375427 [23].

2.1. Search strategy

This meta-analysis conducted a comprehensive search strategy on glucocorticoid use and IVF-ET clinical pregnancy rate. Relevant publications were extracted from the Embase, PubMed, Cochrane Library, Web of Science, China Biomedical Database, Wanfang Data, VIP database, and China National Knowledge Infrastructure(CNKI) until October 2022. The following terms were used: (in vitro fertilization and embryo transfer OR IVF-ET) AND (glucocorticoid OR prednisolone OR dexamethasone OR hydrocortisone OR prednisone OR methylprednisone OR methylprednisolone). References from related studies and articles were also searched. Once duplicates had been eliminated, the researchers examined titles and abstracts of every record and review the full text in order to identify studies eligible for analysis. English words were replaced by Chinese phrases in the Chinese database.

2.2. Inclusion and exclusion criteria

Only studies that met the inclusion criteria were considered: (i) The study type is a randomized controlled trial (RCT), case-control study, or cohort study. (ii) The population was women of childbearing age undergoing IVF-ET. (iii) All the patients in the experimental group received dexamethasone, whereas all the patients in the control group received placebo or no treatment. (iv) The outcome of interest was the clinical pregnancy, which was defined as the detection of a gestational sac on ultra-sound scanning after a positive pregnancy test.

The exclusion criteria were as follow: (i) Case reports, conference or meeting abstracts and review articles. (ii) The subjects of this study are not humans, such as in vivo or in vitro studies. (iii) Studies that did not provide useable data. (iv) Duplicate.

2.3. Data extraction and quality assessment

Two authors independently extracted data from all eligible studies, after which the quality of the articles was evaluated. Disagreements between reviewing authors were settled by consensus which was achieved via discussion among all authors. We extracted data on: publication information (e.g., author's name, year of publication, region, study design, intervention details, duration of treatment, time period, patient age, sample size), outcome indicators (clinical pregnancy rate, and live birth rate, and corresponding number of experimental group events, total number of experimental group events, number of control group events, total number of control group events), study quality, autoantibody, whether the patient is receiving IVF-ET for the first time and follow-up information.

The two review authors independently evaluated the quality of the included randomized controlled trials (RCTs) with the modified Jadad Scoring Scale. The modified Jadad Scale was scored according to literature randomization (0–2 points), concealment of allocation (0–2 points), double blinding (0–2 points), withdrawals, and dropouts (0–1 points). An overall score of 4–7 is considered high-quality study, and 1–3 is considered low-quality [24]. Also, based on the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control and cohort studies, two researchers assessed the quality of studies, separately. The scoring system of this scale was based on 3 components: selection, comparability, outcomes (cohort study)/exposure (case-control study). The highest NOS score available for each publication is 9 stars, with 6 or more stars for high-quality literature and 4–5 stars for moderate quality [25,26].

2.4. Statistical analysis

Statistical analyses were performed with the statistical software Stata 15.0 (Stata Corp., College Station, Tex, USA). Since clinical pregnancy is a dichotomous variable, the results were combined using the Mantel-Haenszel method and expressed as the pooled OR with the corresponding 95% confidence interval (CI). We tested the heterogeneity among studies by Q test at the level of $P = 0.1$, and the degree of statistical heterogeneity was estimated using the I^2 statistic, a value of I^2 <50% indicated no significant statistical heterogeneity, and a fixed-effects model was utilized. Otherwise, statistical heterogeneity was indicated and a random-effects model was used to synthesize the data. To test whether our results were stable, we used the leave-one-out method to conduct the sensitivity analyses. Publication bias was identified by observing the symmetry of funnel graph and by Begg's and Egger's test values. $P < 0.05$ was considered statistically significant [27,28].

3. Results

3.1. Study characteristics

The literature search retrieved a total of 702 records according to the search strategy, from which 65 duplicates were removed. Based on title or abstract, ninety-two were left for full text review and further assessed for eligibility. After full-text assessment of 92 articles, seventy-seven articles were excluded. The flowchart of the searching and selecting process was presented in Fig. 1. Finally, 15 articles [13,19–21,29–39] met the inclusion criteria. Of these, 6 were cohort studies [21,22,30–32,38], 1 was case-control studies [13], and 8 were randomized controlled trials [19,20,29,33–37]. Among them, 9 studies were conducted in Asia [19,20,22,29,30,32–34,38] , 4 in Europe [13,21,35,36] and 2 in the America [31,37]. More detailed information about the included studies was presented in Table 1.

