

### Systematic Review

# Pituitary Suppression with Gonadotropin-Releasing Hormone Agonist Prior to Artificial Endometrial Preparation in Frozen–Thawed Embryo Transfer Cycles: A Systematic Review and Meta-Analysis of Different Protocols and Infertile Populations

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**Abstract:** This study investigates the effect of GnRHa pretreatment on pregnancy outcomes in artificial endometrial preparation for frozen–thawed embryo transfer (AC-FET) cycles. A systematic review of English language studies published before 1 September 2022, was conducted, excluding conference papers and preprints. Forty-one studies involving 43,021 participants were analyzed using meta-analysis, with a sensitivity analysis ensuring result robustness. The study found that GnRHa pretreatment generally improved the clinical pregnancy rate (CPR), implantation rate (IR), and live birth rate (LBR). However, discrepancies existed between randomized controlled trials (RCTs) and observational studies; RCTs showed no significant differences in outcomes for GnRHa-treated cycles. Depot GnRHa protocols outperformed daily regimens in LBR. Extended GnRHa pretreatment (two to five cycles) significantly improved CPR and IR compared to shorter treatment. Women with polycystic ovary syndrome (PCOS) saw substantial benefits from GnRHa pretreatment, including improved CPR and LBR and reduced miscarriage rates. In contrast, no significant benefits were observed in women with regular menstruation. More rigorous research is needed to solidify these findings.

**Keywords:** gonadotropin-releasing hormone agonist; pituitary suppression; frozen–thawed embryo transfer; pregnancy outcomes

# 1. Introduction

Gonadotropin-releasing hormone agonists (GnRHa) are synthetic versions of the naturally occurring GnRH hormone. They are designed to have a longer half-life by replacing a specific amino acid in the native hormone with a different form, making it resistant to degradation. This results in prolonged receptor occupancy, enhancing its therapeutic effects, such as suppressing spontaneous ovulation during a controlled ovarian hyperstimulation (COH)



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cycle. Generally, continuous GnRHa administration desensitizes the pituitary gland by causing GnRH receptor downregulation after the initial "flare" response. Although recent wide-spread use of GnRH antagonist protocols ameliorates the importance of GnRHa in IVF/ICSI cycles due to being a more time-consuming treatment with a higher rate of ovarian hyperstimulation syndrome, COH long protocols with GnRHa can still be considered a first-line treatment for patients with advanced age or endometriotic disorders [1,2], as these drugs decrease cancellation rate through the prevention of premature LH surge and luteinization and enhancement of follicular recruitment, allowing the recovery of a larger number of oocytes and improvement in routine patient treatment schedule [3].

Although steroid hormones are important in reproduction, excessive and sustained exposure to sex steroids has been proven to impair endometrial receptivity [4,5]. Additionally, the intrauterine microenvironment, provided mostly by glandular secretions, is crucial for implantation. Certain inflammatory conditions, such as adenomyosis or polycystic ovarian syndrome, induce an aberrant implantation process, reducing the pregnancy rate [6,7]. Pituitary suppression with a GnRH agonist before embryo transfer could suppress the hypothalamic-pituitary-gonadal axis and theoretically create better endometrial-embryonic synchronization and microenvironment for fertilization. In mice, GnRHa ameliorates the adverse impact of adenomyosis on endometrial receptivity by increasing the quality and quantity of pinopodes, as well as the expression of Hoxa10, Hoxa11, Lif, and integrin b3 during the implantation window [8]. An et al. promoted that depot GnRH agonist administration before artificial endometrial preparation improved pregnancy outcomes [9] by regulating the decidualization markers. Another study revealed that GnRHa pretreatment upregulated implantation-related interleukin 6 and 11 in human endometrial stromal cells [10]. In summary, preclinical data on GnRHa and implantation have demonstrated favorable outcomes, implying that the use of GnRHa prior to transfer could be a feasible option for infertile women. Nevertheless, the translation of a medication from preclinical to clinical settings has not always been successfully achieved. The determination of an optimal treatment modality should be predicated upon the clinical context of the individual patient. It is imperative to acknowledge that there is no universally superior treatment applicable to all patients, as each individual's physiological constitution presents a distinct clinical scenario necessitating a bespoke approach. As the GnRHa-pretreated FET protocol has been considered significantly costly in money and time compared to a conventional approach [11], the decision to use this regimen should be based on the unique characteristics of the patients rather than being applied routinely. Additionally, there have been ongoing discussions regarding the optimal type and duration of GnRHa used in assisted reproductive technology (ART) in terms of cost-effectiveness, patient convenience, and efficacy. While depot GnRHa may require a single high dose for pituitary suppression, the daily low-dose GnRHa protocol involves a lower total dosage but a higher number of injections [12]. In certain cases, such as adenomyosis, longer pituitary suppression using GnRHa may contribute to better treatment outcomes [13], but it also carries an increased risk of side effects [14]. Therefore, it is necessary to further clarify the most suitable approach for the use of GnRHa prior to frozen embryo transfer (FET) in order to achieve the highest success rate.

Through meta-analysis, this study systematically assessed clinical studies focused on the effects of GnRHa treatment before FET with artificial cycles (AC-FET). With more updated and relevant data available, we compared the effectiveness of AC-FET cycles with and without GnRHa pretreatment and the difference in pregnancy outcome between different GnRHa protocols and treatment durations among infertile women suffering a variety of infertility etiologies.

#### 2. Methods

#### 2.1. Search Strategy and Study Selection

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist (PRISMA 2020, Supplementary Table S1). The search was conducted in four primary electronic databases on 19 January 2022: PubMed, EMBASE, Google Scholar, and the Cochrane Library. After screening full texts, we updated our search on 30 August 2022 to obtain more related articles. A manual search was also performed by screening the references of the included and related studies suggested by PubMed and Google Scholar, as listed on the first page of Supplementary Table S2. The suggested keywords were: "(pituitary suppression OR GNRHa OR gonadotropin-releasing hormone agonist) AND (FET OR frozen–thawed embryo transfer) AND (Artificial cycle OR HRT OR Hormonal replacement therapy OR HRC OR Hormonal replacement cycle)". Exclusion criteria were studies with unreliable clinical data, analyses with overlapping data sets, full-text articles not available, non-English articles, book chapters, abstract-only articles, letters, editorials, correspondence, theses, conference papers, reviews, animal studies, case reports, and case series. Additional articles were also retrieved through a manual search. We used Endnote (version 20; Clarivate. Philadelphia, PA, USA) to manage the studies found.

#### 2.2. Population, Intervention, Comparison, Outcomes, and Study Design (PICOS)

Participants included patients indicated for frozen-thawed embryo transfer with artificial endometrial preparation, regardless of infertile etiologies. We conducted comparative meta-analyses to assess the efficacy of pituitary suppression prior to hormonal therapy initiation in FET patients compared to a non-pretreated control group in terms of pregnancy outcomes. Pituitary suppression was managed using GnRHa in short-acting (daily) or long-acting (depot) protocols. The duration of GnRHa administration (number of depot doses or number of treated cycles) was also recorded and analyzed.

The primary outcome was clinical pregnancy rate (CPR), defined as the presence of at least one intrauterine gestational sac (yolk-sac) with or without fetal heart activity under vaginal ultrasound examination.

Secondary outcomes were implantation rate (IR), miscarriage rate (MR), and live birth rate (LBR). Implantation rate was the ratio between the number of sacs observed via ultrasound and embryos transferred. Miscarriage was the loss of one or more intrauterine non-viable fetuses. A live birth was defined as the delivery of one or more fetuses which are viable.

#### 2.3. Systematic Review Protocol and Registration

We registered the protocol in the PROSPERO International Prospective Register of Systematic Reviews. The registration number is CRD42022299259.

#### 2.4. Data Extraction

In an effort to eliminate potential bias, the search was conducted by three separate researchers. The data collected from the studies included the study design, patient demographics, clinical characteristics, and measured outcomes, which were then compared and evaluated among the three individuals. In instances of disagreement, a discussion and voting process were utilized to arrive at a consensus.

Study quality and risk of bias were evaluated by two independent researchers using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [15]. The EPHPP is composed of eight domains, which include analysis, withdrawals and dropouts, data collection practices, selection bias, intervention integrity, blinding, and confounders. Two domains (analysis and intervention integrity) are descriptive and were not used for global rating. For the remaining 6 domains, each domain is rated as weak (1 point), moderate (2 points), or strong (3 points) and the overall quality of a trial is rated as low, moderate, or strong.

#### 2.5. Data Analysis

The study's effect and mean weight were visualized using forest plots and odds ratios (OR) with 95% confidence intervals (95% CIs). The  $I^2$  statistic was employed to assess heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, an  $I^2$  value of 0 indicates no observed heterogeneity,  $I^2$  values from 50–75% represent

moderate heterogeneity, and  $l^2$  values > 75% indicate high heterogeneity. A random-effects model is used when there is heterogeneity between studies, as confirmed by a Cochran's Q test *p*-value of 0.1 or an  $l^2$  of more than 50%. A fixed-effects model was preferred in all other cases. Subgroup analysis was used to investigate sources of heterogeneity. The effectiveness of GnRHa on each specific infertile population was reported in meta-analyses of subset data. Sensitive analysis was performed with the presence of publication bias investigated by Egger's asymmetric test. We analyzed data using R software (version 4.2.2; R Foundation for Statistical Computing; Vienna, Austria), with a two-sided *p*-value of <0.05 considered statistical significance.

#### 3. Results

#### 3.1. Literature Search and Study Selection

A total of 1349 articles were identified from the databases through a systematic search in combination with a manual search of relevant citations (Figure 1). Next, articles remaining after deduplication were screened for their titles and abstracts. Of these articles, 1290 were excluded due to duplication (n = 66), irrelevancy as detected by automation tools (n = 39), and manual screening (n = 1185). Fifty-nine papers remained for the eligibility assessment. Another 18 publications were further excluded because they did not include the outcome of interest (n = 1); reported pituitary suppression prior to IVF/ICSI cycles (n = 2) or GnRHa administration for luteal support (n = 7); or were preprints (n = 7), conference papers (n = 5), and a review (n = 1). Finally, 41 studies met our inclusion criteria for a systematic review (Table 1) and were pooled in the meta-analyses.

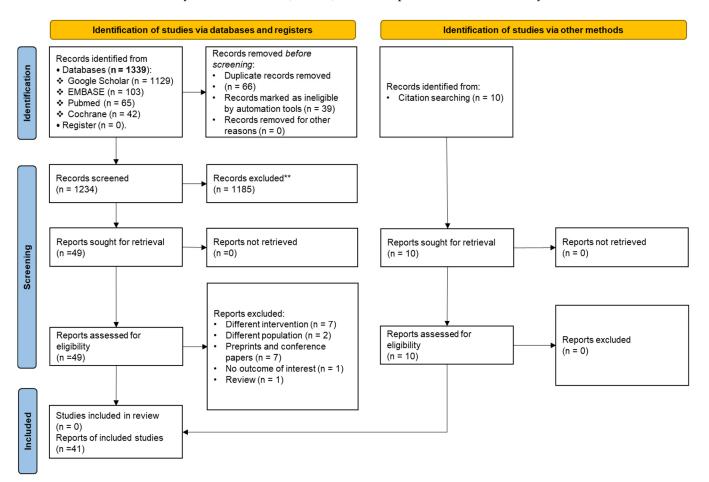
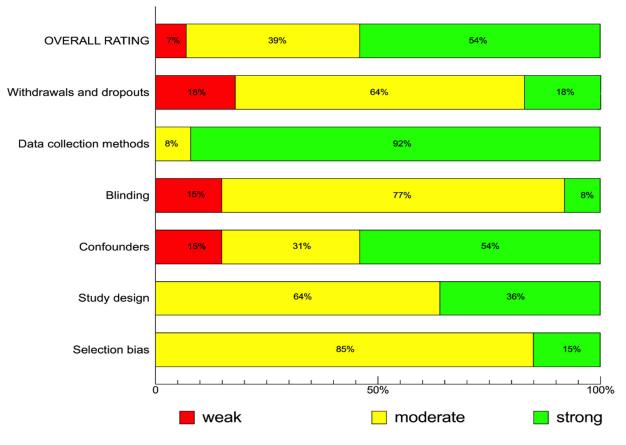


Figure 1. PRISMA flowchart. \*\*: Records that were irrelevant to the research question.

A total of 43,021 participants were recruited in the studies [9–11,16–53]. The final systematic review comprised fourteen randomized controlled trials and twenty-seven observational studies, among which were two non-randomized prospective studies, two case–control studies, nineteen retrospective cohort studies, and four retrospective cohort studies matched using propensity score matching (PSM). Xia et al. (2022) reported the effectiveness of Gn-RHa administration prior to FET in three cohorts of women with no previous implantation failure, one previous implantation failure, or multiple previous implantation failures [48]. The first two cohorts were analyzed via the PSM approach, while the latter was reported without matching. According to the difference in analysis method, these cohorts were analyzed separately. The EPHPP assessment results revealed that most studies were rated as having adequate quality (Figure 2). The inclusion and exclusion of each study are listed in Supplementary Table S3.



**Figure 2.** Summary of study quality assessment using the Effective Public Health Practice Project (EPHPP) quality assessment tool (n = 41 studies)—Data shown as percentage of number of studies.

Egger's test revealed publication biases in the overall CPR, LBR, and MR, as shown in Supplementary Table S4. In order to explore heterogeneity, we conducted a sensitivity analysis using Baujat's method and utilized Baujat plots to identify sources of heterogeneity (Supplementary Figures S1–S3) [54]. The exclusion of outliers via this method did not alter the final results, as evidenced by Supplementary Table S4. No publication bias was observed in other outcomes or subgroup analyses.

# 3.3. Main Findings

# 3.3.1. FET Outcomes between Cycles with and without GnRHa Pretreatment

Overall, pituitary suppression with GnRHa significantly improved the CPR (OR = 1.27, 95% CI: 1.12–1.44,  $I^2$  = 69.4%, p < 0.001), IR (OR = 1.24, 95% CI: 1.07–1.45,  $I^2$  = 70.3%, p = 0.006), and LBR (OR = 1.31, 95% CI: 1.07–1.60,  $I^2 = 78.0\%$ , p = 0.01) except for MR  $(OR = 0.86, 95\% \text{ CI: } 0.68-1.08, I^2 = 53.0\%, p = 0.38)$  (Figure 3).