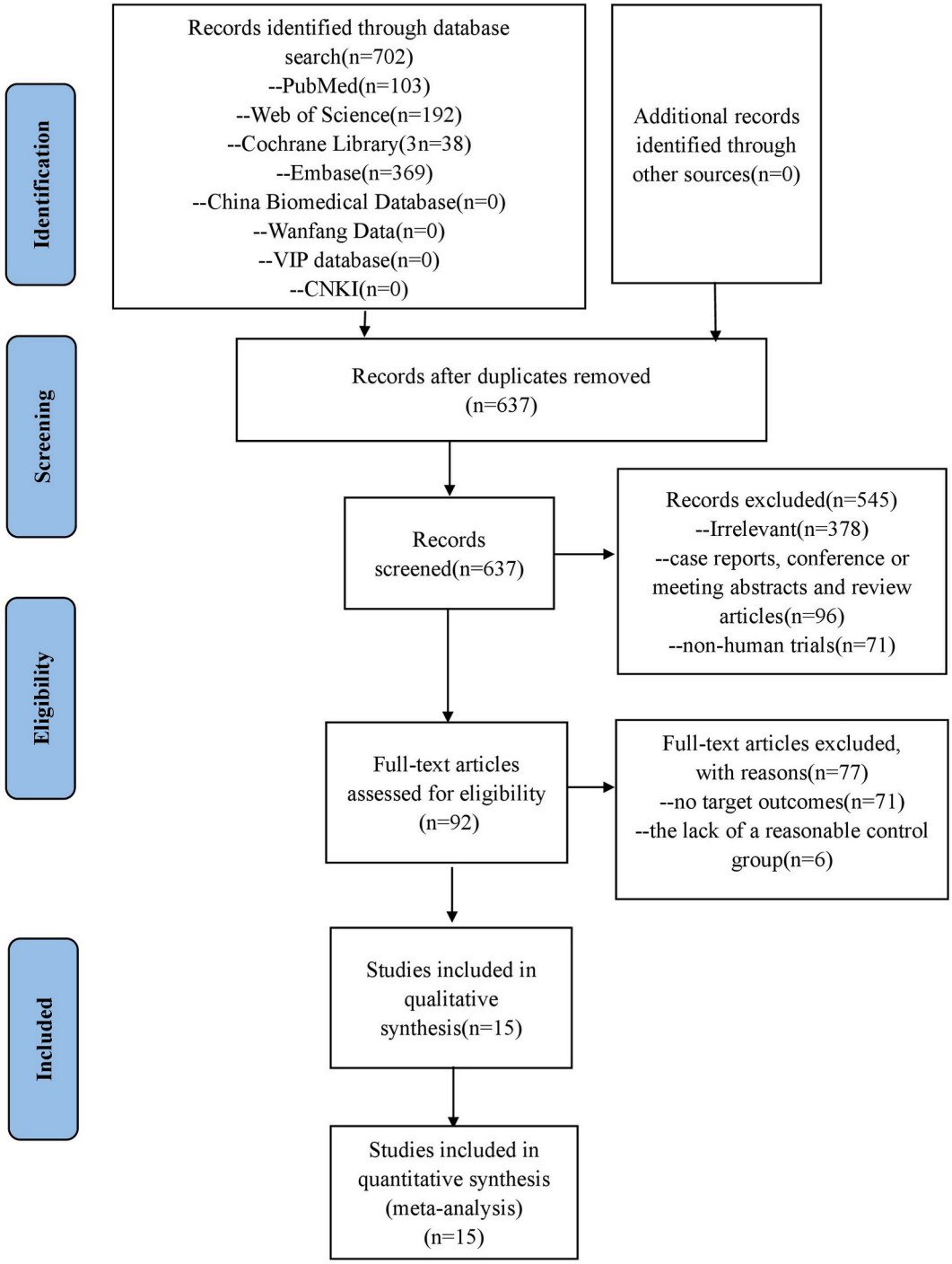

Fig. 1. Perferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) flow chart.