Subgroup	Experir Events			ontrol Total		Weight (random)		Odds Ratio % CI MH, Fixed + Random, 95% CI
Subgroup = Observational stu	dies							
Niu et al., 2013	100	194	36	145	0.6%	2.4%	3 22 [2 01 5 16]	
							3.22 [2.01; 5.16]	
Vijiver et al., 2014	47	280	137	849	1.7%	2.8%	1.05 [0.73; 1.51]	R .
Hebisha et al., 2016	72	110	42	100	0.5%	2.1%	2.62 [1.50; 4.57]	
Guo et al., 2016	39	76	16	44	0.3%	1.5%	1.84 [0.86; 3.95]	
Tsai et al., 2017	21	29	18	31	0.1%	1.0%	1.90 [0.64; 5.60]	
Kang et al., 2018	55	113	20	49	0.4%	1.8%	1.38 [0.70; 2.71]	
Wageh et al., 2018	19	37	29	58	0.3%	1.4%	1.06 [0.46; 2.41]	
Xie et al., 2018	126	252	281	751	2.1%	3.1%	1.67 [1.25; 2.23]	
Mehrafza et al., 2019 ª	33	100	31	103	0.6%	2.0%	1.14 [0.63; 2.07]	
Mehrafza et al., 2019 aa	27	93	31	103	0.6%	1.9%	0.95 [0.51; 1.76]	
Wang et al., 2019	47	92	204	396	1.1%	2.5%	0.98 [0.62; 1.55]	<b></b>
An et al., 2020	401	975	107	338	2.8%	3.2%	1.51 [1.16; 1.96]	<u>i</u>
Dong et al., 2020	90	268	370	996	3.1%	3.2%	0.86 [0.64; 1.14]	
Guerrero-Vargas et al., 2020	17	64	8	35	0.2%	1.1%	1.22 [0.47; 3.20]	
	19	74	22	74				
Naserpoor et al., 2020					0.5%	1.6%	0.82 [0.40; 1.68]	
Qi et al., 2020	147	303	1353	2936	3.9%	3.3%	1.10 [0.87; 1.40]	
Li et al., 2021	65	160	77	181	1.3%	2.6%	0.92 [0.60; 1.42]	
Liu et al., 2021	387	514	363	514	2.7%	3.2%	1.27 [0.96; 1.67]	++ <del>-</del> -
Siristatidis et al., 2021	62	159	24	221	0.4%	2.2%	5.25 [3.09; 8.92]	
Zheng et al., 2021	768	1518	6186	11456	21.2%	3.7%	0.87 [0.78; 0.97]	
Eleftheriadou et al., 2022	865	1949	1121	2658	15.7%	3.7%	1.09 [0.97; 1.23]	
Xia et al., 2022 *	651	1165	610	1165	8.0%	3.6%	1.15 [0.98; 1.36]	<u>₩</u>
Xia et al., 2022 **	687	1133	637	1133	7.4%	3.5%	1.20 [1.01; 1.42]	<u>₩</u> .
Xia et al., 2022 ***	439	785	147	302	2.8%	3.2%	1.34 [1.03; 1.75]	
Li et al., 2022	357	813	104	276	2.6%	3.2%	1.29 [0.98; 1.71]	
Pan et al., 2022	142	290	68	194	1.2%	2.8%	1.78 [1.22; 2.58]	
		846						·
Gan et al., 2022	399		483	1007	6.9%	3.5%	0.97 [0.81; 1.16]	T
Liu et al., 2022	23	43	12	54	0.1%	1.3%	4.03 [1.67; 9.68]	
Wang et al., 2022	223	309	837	1207	2.8%	3.2%	1.15 [0.87; 1.51]	
Mo et al., 2022	72	155	116	294	1.3%	2.7%	1.33 [0.90; 1.97]	+ <del>12</del>
Total (common effect, 95% CI)	1	.2,899	2	7,670	93.2%		1.14 [1.08; 1.19]	<b>†</b>
Total (random effect, 95% CI)						77.4%	1.33 [1.13; 1.55]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Tau <sup>2</sup> = 0.1266; Chi <sup>2</sup>	= 124.18,	df = 29	(P < 0.01)	; I <sup>2</sup> = 77	%			
Subgroup = RCTs								
Simon et al., 1998	14	53	11	52	0.2%	1.2%	1.34 [0.54; 3.30]	
Prato et al., 2002	28	142	34	141	0.8%	2.1%	0.77 [0.44; 1.36]	
El-Toukhy et al. 2004		117	13	117	0.3%			
	28	117 30	13	117 30	0.3%	1.7%	2.52 [1.23; 5.15]	
Davar et al., 2007	28 3	30	2	30	0.1%	1.7% 0.4%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05]	
Davar et al., 2007 Nekoo et al., 2015	28 3 20	30 93	2 24	30 83	0.1% 0.6%	1.7% 0.4% 1.7%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018	28 3 20 9	30 93 60	2 24 7	30 83 40	0.1% 0.6% 0.2%	1.7% 0.4% 1.7% 1.0%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018	28 3 20 9 18	30 93 60 109	2 24 7 16	30 83 40 107	0.1% 0.6% 0.2% 0.4%	1.7% 0.4% 1.7% 1.0% 1.6%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019	28 3 20 9 18 44	30 93 60 109 121	2 24 7 16 35	30 83 40 107 113	0.1% 0.6% 0.2% 0.4% 0.7%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020	28 3 20 9 18 44 38	30 93 60 109 121 88	2 24 7 16 35 24	30 83 40 107 113 90	0.1% 0.6% 0.2% 0.4% 0.7% 0.4%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2% 1.9%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19] 2.09 [1.11; 3.92]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020	28 3 20 9 18 44	30 93 60 109 121	2 24 7 16 35	30 83 40 107 113	0.1% 0.6% 0.2% 0.4% 0.7%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19]	
El-Toukhy et al., 2004 Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021	28 3 20 9 18 44 38	30 93 60 109 121 88	2 24 7 16 35 24	30 83 40 107 113 90	0.1% 0.6% 0.2% 0.4% 0.7% 0.4%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2% 1.9%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19] 2.09 [1.11; 3.92]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021	28 3 20 9 18 44 38 8	30 93 60 109 121 88 31	2 24 7 16 35 24 6	30 83 40 107 113 90 31	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2% 1.9% 0.8%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19] 2.09 [1.11; 3.92] 1.45 [0.44; 4.81]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021 Salama et al., 2021	28 3 20 9 18 44 38 8 109 32	30 93 60 109 121 88 31 172 70	2 24 7 16 35 24 6 111 37	30 83 40 107 113 90 31 171 70	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6%	1.7% 0.4% 1.7% 1.0% 2.2% 1.9% 0.8% 2.5% 1.8%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19] 2.09 [1.11; 3.92] 1.45 [0.44; 4.81] 0.94 [0.60; 1.45] 0.75 [0.39; 1.46]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021 Salama et al., 2021	28 3 20 9 18 44 38 8 109 32 29	30 93 60 109 121 88 31 172 70 93	2 24 7 16 35 24 6 111 37 32	30 83 40 107 113 90 31 171 70 95	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2% 1.9% 0.8% 2.5% 1.8% 2.0%	2.52 [1.23; 5.15] 1.56 [0.24; 10.05] 0.67 [0.34; 1.34] 0.83 [0.28; 2.45] 1.12 [0.54; 2.34] 1.27 [0.74; 2.19] 2.09 [1.11; 3.92] 1.45 [0.44; 4.81] 0.94 [0.60; 1.45] 0.75 [0.39; 1.46]	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021 Salama et al., 2021 Salemi et al., 2021 Xu et al., 2021	28 3 20 9 18 44 38 8 109 32 29 39	30 93 60 109 121 88 31 172 70 93 65	2 24 7 16 35 24 6 111 37	30 83 40 107 113 90 31 171 70 95 68	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6% 0.6% 0.5%	1.7% 0.4% 1.7% 1.0% 2.2% 1.9% 0.8% 2.5% 1.8%	$\begin{array}{c} 2.52 \left[ 1.23 \right] 5.15 \right] \\ 1.56 \left[ 0.24 \right] (1.05 \right] \\ 0.67 \left[ 0.34 \right] (1.34 \right] \\ 0.83 \left[ 0.28 \right] 2.45 \right] \\ 1.12 \left[ 0.54 \right] 2.34 \right] \\ 1.27 \left[ 0.74 \right] 2.19 \right] \\ 2.09 \left[ 1.11 \right] 3.92 \right] \\ 1.45 \left[ 0.44 \right] 4.81 \right] \\ 0.94 \left[ 0.60 \right] 1.45 \right] \\ 0.75 \left[ 0.39 \right] 1.46 \right] \\ 0.89 \left[ 0.48 \right] 1.64 \right] \\ 0.89 \left[ 0.48 \right] 1.64 \right] \\ 0.99 \left[ 0.49 \right] 1.98 \right] \end{array}$	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021 Salama et al., 2021 Salami et al., 2021 Xu et al., 2021 Total (common effect, 95% CI)	28 3 20 9 18 44 38 8 109 32 29 39	30 93 60 109 121 88 31 172 70 93	2 24 7 16 35 24 6 111 37 32	30 83 40 107 113 90 31 171 70 95	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6%	1.7% 0.4% 1.7% 1.6% 2.2% 1.9% 0.8% 2.5% 1.8% 2.0% 1.7%	$\begin{array}{c} 2.52 \left[ 1.23 \right] 5.15 \right] \\ 1.56 \left[ 0.24 \right] (1.05 \right] \\ 0.67 \left[ 0.34 \right] (1.34 \right] \\ 0.83 \left[ 0.28 \right] 2.45 \right] \\ 1.12 \left[ 0.54 \right] 2.34 \right] \\ 1.27 \left[ 0.74 \right] 2.19 \\ 1.45 \left[ 0.44 \right] (2.16 \right] \\ 1.45 \left[ 0.44 \right] (2.16 \right] \\ 0.75 \left[ 0.39 \right] (1.45 \right] \\ 0.75 \left[ 0.39 \right] (1.46 \right] \\ 0.89 \left[ 0.48 \right] (1.98 \right] \\ 0.99 \left[ 0.48 \right] (1.98 \right] \\ 1.09 \left[ 0.91 \right] (1.30 \right] \end{array}$	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020	28 3 20 9 18 44 38 8 109 32 29 39	30 93 60 109 121 88 31 172 70 93 65 1244	2 24 7 16 35 24 6 111 37 32 41	30 83 40 107 113 90 31 171 70 95 68 1208	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6% 0.6% 0.5% 6.8%	1.7% 0.4% 1.7% 1.0% 1.6% 2.2% 1.9% 0.8% 2.5% 1.8% 2.0%	$\begin{array}{c} 2.52 \left[ 1.23 \right] 5.15 \right] \\ 1.56 \left[ 0.24 \right] (1.05 \right] \\ 0.67 \left[ 0.34 \right] (1.34 \right] \\ 0.83 \left[ 0.28 \right] 2.45 \right] \\ 1.12 \left[ 0.54 \right] 2.34 \right] \\ 1.27 \left[ 0.74 \right] 2.19 \right] \\ 2.09 \left[ 1.11 \right] 3.92 \right] \\ 1.45 \left[ 0.44 \right] 4.81 \right] \\ 0.94 \left[ 0.60 \right] 1.45 \right] \\ 0.75 \left[ 0.39 \right] 1.46 \right] \\ 0.89 \left[ 0.48 \right] 1.64 \right] \\ 0.89 \left[ 0.48 \right] 1.64 \right] \\ 0.99 \left[ 0.49 \right] 1.98 \right] \end{array}$	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021 Salama et al., 2021 Salami et al., 2021 Total (common effect, 95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0257; Ch <sup>2</sup>	28 3 20 9 18 44 38 8 109 32 29 39 39	30 93 60 109 121 88 31 172 70 93 65 1244 f = 13 (F	2 24 7 16 35 24 6 111 37 32 41	$30 \\ 83 \\ 40 \\ 107 \\ 113 \\ 90 \\ 31 \\ 171 \\ 70 \\ 95 \\ 68 \\ 1208 \\ 1208 \\ 1^2 = 18\%$	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6% 0.6% 0.6% 0.5% 6.8%	1.7% 0.4% 1.7% 1.6% 2.2% 1.9% 0.8% 2.5% 1.8% 2.0% 1.7%	$\begin{array}{c} 2.52 \left[ 1.23 \right] 5.15 \right] \\ 1.56 \left[ 0.24 \right] (1.05 \right] \\ 0.67 \left[ 0.34 \right] (1.34 \right] \\ 0.83 \left[ 0.28 \right] 2.45 \right] \\ 1.12 \left[ 0.54 \right] 2.34 \right] \\ 1.27 \left[ 0.74 \right] 2.109 \\ 1.11 \left[ 3.92 \right] \\ 1.45 \left[ 0.44 \right] (4.81 \right] \\ 0.94 \left[ 0.60 \right] (1.45 \right] \\ 0.75 \left[ 0.39 \right] (1.45 \right] \\ 0.75 \left[ 0.39 \right] (1.46 \right] \\ 0.89 \left[ 0.48 \right] (1.64 \right] \\ 0.99 \left[ 0.49 \right] (1.98 \right] \\ 1.99 \left[ 0.97 \right] (1.36 \right] \\ 1.09 \left[ 0.87 \right] (1.36 \right] \end{array}$	
Davar et al., 2007 Nekoo et al., 2015 Movahedi et al., 2018 Samsami et al., 2018 Madani et al., 2019 Aghahoseini et al., 2020 Davar et al., 2020 Luo et al., 2021 Salama et al., 2021 Salemi et al., 2021 Xu et al., 2021 Total (common effect, 95% CI)	28 3 20 9 18 44 38 8 109 32 29 39 39	30 93 60 109 121 88 31 172 70 93 65 1244	2 24 7 16 35 24 6 111 37 32 41	30 83 40 107 113 90 31 171 70 95 68 1208	0.1% 0.6% 0.2% 0.4% 0.7% 0.4% 0.1% 1.2% 0.6% 0.6% 0.5% 6.8%	1.7% 0.4% 1.7% 1.6% 2.2% 1.9% 0.8% 2.5% 1.8% 2.0% 1.7%	$\begin{array}{c} 2.52 \left[ 1.23 \right] 5.15 \right] \\ 1.56 \left[ 0.24 \right] (1.05 \right] \\ 0.67 \left[ 0.34 \right] (1.34 \right] \\ 0.83 \left[ 0.28 \right] 2.45 \right] \\ 1.12 \left[ 0.54 \right] 2.34 \right] \\ 1.27 \left[ 0.74 \right] 2.19 \\ 1.45 \left[ 0.44 \right] (2.16 \right] \\ 1.45 \left[ 0.44 \right] (2.16 \right] \\ 0.75 \left[ 0.39 \right] (1.45 \right] \\ 0.75 \left[ 0.39 \right] (1.46 \right] \\ 0.89 \left[ 0.48 \right] (1.98 \right] \\ 0.99 \left[ 0.48 \right] (1.98 \right] \\ 1.09 \left[ 0.91 \right] (1.30 \right] \end{array}$	

Test for subgroup differences (random effects): Chi<sup>2</sup> = 2.35, df = 1 (P = 0.13)

No GnRHa pretreatment GnRHa pretreatment

Figure 3. Cont.

Study or Subgroup	Experin Events			ontrol Total		Weight (random)		Odds Ratio MH, Fixed + Random, 95% Cl
Subgroup = Observational stu	dies							
Niu et al., 2013	127	390	45	280	1.3%	4.1%	2.52 [1.72; 3.70]	
Vijiver et al., 2014	47	239	137	733	1.9%	4.2%	1.06 [0.74; 1.54]	
Hebisha et al., 2016	142	322	60	285	1.3%	4.3%	2.96 [2.06; 4.24]	
Guo et al., 2016	49	145	18	72	0.6%	2.7%	1.53 [0.81; 2.89]	
		181	24	88				
Kang et al., 2018	76				0.7%	3.1%	1.93 [1.11; 3.36]	
Kie et al., 2018	155	575	333	1655	4.5%	5.2%	1.47 [1.18; 1.83]	
Mehrafza et al., 2019 a	34	245	37	258	1.1%	3.4%	0.96 [0.58; 1.59]	
Mehrafza et al., 2019 aa	35	235	37	258	1.1%	3.4%	1.05 [0.63; 1.72]	
An et al., 2020	585	2760	139	950	5.8%	5.3%	1.57 [1.28; 1.92]	
Eleftheriadou et al., 2022	1040	2261	1322	3004	22.0%	5.7%	1.08 [0.97; 1.21]	
Xia et al., 2022 *	830	1994	743	1968	15.6%	5.6%	1.18 [1.03; 1.34]	<b>—</b>
Xia et al., 2022 **	879	1879	830	1889	15.8%	5.6%	1.12 [0.99; 1.28]	
Xia et al., 2022 ***	560	1309	190	491	5.7%	5.2%	1.18 [0.96; 1.46]	++-
Gan et al., 2022	461	1213	549	1400	11.3%	5.5%	0.95 [0.81; 1.11]	-
Liu et al., 2022	29	86	15	107	0.3%	2.4%	3.12 [1.54; 6.32]	
Total (common effect, 95% CI)		13,834		13,438	88.9%	2.170	1.21 [1.15; 1.27]	
Total (random effect, 95% CI)		13,034		10,400	00.070	65.9%	1.40 [1.13; 1.73]	
Heterogeneity: $Tau^2 = 0.1123$ ; Chi <sup>2</sup>	- 70.04 -	6 - 4 4 <i>/</i>		2 - 040	-	00.576	1.40 [1.15, 1.75]	
Subgroup = RCTs								
Simon et al., 1998	17	179	15	167	0.5%	2.3%	1.06 [0.51; 2.20]	
Prato et al., 2002	31	299	36	301	1.2%	3.4%	0.85 [0.51; 1.42]	
El-Toukhy et al., 2004	43	269	26	258	0.8%	3.3%	1.70 [1.01; 2.86]	
Davar et al., 2007	4	64	3	65	0.1%	0.8%	1.38 [0.30; 6.42]	
Nekoo et al., 2015	23	93	30	83	0.9%	2.7%	0.58 [0.30; 1.11]	
	23	136	10	98	0.9%	1.7%		
Movahedi et al., 2018	-						0.62 [0.24; 1.60]	
Madani et al., 2019	58	302	54	280	1.6%	4.0%	0.99 [0.66; 1.50]	
Davar et al., 2020	8	52	6	57	0.2%	1.3%	1.55 [0.50; 4.80]	
Luo et al., 2021	145	245	127	214	2.0%	4.2%	0.99 [0.68; 1.44]	
Salama et al., 2021	54	117	65	127	1.2%	3.4%	0.82 [0.49; 1.35]	
Salemi et al., 2021	54	198	48	201	1.2%	3.7%	1.20 [0.76; 1.88]	
Xu et al., 2021	60	126	58	128	1.1%	3.5%	1.10 [0.67; 1.80]	
Total (common effect, 95% CI)		2080		1979	11.1%		1.01 [0.87; 1.19]	•
Total (random effect, 95% CI)					-	34.1%	1.01 [0.85; 1.20]	•
Heterogeneity: Tau <sup>2</sup> = 0; Chi <sup>2</sup> = 10.	11, df = 11	(P = 0.	52); I <sup>2</sup> = 0'	%				
Total (common effect, 95% CI)		15,914		15,417	100.0%		1.19 [1.13; 1.25]	•
Total (random effect, 95% CI)				_	-	100.0%	1.24 [1.07; 1.45]	<b></b>
Heterogeneity: Tau <sup>2</sup> = 0.0904; Chi <sup>2</sup>								
Test for subgroup differences (com								0.2 0.5 1 2 5
Test for subgroup differences (rand							No. O-D	Ha pretreatment GnRHa pretreat