3.2. *Meta-analysis*

Fifteen articles [13,19–21,29–39] with 19 studies regarding the association between glucocorticoid use and clinical pregnancy rate were included in the overall meta-analysis. Heterogeneity was observed, and the combined effect estimation with a random effect model was displayed in the forest plot. The pooled result indicated that glucocorticoid use was associated with a higher clinical pregnancy rate of IVF-ET (OR = 1.86, 95% CI = 1.27–2.74, P = 0.002; Fig. 2). However, it was found that the use of glucocorticoid was not associated with live birth rate (OR = 1.32, 95% CI = 0.819–2.128, P = 0.254).

Table 1
Characteristics of individual studies included in the meta-analysis.

Study	Region	Study design	Intervention	Duration of treatment	Time period	Age	Sample size		Quality	Autoantibody	First attempts at IVF or not
							Primary outcome (clinical pregnancy rate)	Secondary outcome (live birth rate)			
Ando 1996	Japan	Randomized controlled trial	Five milligrams of predonisolone or 0.5 mg of dexamethasone was administered orally daily during the entire IVF[1] cycle until the pregnancy test was performed. After the pregnancy test became positive, dexamethasone was changed to predonisolone. In LAC[2]-positive patients, low-dose aspirin (81 mg/day) was combined in the same period.	NA	NA	Exp:32.8 ± 3.4 Con:31.5 ± 3.6	Exp:(27/71) Con:(5/68)	NA	High quality	All patients with autoanti- body-positive (antinuclear antibody (ANA), anti-deoxyribonucleic id (DNA) antibody, and lupus anticoagulant (LAC).	NA
Bider 1999	Israel	Retrospective cohort study	Dexamethasone, 0.5 mg.	Initiated on the first day of HMG[3] stimulation and discontinued on the day after ET[4].	NA	Exp:30.1 ± 2.99 Con:32.2 ± 4.57	Exp:(4/20) Con:(13/51)	Exp:(4/20) Con:(10/51)	High quality	NA	YES
Fried 1993	USA	Prospective cohort study	60 mg of methylprednisone x 4 days.	Beginning the day of ovum retrieval.	1990.5–1991.4	Exp: 34.32 ± 4.98 Con:31.85 ± 4.09	Exp:(14/38) Con:(3/27)	NA	High quality	NO	38 were first-time recipients of IVF-ET[5] and 26 were not.
Gao 2021	China	Retrospective cohort study	Combined treatment of prednisone (10 mg/d) and HCQ[6].	NA	2020.1–2021.5	31.44 ± 5.14	Exp:(39/66) Con:(6/30)	NA	High quality	Fifty patients with positive ANA[7] and one hundred autoantibody-negative patients.	NA
GEVA 2000	Israel	Randomized controlled trial	Prednisone, 10 mg per day, and aspirin, 100 mg per day.	Starting 4 weeks before induction of ovulation.	NA	NA	Exp:(29/74) Con:(3/24)	NA	High quality	52 patients seropositive for non-organ-specific autoantibodies, i.e., *anti*-cardiolipin antibodies (ACA),anti-nuclear antibodies (ANA), anti-double-stranded (ds) DNA, rheumatoid factor(RF),	NO

(*continued on next page*)

Table 1 (*continued*)