Guo et al., 2016         3           Kang et al., 2018         4           Xie et al., 2018         10           Wang et al., 2018         10           Wang et al., 2019         3           An et al., 2020         29           Dong et al., 2020         4           Guerero-Vargas et al., 2020         10           Li et al., 2021         30           Siristatidis et al., 2021         5           Zheng et al., 2021         5           Zheng et al., 2021         5           Xia et al., 2022 *         52           Xia et al., 2022 **         52           Xia et al., 2022         24           Pan et al., 2022         24           Pan et al., 2022         10           Wang et al., 2022         19           Gan et al., 2022         30	37         92           99         975           77         268           11         64           63         0338           160         30338           160         99           514         514           66         1949           78         1518           66         1949           77         1165           70         1133           77         785           66         290           55         309           502         846	i         11           i         16           i         220           i         26           i         240           i         240           i         1051           i         43           i         1051           i         438           i         98           i         978           i         535           i         117           i         72           i         438           i         433	181 514 221 11456 2658 1165 1133 302 276 194 1207	1.8% 0.3% 0.9% 2.8% 2.8% 0.1% 4.3% 1.0% 3.8% 0.2% 2.2% 1.7.4% 9.1% 8.8% 3.1% 2.5% 1.1%	3.9% 2.5% 2.8% 4.2% 3.6% 4.2% 4.0% 1.4% 3.5% 4.3% 4.3% 4.6% 4.5% 4.5% 4.5% 4.3% 4.2% 3.5% 4.5% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.5% 4.3% 4.5% 4.3% 4.5% 4.5% 4.3% 4.5% 4.3% 4.5% 4.5% 4.3% 4.5% 4.5% 4.3% 4.5% 4.5% 4.3% 4.5% 4.5% 4.3% 4.5% 4.5% 4.3% 4.3% 4.5% 4.3% 4.5% 4.5% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.5% 4.3% 4.3% 4.5% 4.5% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3%	$\begin{array}{c} 0.98 \ [0.67; \ 1.44] \\ 2.43 \ [1.07; \ 5.51] \\ 1.47 \ [0.73; \ 2.97] \\ 1.72 \ [1.28; \ 2.32] \\ 1.44 \ [0.90; \ 2.30] \\ 1.52 \ [1.14; \ 2.04] \\ 0.67 \ [0.47; \ 0.95] \\ 2.21 \ [0.57; \ 8.54] \\ 0.97 \ [0.75; \ 8.54] \\ 0.97 \ [0.75; \ 8.54] \\ 0.97 \ [0.75; \ 8.54] \\ 1.09 \ [0.64; \ 1.65] \\ 1.18 \ [0.92; \ 1.52] \\ 1.353 \ [6.45; \ 28.38] \\ 0.87 \ [0.78; \ 0.97] \\ 1.00 \ [0.88; \ 1.13] \\ 1.11 \ [0.94; \ 1.30] \\ 1.13 \ [0.96; \ 1.33] \\ 1.32 \ [1.01; \ 1.73] \\ 1.23 \ [0.90; \ 1.67] \\ 2.02 \ [1.43; \ 3.06] \\ 1.30 \ [1.01; \ 1.73] \\ 2.02 \ [1.43; \ 3.06] \\ 1.30 \ [1.01; \ 1.69] \end{array}$	
Guo et al., 2016         3           Kang et al., 2018         4           Xie et al., 2018         4           Xie et al., 2018         10           Wang et al., 2019         3           An et al., 2020         29           Dong et al., 2020         4           Guerrero-Vargas et al., 2020         10           Li et al., 2021         30           Siristatidis et al., 2021         57           Eleftheriadou et al., 2022         71           Xia et al., 2022 **         52           Xia et al., 2022 **         57           Xia et al., 2022         10           Wang et al., 2022         10           Wang et al., 2022         24           Pan et al., 2022         10           Wang et al., 2022         10           Wo et al., 2022         10           Wang et al., 2022         10           Wo et al., 2022         10           Wo et al., 2022         10           Wo et al., 2022         10           Mo et al., 2022         10           Ho et al., 2022	44         76           77         113           55         252           77         929           99         975           77         9268           11         64           66         303           88         160           99         514           58         159           58         159           58         1518           66         1949           77         7855           166         813           166         290           95         309           92         846	i         11           i         16           i         220           i         26           i         240           i         240           i         1051           i         43           i         1051           i         438           i         98           i         978           i         535           i         117           i         72           i         438           i         433	44 49 751 396 338 996 35 2936 181 514 221 11456 2658 1165 1133 302 2766 194 1207	0.3% 0.4% 2.1% 0.9% 2.6% 2.8% 0.1% 4.3% 1.0% 3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 3.4%	2.5% 2.8% 4.2% 3.6% 4.2% 4.0% 1.4% 4.3% 3.5% 4.3% 2.7% 4.6% 4.5% 4.5% 4.5% 4.2% 3.5% 3.5% 3.8%	2 43 [1.07; 5.51] 1.47 [0.73; 2.97] 1.72 [1.28; 2.32] 1.44 [0.90; 2.30] 1.52 [1.14; 2.04] 0.67 [0.47; 0.95] 2.21 [0.57; 8.54] 0.97 [0.75; 1.24] 1.00 [0.61; 1.65] 1.18 [0.92; 1.52] 13.53 [6.45; 28.38] 0.87 [0.78; 0.97] 1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.00 [1.34; 3.06]	
Kang et al., 2018       4         Xie et al., 2018       10         Wang et al., 2019       3         An et al., 2020       29         Dong et al., 2020       4         Guerrero-Vargas et al., 2020       10         Li et al., 2021       3         Liu et al., 2021       57         Zheng et al., 2021       57         Zheng et al., 2022 **       57         Xia et al., 2022 **       57         Xia et al., 2022 **       35         Li et al., 2022 **       35         Li et al., 2022 **       36         Mang et al., 2022       10         Wang et al., 2022       10         Wang et al., 2022       5         Total (common effect, 95% CI)         Total (random effect, 95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.2379; Ch <sup>2</sup> = 111.5	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	16         16           2200         220           126         76           5         76           3         1051           43         1051           43         288           9         978           5         535           5         117           5         72           433         685	49 751 396 338 996 35 2936 181 514 221 11456 2658 1165 1133 302 276 194 1207	0.4% 2.1% 0.9% 2.6% 2.8% 0.1% 4.3% 0.2% 0.2% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1%	2.8% 4.2% 4.2% 4.0% 4.3% 3.5% 4.3% 2.7% 4.6% 4.6% 4.5% 4.5% 4.5% 4.2% 3.5% 3.8%	$\begin{array}{c} 1.47 \left[ 0.73 ; 2.97 \right] \\ 1.72 \left[ 1.28 ; 2.32 \right] \\ 1.44 \left[ 0.90 ; 2.30 \right] \\ 1.52 \left[ 1.14 ; 2.04 \right] \\ 0.67 \left[ 0.47 ; 0.95 \right] \\ 2.21 \left[ 0.57 ; 8.54 \right] \\ 0.97 \left[ 0.75 ; 1.24 \right] \\ 1.00 \left[ 0.61 ; 1.65 \right] \\ 1.18 \left[ 0.92 ; 1.52 \right] \\ 13.53 \left[ 6.45 ; 28.38 \right] \\ 0.87 \left[ 0.78 ; 0.97 \right] \\ 1.00 \left[ 0.88 ; 1.13 \right] \\ 1.11 \left[ 0.94 ; 1.30 \right] \\ 1.13 \left[ 0.96 ; 1.33 \right] \\ 1.32 \left[ 1.07 ; 1.67 \right] \\ 2.20 \left[ 1.34 ; 3.06 \right] \end{array}$	
Xie et al., 2018       10         Wang et al., 2019       3         An et al., 2020       29         Dong et al., 2020       4         Guerrero-Vargas et al., 2020       10         Li et al., 2021       30         Siristatidis et al., 2021       57         Eleftheriadou et al., 2022       71         Xia et al., 2022 **       57         Xia et al., 2022 **       57         Xia et al., 2022 **       57         Xia et al., 2022 **       50         Wang et al., 2022 **       24         Pan et al., 2022       10         Wang et al., 2022       24         Mo et al., 2022       50         Total (random effect, 95% CI)       Total (random effect, 95% CI)         Total (random effect, 95% CI)       Total (random effect, 95% CI)	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	2         220           126         76           2         126           3         240           3         1051           4         3           4         288           9         9           4         43           5         535           5         117           5         72           4         72           4         488           5         535           5         117           72         433           685         685	751 396 338 996 35 2936 181 514 221 11456 2658 1165 1133 302 276 194 1207	2.1% 0.9% 2.6% 2.8% 0.1% 4.3% 1.0% 3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	$\begin{array}{c} 4.2\% \\ 3.6\% \\ 4.2\% \\ 4.0\% \\ 1.4\% \\ 4.3\% \\ 3.5\% \\ 4.3\% \\ 2.7\% \\ 4.6\% \\ 4.6\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.2\% \\ 3.8\% \end{array}$	$\begin{array}{c} 1.72 \left[ 1.28 ; 2.32 \right] \\ 1.44 \left[ 0.90 ; 2.30 \right] \\ 1.52 \left[ 1.14 ; 2.04 \right] \\ 0.67 \left[ 0.47 ; 0.95 \right] \\ 2.21 \left[ 0.57 ; 8.54 \right] \\ 0.97 \left[ 0.75 ; 1.24 \right] \\ 1.00 \left[ 0.61 ; 1.65 \right] \\ 1.18 \left[ 0.92 ; 1.52 \right] \\ 1.53 \left[ 6.45 ; 28.38 \right] \\ 0.87 \left[ 0.78 ; 0.97 \right] \\ 1.00 \left[ 0.88 ; 1.13 \right] \\ 1.11 \left[ 0.94 ; 1.30 \right] \\ 1.13 \left[ 0.96 ; 1.33 \right] \\ 1.32 \left[ 1.07 ; 1.73 \right] \\ 1.23 \left[ 0.90 ; 1.67 \right] \\ 2.02 \left[ 1.34 ; 3.06 \right] \end{array}$	
Wang et al., 2019       3         An et al., 2020       29         Dong et al., 2020       4         Querrero-Vargas et al., 2020       1         Qi et al., 2020       10         Li et al., 2021       3         Siristatidis et al., 2021       57         Eleftheriadou et al., 2022       71         Kia et al., 2022 *       52         Xia et al., 2022 *       57         Xia et al., 2022 *       57         Xia et al., 2022 *       24         Pan et al., 2022       10         Wang et al., 2022       19         Gan et al., 2022       19         Gan et al., 2022       57         Total (common effect, 95% CI)         Total (candom effect, 95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	37         92           99         975           77         268           11         64           63         0338           160         30338           160         99           514         514           66         1949           78         1518           66         1949           77         1165           70         1133           77         785           66         290           55         309           502         846	126         76           76         240           3         1051           1         43           288         9           3         4750           9         78           4750         978           5         117           5         117           72         72           433         685	396 338 996 35 2936 181 514 221 11456 2658 1165 1133 302 276 194 1207	0.9% 2.6% 2.8% 1.0% 3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	3.6% 4.2% 4.0% 1.4% 4.3% 2.7% 4.6% 4.6% 4.5% 4.5% 4.5% 4.5% 4.5% 4.3% 3.8%	$\begin{array}{c} 1.44 \left[ 0.90; \ 2.30 \right] \\ 1.52 \left[ 1.14; \ 2.04 \right] \\ 0.67 \left[ 0.47; \ 0.95 \right] \\ 2.21 \left[ 0.57; \ 8.54 \right] \\ 0.97 \left[ 0.75; \ 1.24 \right] \\ 1.00 \left[ 0.61; \ 1.65 \right] \\ 1.18 \left[ 0.92; \ 1.52 \right] \\ 13.53 \left[ 6.45; 28.38 \right] \\ 0.87 \left[ 0.78; \ 0.97 \right] \\ 1.00 \left[ 0.88; \ 1.13 \right] \\ 1.11 \left[ 0.94; \ 1.30 \right] \\ 1.13 \left[ 0.96; \ 1.33 \right] \\ 1.23 \left[ 0.90; \ 1.67 \right] \\ 2.00 \left[ 1.34; \ 3.06 \right] \end{array}$	
An et al., 2020       29         Dong et al., 2020       4         Suerrero-Vargas et al., 2020       1         ja et al., 2020       10         ja et al., 2020       10         ja et al., 2020       10         ja et al., 2021       3         ju et al., 2021       3         ju et al., 2021       57         Siristatidis et al., 2021       57         Eleftheriadou et al., 2022 **       52         Kia et al., 2022 **       57         Kia et al., 2022 **       57         Si et al., 2022       10         Nang et al., 2022       10         Nang et al., 2022       10         San et al., 2022       10         Mo et al., 2022       50         Total (common effect, 95% CI)         Total (random effect, 95% CI)         Ideterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	99         975           7         268           11         64           96         303           88         160           99         514           99         514           88         150           98         159           88         1518           66         1949           77         1165           70         1133           77         785           86         813           96         290           95         309           902         846	5         76           6         240           3         1051           4         38           9         43           4         288           9         9           4750         978           5         535           5         117           5         722           433         685	338 996 35 2936 181 514 221 11456 2658 1165 1133 302 276 194 1207	2.6% 2.8% 0.1% 4.3% 0.2% 22.9% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	4.2% 4.0% 1.4% 4.3% 3.5% 4.3% 4.6% 4.6% 4.6% 4.5% 4.5% 4.5% 4.3% 4.2% 3.8%	$\begin{array}{c} 1.52 \left[ 1.14 ; \ 2.04 \right] \\ 0.67 \left[ 0.47 ; \ 0.95 \right] \\ 2.21 \left[ 0.57 ; \ 8.54 \right] \\ 0.97 \left[ 0.75 ; \ 1.24 \right] \\ 1.00 \left[ 0.61 ; \ 1.65 \right] \\ 1.18 \left[ 0.92 ; \ 1.52 \right] \\ 3.53 \left[ 6.45 ; 28.38 \right] \\ 0.87 \left[ 0.78 ; \ 0.97 \right] \\ 1.00 \left[ 0.88 ; \ 1.13 \right] \\ 1.11 \left[ 0.94 ; \ 1.30 \right] \\ 1.13 \left[ 0.96 ; \ 1.33 \right] \\ 1.32 \left[ 1.01 ; \ 1.73 \right] \\ 1.23 \left[ 0.90 ; \ 1.67 \right] \\ 2.02 \left[ 1.34 ; \ 3.06 \right] \end{array}$	
Dong et al., 2020         4           Guerrero-Vargas et al., 2020         1           Di et al., 2020         10           Li et al., 2021         30           Siristatidis et al., 2021         57           Siristatidis et al., 2021         57           Eleftheriadou et al., 2022         71           Kia et al., 2022 **         57           Kia et al., 2022 **         57           Kia et al., 2022 **         52           Jan et al., 2022         14           Van get al., 2022         19           San et al., 2022         19           Gat al., 2022         19           San et al., 2022         19           Gat et al., 2022         19           San et al., 2022         19           Total (common effect, 95% CI)         10           fotal (random effect, 95% CI)         11.5	47         268           11         64           66         303           88         160           99         514           88         159           88         1518           88         1518           61         1949           77         1165           70         1133           77         785           86         813           96         290           95         309           92         846	3         240           4         3           5         1051           6         288           9         9           4750         978           5         4750           9         5           6         535           5         1157           5         72           6         433           9         685	996 35 2936 181 514 221 11456 2658 1145 1133 302 276 194 1207	2.8% 0.1% 4.3% 0.2% 22.9% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	$\begin{array}{c} 4.0\% \\ 1.4\% \\ 4.3\% \\ 3.5\% \\ 4.3\% \\ 2.7\% \\ 4.6\% \\ 4.6\% \\ 4.6\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.3\% \\ 4.2\% \\ 3.8\% \end{array}$	$\begin{array}{c} 0.67 \\ 0.47 \\ 0.97 \\ 0.75 \\ 1.24 \\ 1.075 \\ 1.24 \\ 1.00 \\ 1.075 \\ 1.24 \\ 1.00 \\ 1.075 \\ 1.24 \\ 1.00 \\ 1.075 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 \\ 1.52 $	