Study	Region	Study design	Intervention	Duration of treatment	Time period	Age	Sample size		Quality	Autoantibody	First attempts at IVF or not
							Primary outcome (clinical pregnancy rate)	Secondary outcome (live birth rate)			
										and lupus anti-coagulant (LAC).	
Kolanska 2021	France	Cohort	Combined treatment of prednisone 10 mg/day and low-dose aspirin or intralipids.	NA	2015.12–2018.10	36 ± 3	Exp:(48/110) Con:(20/230)	NA	High quality	NA	NA
Lee 1994	Korea	Randomized controlled trial	Various doses of 16/3-methylprednisolone (0,16 or 60 mg/day)for 4 days from the day of oocyte retrieval.	NA	1992.12–1993.3	Exp(with FSH[8]/HMG) : 31.78 ± 0.43Con(with FSH/HMG): 32.50 ± 0.59 Exp:(with GnRHa[9]/FSH/HMG):32.25 ± 0.50Con:(with GnRHa/FSH/HMG): 31.35 ± 0.64	with FSH/HMG: Exp:(22/66) Con:(14/38) with GnRHa/FSH/HMG: Exp:(13/54) Con:(3/17)	NA	High quality	NO	116 cycles were receiving IVF-ET for the first time and 59 were not
Litwicka 2015	Italy	Randomized, prospective, controlled trial	The low-dose Prednisolone(5 mg)	From the day of oocyte retrieval.	2011.1–2012.4	Exp:34.6 ± 3.2 (ATA[10]-positive) Con:35.0 ± 3.2 (ATA-positive) 33.7 ± 4.1 (ATA-nagative)	Exp:(14/30) Con:(56/164)	Exp:(14/30) Con:(60/164)	High quality	60 patients with ATA-positive.	NA
Liu 2018	China	Randomized controlled trial	Treated with oral dexamethasone 0.75 mg/d.	2 years	2015.7–2015.10	Exp:28.98 ± 3.41 Con:28.75 ± 2.99	Exp:(99/160) Con:(98/157)	NA	High quality	NO	YES
Mitic 2019	Serbia	Prospective case-control study	Treatment consisting of dexamethasone (0.5 mg/day) plus ASA[11] (100 mg/day).	Starting on the day of embryo transfer.	2017.9–2018.10	Exp:34.80 ± 4.06 Con:36.29 ± 4.67	Exp:(28/64) Con:(42/146)	NA	High quality	NO	NA
Moffitt 1995	Swedish	Randomized, prospective, double-blinded, placebo-controlled trial	16 mg oral6-ex-methylprednis-olone for four evenings (treated with 250 mg oral tetracycline four times per day for 4 days).	Starting the evening of retrieval or the evening before thawing cryopre-served embryos.	1993.1–1993.9	Exp:34.6 ± 3.8 Con:34.9 ± 4.0	Exp:(9/28) Con:(11/33)	NA	High quality	NO	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Region	Study design	Intervention	Duration of treatment	Time period	Age	Sample size		Quality	Autoantibody	First attempts at IVF or not
							Primary outcome (clinical pregnancy rate)	Secondary outcome (live birth rate)			
Mottla 1996	America	Randomized, double-blind, placebo-controlled clinical trial	Prednisone	NA	NA	NA	Exp:(17/39) Con:(12/36)	NA	High quality	NO	NA
Ying 2012	China	Retrospective cohort study	With methylprednisolone plus low-dose aspirin.	NA	2010.9–2011.6	Exp:32.1 ± 4.0 Con:31.9 ± 4.9 (ACA+) 32.2 ± 4.4	Exp:(20/56) Con:(249/578)	NA	High quality	116 patients with ACA[12]+.	NA
Zhang 2019	China	Randomized controlled trial	Dexamethasone (DXM 5 mg), hyaluronidase (1500 U), and saline (added up to 20 mL).	Seven treatment days after menstruation until clinical pregnancy was determined.	2015.2–2017.6	Exp:33.45 ± 4.32 34.27 ± 3.61 Con:32.21 ± 4.16	Exp:(50/109) Con:(38/126)	Exp:(40/109) Con:(22/126)	High quality	NA	NO
Zhou 2022	China	Retrospective cohort study	Treated with prednisone (10 mg/d) and aspirin (100 mg/d).	On the day of embryo transfer and continued until clinical pregnancy was determined.	2017–2020	Exp:31.5 (29.0–35.0) (fresh) 30.0 (28.0–34.8) (frozen) Con:31.0 (29.0–35.0) (fresh) 30.0 (28.0–34.0) (frozen)	Fresh embryo transfer cycles: Exp:(47/74) Con:(65/113) Frozen-thawed embryo transfer cycles: Exp:(47/76) Con:(48/83)	Fresh embryo transfer cycles: Exp:(35/74) Con:(56/113) Frozen-thawed embryo transfer cycles: Exp:(34/76) Con:(39/83)	High quality	All patients with positive thyroid autoimmune antibodies(TPOAb[13] and/or TgAb[14]).	YES