Buerrero-Vargas et al., 2020         1           Die tal., 2020         10           Li et al., 2021         3           Juie tal., 2021         30           Siristatidis et al., 2021         5           Zheng et al., 2021         57           Eleftheriadou et al., 2022         71           Fleifheriadou et al., 2022         71           Kia et al., 2022 **         57           Kia et al., 2022 **         57           Kia et al., 2022 **         57           Si an et al., 2022         24           Pan et al., 2022         19           Gan et al., 2022         19           Gan et al., 2022         19           Total (common effect, 95% Cl)         10           Jotal (random effect, 95% Cl)         11.5	1         64           16         303           160         99           18         160           19         514           18         159           18         1518           16         1949           27         1165           10         1133           77         785           166         813           106         290           105         309           102         846	3         3           1051         43           288         9           4750         978           535         535           5117         72           72         43           685         685	35 2936 181 514 221 11456 2658 1165 1133 302 276 194 1207	0.1% 4.3% 1.0% 3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	$1.4\% \\ 4.3\% \\ 3.5\% \\ 4.3\% \\ 2.7\% \\ 4.6\% \\ 4.6\% \\ 4.5\% \\ 4.5\% \\ 4.5\% \\ 4.3\% \\ 4.2\% \\ 3.8\%$	2.21 [0.57; 8.54] 0.97 [0.75; 1.24] 1.00 [0.61; 1.65] 1.18 [0.92; 1.52] 13.53 [6.45; 28.38] 0.87 [0.78; 0.97] 1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Qi et al., 2020         10           i et al., 2021         3           i.u et al., 2021         3           j.u et al., 2021         3           j.u et al., 2021         5           Zheng et al., 2021         57           Eleftheriadou et al., 2022         71           Kia et al., 2022 **         52           Kia et al., 2022 **         57           Kia et al., 2022 **         35           .i et al., 2022         24           Pan et al., 2022         10           Wang et al., 2022         19           Gan et al., 2022         19           Gan et al., 2022         5           Total (common effect, 95% Cl)           feterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	06         303           38         160           99         514           88         159           88         1518           16         1949           27         1165           70         1133           77         785           166         813           166         2900           95         309           92         846	3       1051         43       288         9       9         4750       978         5       4750         9       978         5       498         5       535         5       117         3       72         43       685	2936 181 514 221 11456 2658 1165 1133 302 276 194 1207	4.3% 1.0% 3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	4.3% 3.5% 4.3% 2.7% 4.6% 4.6% 4.5% 4.5% 4.5% 4.3% 4.2% 3.8%	0.97 [0.75; 1.24] 1.00 [0.61; 1.65] 1.18 [0.92; 1.52] 13.53 [6.45; 28.38] 0.87 [0.78; 0.97] 1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
i et al., 2021 3 iu et al., 2021 30 iii et al., 2021 57 iiistatidis et al., 2021 57 icheng et al., 2021 57 icheftheriadou et al., 2022 71 iii at al., 2022 ** 57 iii et al., 2022 ** 57 ii et al., 2022 ** 35 ii et al., 2022 ** 35 ii et al., 2022 ** 35 ii et al., 2022 10 Vang et al., 2022 10 Vang et al., 2022 19 San et al., 2022 19 San et al., 2022 20 if otal (common effect, 95% CI) fotal (random effect, 95% CI) ieterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	38         160           99         514           58         159           78         1518           16         1949           27         1165           70         1133           57         785           16         813           96         290           95         309           92         846	43       288       9       4750       978       4750       978       498       535       117       72       43       685	181 514 221 11456 2658 1165 1133 302 276 194 1207	1.0% 3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	3.5% 4.3% 2.7% 4.6% 4.6% 4.5% 4.5% 4.3% 4.2% 3.8%	1.00 [0.61; 1.65] 1.18 [0.92; 1.52] 13.53 [6.45; 28.38] 0.87 [0.78; 0.97] 1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
iu et al., 2021         30           Siristatidis et al., 2021         5           Pheng et al., 2021         57           Silent et al., 2022         71           Kia et al., 2022 **         57           Kia et al., 2022 **         57           Kia et al., 2022 **         57           Leftheriadou et al., 2022 **         52           Sia et al., 2022         24           Pan et al., 2022         19           San et al., 2022         19           San et al., 2022         19           Son et al., 2022         5           Fotal (common effect, 95% CI)         11           Jetterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	9         514           58         159           78         1518           16         1949           27         1165           70         1133           57         785           16         290           95         309           92         846	288           9           4750           978           498           535           117           72           43           685	514 221 11456 2658 1165 1133 302 276 194 1207	3.8% 0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	4.3% 2.7% 4.6% 4.5% 4.5% 4.5% 4.3% 4.2% 3.8%	1.18 [0.92; 1.52] 13.53 [6.45; 28.38] 0.87 [0.78; 0.97] 1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Siristatidis et al., 2021       5         Zheng et al., 2021       57         Eleftheriadou et al., 2022       71         Kia et al., 2022 **       57         Kia et al., 2022 **       57         Kia et al., 2022 **       57         Left.print       35         Left.print       3022         Pan et al., 2022       10         Wang et al., 2022       19         Gan et al., 2022       19         Gan et al., 2022       19         Total (common effect, 95% Cl)       10         Ideterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	58         159           78         1518           16         1949           27         1165           70         1133           57         785           16         290           95         309           92         846	9 9 4750 978 5 498 3 535 5 117 3 72 9 43 9 685	221 11456 2658 1165 1133 302 276 194 1207	0.2% 22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	2.7% 4.6% 4.5% 4.5% 4.5% 4.3% 4.2% 3.8%	13.53 [6.45; 28.38] 0.87 [0.78; 0.97] 1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Zheng et al., 2021       57         Zheftheriadou et al., 2022       71         Zieftheriadou et al., 2022       71         Kia et al., 2022 **       52         Kia et al., 2022 **       55         Li et al., 2022       10         Wang et al., 2022       10         Wang et al., 2022       10         Wang et al., 2022       10         Mo et al., 2022       10         Fotal (common effect, 95% CI)       5         Fotal (random effect, 95% CI)       11         Jeterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5       11.5	1518           16         1949           16         1949           17         1165           10         1133           17         785           16         813           16         290           15         309           102         846	4750 978 5498 5535 5117 72 43 685	11456 2658 1165 1133 302 276 194 1207	22.9% 17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	4.6% 4.6% 4.5% 4.5% 4.3% 4.2% 3.8%	0.87 (0.78; 0.97) 1.00 (0.88; 1.13) 1.11 (0.94; 1.30) 1.13 (0.96; 1.33) 1.32 (1.01; 1.73) 1.23 (0.90; 1.67) 2.02 (1.34; 3.06)	
Zheng et al., 2021     57       Zheftheriadou et al., 2022     71       Zieftheriadou et al., 2022     71       Kia et al., 2022 **     52       Kia et al., 2022 **     57       Kia et al., 2022 **     35       Ji et al., 2022     24       Pan et al., 2022     10       Wang et al., 2022     10       Wang et al., 2022     19       Gan et al., 2022     19       Go et al., 2022     30       Fotal (common effect, 95% CI)       Fotal (random effect, 95% CI)       Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	16         1949           1165         1165           1133         1133           117         785           16         813           16         290           15         309           12         846	978 498 535 117 72 43 685	2658 1165 1133 302 276 194 1207	17.4% 9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	4.6% 4.5% 4.5% 4.3% 4.2% 3.8%	1.00 [0.88; 1.13] 1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Eleftheriadou et al., 2022         71           (ia et al., 2022 **         52           (ia et al., 2022 ***         55           (ia et al., 2022 ***         35           i et al., 2022 ***         35           i et al., 2022 ***         35           an et al., 2022         19           3an et al., 2022         19           3an et al., 2022         30           Mo et al., 2022         30           Mo et al., 2022         30           Fotal (common effect, 95% CI)           Fotal (random effect, 95% CI)           eterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	27         1165           70         1133           57         785           16         813           16         290           15         309           102         846	498 535 117 72 43 685	1165 1133 302 276 194 1207	9.1% 8.8% 3.1% 2.5% 1.1% 3.4%	4.5% 4.5% 4.3% 4.2% 3.8%	1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Kia et al., 2022 **       57         Kia et al., 2022 ***       35         i et al., 2022 ***       35         at al., 2022       24         an et al., 2022       10         Wang et al., 2022       19         Gan et al., 2022       19         Gan et al., 2022       30         No et al., 2022       5         Fotal (common effect, 95% Cl)         feterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	70 1133 57 785 16 813 16 290 15 309 12 846	535 117 72 43 685	1133 302 276 194 1207	8.8% 3.1% 2.5% 1.1% 3.4%	4.5% 4.3% 4.2% 3.8%	1.11 [0.94; 1.30] 1.13 [0.96; 1.33] 1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Kia et al., 2022 ***       35         i et al., 2022       24         an et al., 2022       19         Jan et al., 2022       19         Jan et al., 2022       30         Mo et al., 2022       30         Jof et al., 2022       30         Fotal (common effect, 95% CI)         Fotal (random effect, 95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	67 785 6813 6290 95 309 92 846	6 117 72 43 685	302 276 194 1207	3.1% 2.5% 1.1% 3.4%	4.3% 4.2% 3.8%	1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Kia et al., 2022 ***       35         i et al., 2022       24         an et al., 2022       19         Jan et al., 2022       19         Jan et al., 2022       30         Mo et al., 2022       30         Jof et al., 2022       30         Fotal (common effect, 95% CI)         Fotal (random effect, 95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	67 785 6813 6290 95 309 92 846	6 117 72 43 685	302 276 194 1207	3.1% 2.5% 1.1% 3.4%	4.3% 4.2% 3.8%	1.32 [1.01; 1.73] 1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
i et al., 2022 24 Pan et al., 2022 10 Vang et al., 2022 19 San et al., 2022 30 Mo et al., 2022 5 Total (common effect, 95% CI) Fotal (random effect, 95% CI) Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	46 813 6 290 95 309 92 846	72 43 685	276 194 1207	2.5% 1.1% 3.4%	4.2% 3.8%	1.23 [0.90; 1.67] 2.02 [1.34; 3.06]	
Pan et al., 2022         10           Wang et al., 2022         19           Gan et al., 2022         30           Mo et al., 2022         5           Fotal (common effect, 95% Cl)         5           Total (random effect, 95% Cl)         1           Jeterogeneity: Tau <sup>2</sup> = 0.2379; Ch <sup>2</sup> = 111.5         1	06 290 05 309 02 846	43 685	194 1207	1.1% 3.4%	3.8%	2.02 [1.34; 3.06]	
Vang et al., 2022         19           San et al., 2022         30           Mo et al., 2022         5           Fotal (common effect, 95% CI)         5           Fotal (random effect, 95% CI)         4           Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5         5	95 309 92 846	685	1207	3.4%			14
San et al., 2022         30           Mo et al., 2022         5           Total (common effect, 95% CI)           Fotal (random effect, 95% CI)           Ideterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	846						i 🖛
Vio et al., 2022         5           Total (common effect, 95% CI)         5           Total (random effect, 95% CI)         1           Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5         1			1007	6.7%	4.4%	1.07 [0.89; 1.30]	-
Total (common effect, 95% Cl) Total (random effect, 95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	57 155	73		1.1%	3.8%	1.76 [1.16; 2.68]	
Total (random effect, 95% CI) Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	12,214		26,992	96.4%		1.10 [1.05; 1.16]	•
Heterogeneity: Tau <sup>2</sup> = 0.2379; Chi <sup>2</sup> = 111.5	,				84.5%	1.34 [1.06; 1.70]	•
Subaroup = RCTs	1, df = 21	(P < 0.01	); I <sup>2</sup> = 810	%			
El-Toukhy et al., 2004 2	23 117	10	117	0.3%	2.6%	2.62 [1.19; 5.78]	<u> </u>
Madani et al., 2019 3	8 121	31	113	0.7%	3.3%	1.21 [0.69; 2.13]	— <del>———</del>
uo et al., 2021 8	35 172	92	171	1.6%	3.8%	0.84 [0.55; 1.28]	
Salemi et al., 2021 2	20 93	21	95	0.5%	2.9%	0.97 [0.48; 1.93]	
Ku et al., 2021 3	65 65	32	68	0.5%	2.9%	1.03 [0.52; 2.03]	
Total (common effect, 95% CI)	568		564	3.6%		1.09 [0.84; 1.41]	*
Fotal (random effect, 95% CI)					15.5%	1.14 [0.68; 1.89]	+
leterogeneity: Tau <sup>2</sup> = 0.0695; Chi <sup>2</sup> = 6.44,	df = 4 (P	= 0.17); l <sup>2</sup>	= 38%				
Total (common effect, 95% Cl)	12,782	2	27,556	100.0%		1.10 [1.05; 1.16]	•
Total (random effect, 95% CI)			2		100.0%	1.31 [1.07; 1.60]	► • • • • • • • • • • • • • • • • • • •
Heterogeneity: Tau <sup>2</sup> = 0.2032; Chi <sup>2</sup> = 117.9							
Fest for subgroup differences (common eff Fest for subgroup differences (random effe							0.1 0.5 1 2 10 nRHa pretreatment GnRHa pretreat