[1]IVF:In Vitro Fertilization; [2]LAC: Lupus anticoagulant; [3]HMG:Human menopausal gonadotropin; [4]ET:Embryo transfer; [5]IVF-ET:In vitro fertilization and embryo transfer; [6]HCQ:Hydroxychloroquine; [7]ANA:Antinuclear antibody; [8]FSH:Follicle-stimulating hormone; [9]GnRHa:Gonadotrophin releasing hormone agonist; [10]ATA:Antithyroid antibodies; [11]ASA:Acetylsalicylic acid; [12]ACA:Anticardiolipin antibody; [13]TPOAb:Thyroid peroxidase antibody; [14]TgAb:Anti-thyroglobulin antibodies.

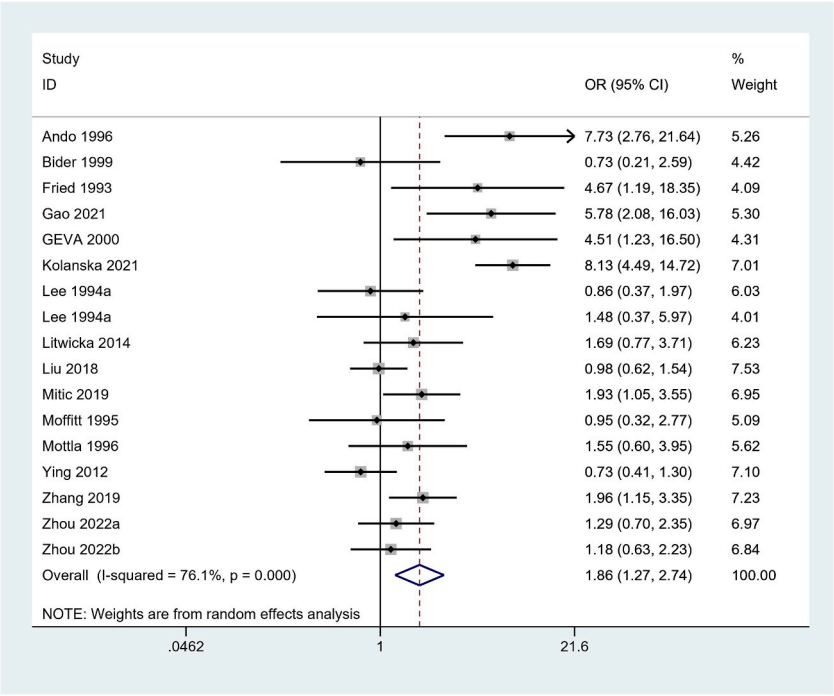

Fig. 2. Forest plot: Association of glucocorticoid use with clinical pregnancy rates in women undergoing IVF-ET.

3.3. Subgroup analyses

In subgroup analysis, according to region, the same result was found in the 11 studies of eastern countries (OR = 1.59, 95% CI = 1.04–2.41, P = 0.031), and 6 studies of western countries reported OR of 2.41 (95% CI = 1.2–4.87, P = 0.014). Based on the study type, observational studies and the randomized controlled trials had the same results, in which the OR of the observational studies was 2.03 (95% CI = 1.04–3.98, P = 0.038), and the OR of the randomized controlled trials was 1.69 (95% CI = 1.09–2.61, P = 0.019). In terms of being positive for autoantibodies, patients with positive autoantibodies (OR = 2.09, 95% CI = 1.12–3.89, P = 0.02) showed better results than those with negative autoantibodies (OR = 1.29, 95% CI = 0.97–1.71, P = 0.082). Subgroup analysis was stratified according to whether patients were receiving IVF-ET for the first time, the results showed that the OR value of patients receiving IVF-ET for the first time was 1.16 (95% CI = 0.88–1.53, P = 0.298) and that of patients receiving IVF-ET for the non-first time was 2.26 (95% CI = 1.47–3.48 , P < 0.001). In subgroup analysis classified by glucocorticoid type (i.e., intermediate-acting, long-acting glucocorticoids), the OR for intermediate-acting glucocorticoids (OR = 1.90, 95% CI = 1.13–3.19, P = 0.015) and the OR for the 4 studies using long-acting glucocorticoids was 1.38 (95% CI = 1.03–1.85, P = 0.03). No statistically significant effect of the presence (OR = 4.80, 95% CI = 1.69–13.58, P = 0.003) or absence (OR = 1.33, 95% CI = 1.09–1.62, P = 0.005) of endometriosis in patients on clinical pregnancy rates was found. The results for glucocorticoids only (OR = 1.77, 95% CI = 0.88–3.55, P = 0.11) and when they were combined with other medications (OR = 1.90, 95% CI = 1.20–3.03, P = 0.007) were consistent. All results of the subgroup analyses were presented in Table 2.

3.4. Sensitivity analyses and publication bias

Sensitivity analysis was achieved by the leave-one-out method, which demonstrated a stable result. The funnel plot shape was symmetrically distributed and the Begg's test and Egger's test suggested no publication bias (Begg's test: Z = 0.78; P = 0.434; Egger's test: t = 0.98; P = 0.340; Fig. 3).

4. Discussion

Whether glucocorticoids can improve the clinical pregnancy rate in women receiving IVF-ET has been controversial and concerned. We used a meta-analysis of eight RCTs, six cohort studies, and one case-control study to show that glucocorticoid use was effective in improving the clinical pregnancy rate in IVF-ET. In subgroup analyses, the results of the eleven studies conducted in eastern countries were similar to those of the six studies conducted in western countries, suggesting that glucocorticoids have a positive effect on the clinical pregnancy rate of IVF-ET. In case of study design, eight observational studies and nine randomized controlled trials have also demonstrated an association between glucocorticoids and higher clinical pregnancy rates. Furthermore, in the stratified analysis by autoantibodies, the clinical pregnancy rate of patients with positive autoantibodies, including antinuclear antibody (ANA), antithyroid

Table 2
Summary of pooled ORs with CIs in the subgroup analyses.

Group	No. of studies	OR(95%CI)	Heterogeneity		Significance		Model
			I2	P	Z	P	
Overall	17	1.86 (1.27,2.74)	76.1	<0.001	3.16	0.002	Random
Geographic locations							
Eastern countries	11	1.59 (1.04,2.41)	69.5	<0.001	2.16	0.031	Random
Western countries	6	2.41 (1.20,4.87)	76.6	0.001	2.46	0.014	Random
Study design							
Observational studies	8	2.03 (1.04,3.98)	84.7	<0.001	2.07	0.038	Random
Randomized controlled trials	9	1.69 (1.09,2.61)	59.1	0.012	2.35	0.019	Random
Positive for autoantibody							
Yes	7	2.09 (1.12,3.89)	77.1	<0.001	2.32	0.02	Random
No	7	1.29 (0.97,1.71)	24.1	0.246	1.74	0.082	Fixed
First attempts at IVF							
Yes	7	1.16 (0.88,1.53)	0.2	0.422	1.04	0.298	Fixed
No	5	2.26 (1.47,3.48)	1.9	0.396	3.75	<0.001	Fixed
Class of glucocorticoids							
Long-acting glucocorticoids	4	1.38 (1.03,1.85)	50	0.111	2.17	0.03	Fixed
Intermediate-acting glucocorticoids	12	1.90 (1.13,3.19)	78.3	<0.001	2.43	0.015	Random
Use of other drugs							
Yes	9	1.90 (1.20,3.03)	71.4	<0.001	2.71	0.007	Random
No	7	1.77 (0.88,3.55)	82	<0.001	1.6	0.11	Random
Combination of endometriosis							
Yes	3	4.80 (1.69,13.58)	85.6	0.001	2.96	0.003	Random
No/NA	14	1.33 (1.09,1.62)	47.7	0.024	2.81	0.005	Fixed