Figure 3. Cont.

Study or Subgroup	Experin Events			ontrol Total	Weight (common)			Odds Ratio I MH, Fixed + Random, 95% CI
Subgroup = Observational stu	dies							
Vijiver et al., 2014	27	47	90	137	1.8%	3.4%	0.70 [0.36; 1.39]	
Guo et al., 2016	5	39	3	16	0.3%	1.4%	0.64 [0.13; 3.06]	<b>•</b>
Kang et al., 2018	7	55	4	20	0.5%	1.7%	0.58 0.15; 2.26]	
Wageh et al., 2018	2	19	3	29	0.2%	1.1%	1.02 [0.15; 6.75]	
Xie et al., 2018	18	126		281	1.9%	3.7%	1.03 [0.57; 1.89]	
Mehrafza et al., 2019 ª	9	33		31	0.6%	2.2%	1.08 [0.35; 3.27]	
Mehrafza et al., 2019 a	6	27		31	0.5%	2.0%	0.82 [0.24; 2.76]	
Wang et al., 2019	5	47	30	204	0.9%	2.5%	0.69 [0.25; 1.89]	
An et al., 2020	61	401	18	107	2.2%	3.8%	0.89 [0.50; 1.58]	<b>_</b>
Dong et al., 2020	41	90	122	370	2.4%	4.1%	1.70 [1.07; 2.72]	-
Naserpoor et al., 2020	2	19	4	22	0.3%	1.1%	0.53 [0.09; 3.27]	
	34	147		1353	3.4%			
Qi et al., 2020	27	65	249 34	77	1.7%	4.3% 3.5%	1.33 [0.89; 2.00]	
Li et al., 2021	73	387	71	363	5.5%	4.5%	0.90 [0.46; 1.75]	<u>.</u>
Liu et al., 2021							0.96 [0.66; 1.38]	_ T
Siristatidis et al., 2021	4	62		24	1.9%	1.8%	0.04 [0.01; 0.15]	<u>_</u>
Zheng et al., 2021	160	768	1104	6186	17.7%	4.9%	1.21 [1.01, 1.46]	
Eleftheriadou et al., 2022	223	865	252	1121	15.0%	4.9%	1.20 [0.97; 1.47]	<u> </u>
Xia et al., 2022 *	117	651	96	610	7.5%	4.7%	1.17 [0.87; 1.58]	
Xia et al., 2022 **	111	687	94	637	7.5%	4.7%	1.11 [0.83; 1.50]	
Xia et al., 2022 ***	81	439		147	3.1%	4.1%	0.96 [0.60; 1.55]	
Li et al., 2022	81	357		104	2.3%	3.9%	1.16 [0.68; 1.99]	
Pan et al., 2022	31	142		68	2.4%	3.6%	0.48 [0.25; 0.91]	
Wang et al., 2022	25	223	143	837	4.9%	4.2%	0.61 [0.39; 0.96]	
Gan et al., 2022	90	399		483	8.5%	4.6%	0.77 [0.57; 1.05]	
Mo et al., 2022	12	72		116	1.8%	3.2%	0.57 [0.27; 1.21]	
Total (common effect, 95% CI)		6167		13,374	94.7%		1.03 [0.94; 1.12]	1
Total (random effect, 95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.1676; Chi <sup>2</sup>	= 55.74, c	lf = 24	(P < 0.01)	; I <sup>2</sup> = 57		83.9%	0.89 [0.71; 1.10]	•
Subgroup = RCTs								
Simon et al., 1998	7	14	0	11	0.0%	0.5%	23.00 [1.14; 465.16]	ļ
Prato et al., 2002	5	28		34	0.3%	1.6%	1.63 [0.39; 6.76]	<b>.</b>
El-Toukhy et al., 2004	5	28		13	0.3%	1.4%	0.72 [0.14; 3.63]	
Nekoo et al., 2015	2	20		24	0.3%	1.1%	0.56 [0.09; 3.40]	
Samsami et al., 2018	2	18		16	0.2%	1.0%	1.40 [0.20; 9.66]	
Madani et al., 2019	11	44	_	35	0.6%	2.4%	1.12 [0.40; 3.19]	
	1	38	8	24	0.9%	0.9%	0.05 [0.01; 0.47]	
Aghahoseini et al., 2020	16	109						
Luo et al., 2021	0	32		111	1.0%	3.1%	1.30 [0.59; 2.84]	_
Salama et al., 2021	9	29		37 32	0.5%	0.5%	0.07 [0.00; 1.38]	
Salemi et al., 2021							0.86 [0.29; 2.51]	
Xu et al., 2021	2	39	7	41	0.6%	1.3%	0.26 [0.05; 1.35]	
Total (common effect, 95% CI)		399		378	5.3%	10 401	0.83 [0.57; 1.21]	I
	- 19 17 6	if = 10	(P = 0.05)	; I <sup>2</sup> = 45	- %	16.1%	0.75 [0.31; 1.82]	
Total (random effect, 95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.9915; Chi <sup>2</sup>	- 10.17, 0							9
		6566		13,752	100.0%		1.01 [0.93; 1.10]	
Heterogeneity: Tau <sup>2</sup> = 0.9915; Chi <sup>2</sup> Total (common effect, 95% Cl)		6566		13,752	100.0%	100.0%		•
Heterogeneity: Tau <sup>2</sup> = 0.9915; Chi <sup>2</sup>						100.0%	1.01 [0.93; 1.10] 0.86 [0.68; 1.08]	· · · · · · · · · · · · · · · · · · ·