antibodies (ATA), anticardiolipin antibody (ACA), etc., was significantly increased, while that of patients with negative autoantibodies was not increased, which may be related to the participation of glucocorticoids in the immunoregulatory treatment of autoimmune diseases as immunosuppressants. It has also been suggested that therapy with glucocorticoid may correct the autoimmune and inflammatory processes behind the production of autoimmune antibodies and reduce their circulating levels, thus limiting the negative effects on pregnancy development [22,35]. Besides, women who had received IVF-ET and used glucocorticoid again showed a higher clinical pregnancy rate, while those who had received IVF-ET for the first time showed no correlation with glucocorticoid use, which may be related to the inhibition of the endometrial inflammation caused by multiple IVF-ET operations [30,40]. The results of the subgroup analysis classified according to the duration of glucocorticoid action (i.e., use of intermediate-acting or long-acting glucocorticoids) were identical and may be related to the fact that the basic mechanisms of action and effects of the different types of hormones chosen for the study did not differ significantly. Endometriosis in patients has no influence on clinical pregnancy rates whether it is present or absent, which is likely because glucocorticoids have similar immunosuppressive and anti-inflammatory effects

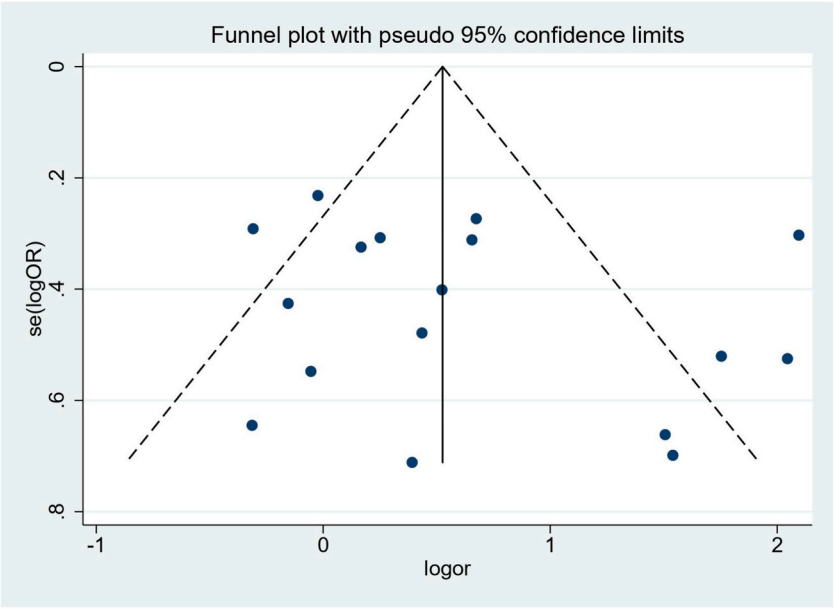

Fig. 3. Funnel plot.

in individuals with endometriosis. There was no statistically significant difference in the results whether glucocorticoids were used with or without other medications, which may indicate that glucocorticoids are primarily responsible for the increased clinical pregnancy rate in IVF-ET patients. Sensitivity analysis showed that when we applied the leave-one-out method, the results did not materially change, indicating stable results from this meta-analysis.