**Figure 3.** Forest plots of meta-analysis for pregnancy outcomes following AC-FET cycles with and without GnRHa pretreatment [9–11,16–53]. (A) Clinical Pregnancy Rate. (B) Implantation Rate. (C) Live Birth Rate. (D) Miscarriage Rate. \*, \*\*, and \*\*\*: three populations of infertile women were reported in the same study with matched or non-matched designs. <sup>a</sup> and <sup>aa</sup>: two different protocols were applied in the same study. RCTs: randomized controlled trials.

However, there were discrepancies in subgroup analysis for the study design. While subgroup analysis on observational studies demonstrated favorable outcomes, subgroup analysis on RCTs promoted non-significantly different chances of pregnancy among GnRHapretreated FET cycles in comparison to conventional AC-FETs (Table 2 (A) and Figure 3). Albeit insignificant, analysis of RCTs still demonstrated a slightly better LBR among women receiving GnRHa prior to embryo transfer. The limited number of participants in RCTs included in this analysis (1244 cycles with GnRHa and 1208 controls) could contribute to the results.

					•		
Author	Country	Research Design	Number of Participants (Case/Control)	Diagnosis of Participants	Drug Use	Artificial Endometrial Preparation Protocol	Protocol
Simon A. (1998) [16]	Israel	RCT	53/53	Mixed	Triptorelin pamoate	Step-up	One dose of depot GnRHa 3.75 mg IM at preceding early follicular phase (irregular cycle) or mid-luteal phase (regular cycle)
Prato L. D. (2002) [17]	Italy	RCT	146/150	Tubal, idiopathic, or male factors	Triptorelin pamoate	Step-up	One dose of depot GnRHa 3.75 mg IM at preceding mid-luteal phase
El-Toukhy T. (2004) [18]	United Kingdom	RCT	117/117	Mixed	Bureselin acetate	Fixed-dose	GnRHa 400 mcg nasally every day from preceding mid-luteal phase to the day before P4 administration
Davar R. (2007) [19]	Iran	RCT	30/30	Mixed	Bureselin acetate	Step-up	Daily GnRHa 0.5 mg SC daily from preceding mid-luteal phase to the day before P4 administration
Niu Z. (2013) [20]	China	Retrospective cohort study	194/145	Adenomyosis	Leuproreline acetate	Step-up	Two doses of depot GnRHa: 1st dose: 3.75 mg IM and 2nd dose: 1.875 mg IM at 2 consecutive early follicular phase
Vijiver A. (2014) [21]	Belgium	Retrospective cohort study	280/849	Mixed	Bureselin acetate	Step-up	GnRHa 600 mcg nasally every day from preceding mid-luteal phase to the day before P4 administration
Nekoo E. A. (2015) [22]	Iran	RCT	93/83	Male factor	Triptorelin pamoate	Step-up	One dose of depot GnRHa 3.75 mg IM at preceding mid-luteal phase
Hebisha S. (2016) [24]	Egypt	Prospective cohort study	110/100	Mixed	Triptorelin acetate	Fixed-dose	Daily GnRHa—0.1 mg SC from preceding mid-luteal phase—0.05 mg SC from E2 administration day to day before P4 administration
Guo S. (2016) [23]	China	Retrospective cohort study	76/44	Adenomyosis	Triptorelin acetate	NR	Depot GnRHa—one dose 3.75 mg IM—early follicular phase
Tsai H. W. (2017) [25]	Taiwan	Retrospective cohort study	29/31	PCOS	Leuprolide acetate	Fixed-dose	Depot GnRHa—two dose 3.75 mg IM

**Table 1.** Characteristics of the studies in the systematic review and meta-analysis.

	Table	<b>1.</b> <i>Cont.</i>					
Author	Country	Research Design	Number of Participants (Case/Control)	Diagnosis of Participants	Drug Use	Artificial Endometrial Preparation Protocol	Protocol
Kang J. (2018) [26]	Korea	Retrospective cohort study	113/49	Mixed with exclusion of PCOS	Buserelin acetate	Step-up	Daily GnRHa—0.1 mg SC from preceding mid-luteal phase for 14 days
Movahedi S. (2018) [27]	Iran	RCT	60/40	Mixed with exclusion of endometriosis	Buserelin acetate	Step-up	Daily GnRHa—0.5 mg SC from preceding mid-luteal phase
Samsami A. (2018) [28]	Iran	RCT	109/107	Mixed	Buserelin acetate	Step-up	Daily GnRHa—0.5 mg SC from preceding mid-luteal phase, 0.3 mg SC from E2 administration day
Wageh A. (2018) [29]	Egypt	Retrospective cohort study	37/58	PCOS	Triptorelin acetate	Step-up	Daily GnRHa—0.1 mg SC from preceding mid-luteal phase
Xie D. (2018) [30]	China	Retrospective cohort study	252/751	Mixed	Leuprorelin acetate	Step-up	Depot GnRHa—one or two dose (per 4 week) 3.75 mg IM—early follicular phase
Madani T. (2019) [31]	Iran	RCT	121/113	Mixed	Buserelin acetate	Step-up	Daily GnRHa—0.5 mg SC from preceding mid-luteal phase
Mehrafza M. (2019) [32]	Iran	Retrospective cohort study	193/103	Mixed	Bureselin acetate/ Triptorelin pamoate	Step-up	Daily GnRHa—0.3 mg SC from preceding mid-luteal phase—0.2 mg SC from E2 administration to day 6 or depot GnRHa—one dose 1.875 mg IM—mid-luteal phase
Wang Z. (2019) [33]	China	Retrospective cohort study	92/396	Endometrial polyp	Bureselin acetate	Step-up	Depot GnRHa—one dose 0.8-3.75 mg IM—mid-luteal phase
Aghahoseini M. (2020) [34]	Iran	RCT	88/90	PCOS	Triptorelin acetate	Step-up	Depot GnRHa 3.75 mg—two doses with an interval of 4 weeks, beginning at 8 weeks before estradiol administration
An J. (2020) [9]	China	Retrospective cohort study	975/338	Mixed with exclusion of endometriosis	Leuprolide acetate	Fixed-dose	Depot GnRHa 1.875 mg—mid-luteal phase—one to three doses for each three weeks