The underlying mechanism by which glucocorticoids increase the clinical pregnancy rate in IVF-ET patients is not fully understood. Studies have shown that glucocorticoids inhibit immune processes, which is an important mechanism. As early as 1990, Cohen et al. suggested that micro procedures such as egg extraction might compromise some of the protective properties of the zona pellucida, while glucocorticoid therapy was thought to reduce the presence of uterine lymphocytes or peripheral immune cells dominated by segmented neutrophils. In addition, daily prednisolone therapy from the first day of the menstrual cycle was found to reduce the number of uNK cells, which are thought to be associated with repeated miscarriages and repeated implant failures [29,41]. The effect of glucocorticoid on the response of natural killer (NK) cells is determined by the local cytokine environment. Dexamethasone has been shown to enhance the proliferation, reactivity, and survival of primary NK cells stimulated by IL-2 plus IL-12; However, dexamethasone slightly induced primary NK cell death when incubated with IL-15. The number of uterine NK cells was significantly associated with the IL-18/IL-18BP ratio, which is associated with excess uNK cells in patients with implant failure [13,29,42]. Different glucocorticoids can regulate NK cell response in different ways, which may be related to improving the clinical pregnancy rate of IVF-ET patients. The immunosuppressive effect of glucocorticoids was also shown to inhibit the inflammatory response caused by embryo transfer. All the procedures required for embryo transfer can lead to inflammatory reactions, especially endometrial inflammation. When inflammation occurs, macrophages and immunoactive cells will migrate to the inflammatory lesions, accompanied by the release of interleukin-1, oxygen free radicals and prostaglandin in large quantities, which may destroy the normal uterine environment and be adverse to the embryo, and even embryo phagocytosis may occur. The effect of glucocorticoids, it was found, was to reverse this process and restore normal conditions to the endometrium [30,36]. Polak et al. 's hypothesis also support this view [29,31]. The harmful components of the inflammatory process include, in addition to the cytotoxic soluble products of leukocytes, specific cytokines that inhibit embryonic growth and induce the expression of major histocompatibility antigen trophoblast. Once these antigens are expressed, trophoblast cells are vulnerable to cytotoxic T cell attacks. Glucocorticoid use reduces the number of white blood cells involved in embryo transfer stimulation and weakens the response of these cells. Glucocorticoids can also intervene extracellular matrix and specific proteins through modification, affect their secretion and deformation, and prevent the excessive development of inflammatory reactions, repair the damaged endometrium [36,43,44]. Ando et al. also noted that continued use of corticosteroids improved oocyte and embryo quality. Glucocorticoids may improve the quality of oocytes by increasing the sensitivity of ovary to gonadotropin and thus improving the local microenvironment of ovary. It may also be that glucocorticoids play a licensing role in overcoming the state of the damaged embryo or uterus [19,29,36,45]. Glucocorticoids play an important role in endocrine. In the process of ovulation induction, glucocorticoids can inhibit the secretion of progesterone, conducive to ovulation. After gonadotropin stimulation of mature oocytes, luteinized granulosa cells extracted from the cumulus complex increased the rate of estradiol and progesterone secretion associated with prednisolone dose. This effect occurs even independently of the concurrent stimulation of human chorionic gonadotropin (HCG) and does not involve follicle stimulating hormone (FSH) receptor interaction. Dexamethasone may also sensitize the ovaries to gonadotropin stimulation during IVF treatment, reducing the amount of gonadotropin required and the number of days of stimulation during the cycle. The above endocrine mechanisms are conducive to improving the clinical pregnancy rate of IVF-ET [19,29,30,46–48]. Glucocorticoids may also improve clinical pregnancy rates by improving embryo implantation. Glucocorticoids promote embryo attachment by enhancing fibridenin synthesis, increase trophoblast mRNA expression of cell motor gene PLCG1 by enhancing trophoblast growth, and alter decidulo-trophoblast interaction to reduce postimplantation death [22,30,31]. Our meta-analysis confirmed that glucocorticoids can effectively improve the clinical pregnancy rate, but the possible mechanism remains to be fully explored.

There are some limitations that need to be mentioned. First, although our search strategy is rigorous and comprehensive, there may be some potential studies not included in this study. Second, due to the limitations of the original research and the differences in hormone doses utilized in each trial, the subgroup analysis could not be carried out. Thirdly, the sample size of many studies is relatively small, so more high-quality and large sample RCTs were needed in the future, to further improve the results of this study.

Despite the above limitations, the following advantages of this study should be acknowledged. To our knowledge, this is the first meta-analysis to clarify the association between glucocorticoid use and clinical pregnancy rates in IVF-ET patients. Our research included a large number of articles, involved a considerable number of studies, high credibility. In addition, when we performed the sensitivity analysis using the leave-one-out method, the results of the meta-analysis did not materially change because the results were robust. Moreover, there is no publication bias on the surface of Begg's and Egger's test.

In conclusion, the use of glucocorticoids while performing IVF-ET can effectively improve the clinical pregnancy rate. Clinicians can appropriately add glucocorticoids to IVF-ET patients, especially those who have received multiple failures of IVF-ET and those with positive autoantibodies, so as to improve the clinical pregnancy rate of patients.

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Author contribution statement

Yaxuan Lv, Yue Chen, Lei Hu, Haitian Ding, Mengqing Liu, Hailong Li, Yuyang Hou, and Qiong Xing: Conceived and designed the

experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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