	Table	<b>1.</b> <i>Cont.</i>							
Author	Country	Research Design	Number of Participants (Case/Control)	Diagnosis of Participants	Drug Use	Artificial Endometrial Preparation Protocol	Protocol		
Davar R. (2020) [35]	Iran	RCT	34/33	RIF	Triptorelin acetate	Step-up	Daily GnRHa—0.1 mg SC from preceding mid-luteal phase—0.05 mg SC from E2 administration day to day before P4 administration		
Dong M. (2020) [36]	China	Retrospective cohort study	268/996	Elderly patients	NR	Step-up	Depot GnRHa—one dose 3.75 mg IM—early follicular phase		
Guerrero-Vargas J. J. (2020) [37]	Spain	Retrospective cohort study	64/35	Mixed	Leuprolide acetate/ triptorelin acetate	Step-up	Daily GnRHa—1 mg SC (Leuprolide acetate) or 0.1 mg (triptorelin acetate) from preceding mid-luteal phase, then reduce by half if pituitary suppression achieved		
Naserpoor L. (2020) [38]	Iran	Retrospective case–control study	74/74	Mixed	Buserelin acetate	Step-up	0.5 mg/day initiated from the 19th day of the previous menstrual cycle, then reduce by half at E2 initiation		
Qi Q. (2020) [39]	China	Retrospective cohort study	303/2936	Mixed	Leuprorelin acetate/ Triptorelin acetate	Fixed-dose	Depot GnRHa—one dose 3.75 mg IM at preceding early follicular phase		
Li M. (2021) [40]	China	Retrospective cohort study	160/181	Adenomyosis	Triptorelin/ Leuproreline	Step-up	Depot GnRHa $\geq$ one dose 3.75 mg IM at early follicular phase each month		
Liu X. (2021) [41]	China	PSM retrospective cohort study	514/514	PCOS	Triptorelin acetate	Step-up	Depot GnRHa—1 dose 3.75 mg IM—early follicular phase		
Luo L. (2021) [11]	China	RCT	172/171	PCOS	Triptorelin acetate	Step-up	Depot GnRHa—1 dose 1 mg IM—early follicular phase		
Salama K. M. (2021) [42]	Egypt	RCT	70/70	Mixed	Triptoreline acetate	Step-up	One dose depot GnRHa 3.75 mg—mid-luteal phase		
Salemi S. (2021) [43]	Iran	RCT	106/106	PCOS	Bureselin acetate	Step-up	Daily GnRHa—0.5 mg SC from preceding mid-luteal phase for 14 days		

	lable 1.	Cont.						
Author	Country	Research Design	Number of Participants (Case/Control)	Diagnosis of Participants	Drug Use	Artificial Endometrial Preparation Protocol	Protocol	
Siristatidis C. (2021) [44]	Greece	Retrospective cohort study	159/221	Normal ovulatory women without PCOS	NR	Step-up	Daily GnRHa—dose NR	
Xu J. (2021) [45]	China	RCT	65/68	Mixed with exclusion of endometriosis and PCOS	Triptorelin acetate	Fixed-dose	Depot GnRHa—1 dose 3.75 mg IM—early follicular phase	
Zheng Q. Z. (2021) [46]	China	Retrospective cohort study	1518/11,456	Mixed	Leuproreline acetate	Step-up	Depot GnRHa—one dose 3.75 mg IM—mid-luteal phase	
Eleftheriadou A. (2022) [47]	United Kingdom	Non-randomized prospective cohort study	1949/2658	Mixed	Buserelin acetate	Step-up	Daily GnRHa—0.5 mg SC from preceding mid-luteal phase until P4 commencement	
Xia L. (2022) * [48]	China	PSM retrospective cohort study	1165/1165	Women without previous FET failure	Triptorelin embonate	Step-up	Depot GnRHa—one dose 3.75 mg IM—early follicular phase	
Xia L. (2022) ** [48]	China	PSM retrospective cohort study	1133/1133	Women with one previous FET failure	Triptorelin embonate	Step-up	Depot GnRHa—one dose 3.75 mg IM—early follicular phase	
Xia L. (2022) *** [48]	China	Retrospective cohort study	785/302	Women with more than one FET failure	Triptorelin embonate	Step-up	Depot GnRHa—one dose 3.75 mg IM—early follicular phase	
Li L. (2022) [10]	China	Retrospective cohort study	853/290	Women with ovulation and regular cycle	Leuprorelin acetate	Fixed-dose	Depot GnRHa 1.875 mg at mid-luteal phase for 3-5 cycles consecutively	
Pan D. (2022) [49]	China	Retrospective cohort study	290/194	Older patients >35 yrs with RIF and without adenomyosis and endometriosis	Triptorelin acetate	Step-up	Depot GnRHa—one dose 3.75 mg IM—early follicular phase	

Table 1. Cont.

	Table	<b>1.</b> <i>Cont.</i>					
Author	Country	Research Design	Number of Participants (Case/Control)	Diagnosis of Participants	Drug Use	Artificial Endometrial Preparation Protocol	Protocol
Wang Y. (2022) [50]	China	PSM retrospective cohort study	309/1207	PCOS	Triptorelin embonate	Step-up	Depot GnRHa—one dose 3.75 mg IM—early follicular phase
Gan R. X. (2022) [51]	China	Retrospective cohort study	846/1007	Women with history of cesarean scar(s)	Triptorelin acetate	Fixed-dose and Step-up	Depot GnRHa—one dose 1.875 mg IM—early follicular phase
Mo M. (2022) [52]	China	PSM retrospective cohort study	155/294	women with history of intrauterine adhesion	Leuprorelin acetate	Step-up	Depot GnRHa—one dose 3.75 mg IM—mid-luteal phase
Liu Y. (2022) [53]	China	Retrospective case–control study	43/54	Women with persistent thin endometrium	Leuprorelin acetate	Step-up	Depot GnRHa—1st dose: 1.5 mg IM At early follicular phase and 28 days later 2nd dose: 1.5 mg IM (14 days before E2 initiation)

\*, \*\*, and \*\*\*: three populations of infertile women were reported in the same study with matched or non-matched designs. PCOS: Polycystic Ovarian Syndrome; PSM: Propensity Score Matching; GnRHa: Gonadotropin releasing hormone agonist. NR: Non-Reported. P4: progesterone; E2: Estradiol; IM: Intramuscular; SC: Subcutaneous RCT: Randomized Controlled Trial; RIF: Repeated Implantation Failure.

	Outcomes	I2	OR (95% CI)	р	p-Value for Subgroup Differences <sup>κ</sup>						
(A) Subgrouping: Study design											
CPR	RCTs (k = 14) Observational studies (k = 30)	18.00% 77.20%	1.09 (0.87–1.36) 1.33 (1.13–1.55)	0.45 <0.001 *	0.13						
IR	RCTs (k = 12) Observational studies (k = 15)	0.00% 80.80%	1.01 (0.85–1.20) 1.40 (1.13–1.73)	0.88 0.004	0.04 *						
LBR	RCTs (k = 5) Observational studies (k = 22)	37.80% 81.30%	1.14 (0.68–1.41) 1.34 (1.06–1.70)	0.63 0.02	0.44						
MR	RCTs ( $k = 11$ ) Observational studies ( $k = 25$ )	44.60% 56.70%	0.75 (0.31–1.82) 0.89 (0.71–1.10)	0.49 0.26	0.70						
(B) Subgrouping: Type of GnRHa protocol											
CPR	Depot GnRHa (k = 29) Daily GnRHa (k = 14)	72.10% 0.00%	1.25 (1.08–1.44) 1.11 (1.02–1.21)	0.004 * 0.02 *	0.15						
IR	Depot GnRHa (k = 17) Daily GnRHa (k = 10)	78.90% 1.70%	1.28 (1.02–1.59) 1.17 (0.96–1.42)	0.03 * 0.08	0.51						
LBR	Depot GnRHa (k = 19) Daily GnRHa (k = 7)	72.10% 26.80%	1.19 (1.04–1.37) 1.14 (0.86–1.52)	0.02 * 0.18	0.75						
MR	Depot GnRHa (k = 25) Daily GnRHa (k = 10)	48.20% 0.00%	0.93 (0.75–1.15) 1.10 (0.95–1.28)	0.48 0.16	0.16						
	(C) Subgrouping	g: Duration of pitu	uitary suppression with	GnRHa							
CPR	Within one cycle (k = 37) More than one cycle (k = 6)	61.30% 66.40%	1.17 (1.04–1.32) 2.00 (1.29–3.10)	0.01 * 0.01 *	0.003 *						
IR	Within one cycle ( $k = 24$ ) More than one cycle ( $k = 3$ )	56.70% 64.40%	1.16 (1.02–1.32) 2.07 (0.97–4.43)	0.03 * 0.05 *	0.002 *						
LBR	Within one cycle ( $k = 24$ ) More than one cycle ( $k = 2$ )	77.80% 37.90%	1.28 (1.03–1.60) 1.42 (0.24–8.39)	0.03 * 0.24	0.58						
MR	Within one cycle ( $k = 32$ ) More than one cycle ( $k = 3$ )	53.70% 72.60%	0.87 (0.69–1.09) 0.50 (0.01–24.11)	0.21 0.52	0.54						

**Table 2.** Subgroup analyses of interested FET outcomes in women with and without GnRHa pretreatment. (A) Subgroup analysis of study design. (B) Subgroup analysis of the type of GnRHa (C) Subgroup analysis of the duration of pituitary suppression with GnRHa.

<sup>k</sup>: All subgroup analyses were conducted using a random-effects model, chosen in response to the significant heterogeneity observed within the overall study population. \*: Statistically significant. CPR: Clinical Pregnancy Rate; GnRHa: Gonadotropin Releasing Hormone agonist; IR: Implantation Rate; LBR: Live Birth Rate; MR: Miscarriage Rate; RCT: Randomized Controlled Trial.

# 3.3.2. Subgroup Meta-Analysis of Different Down-Regulation Protocols and Treatment Durations of Pituitary Suppression with GnRHa Prior to Artificial FET Cycles

All subgroup meta-analyses in this study were conducted using a random-effects model, chosen in response to the significant heterogeneity observed within the overall study population. The short-acting regimen (daily protocol) was associated with higher CPR (OR = 1.11, 95% CI: 1.02–1.21,  $I^2 = 0.0\%$ , p = 0.02) compared with the control. The differences in IR (OR = 1.17, 95% CI: 0.96–1.42,  $I^2 = 1.7\%$ , p = 0.08), LBR (OR = 1.14, 95% CI: 0.86–1.52,  $I^2 = 26.8\%$ , p = 0.18) and MR (OR = 1.10, 95% CI: 0.95–1.28,  $I^2 = 0.0\%$ , p = 0.16), however, were not considerably different. On the other hand, pituitary suppression with long-acting GnRHa (depot protocol) improved CPR (OR = 1.25, 95% CI: 1.08–1.44,  $I^2 = 72.1\%$ , p = 0.004), IR (OR = 1.28, 95% CI: 1.02–1.59,  $I^2 = 78.9\%$ , p = 0.03), and also LBR (OR = 1.19, 95% CI: 1.04–1.37,  $I^2 = 72.1\%$ , p = 0.02), accompanied by insignificant changes in MR (OR = 0.93, 95% CI: 0.75–1.15,  $I^2 = 48.2\%$ , p = 0.48). Comparing the two protocols, pregnancy outcomes after FET seemed to be slightly improved with depot GnRHa administration. However, their differences were not significant (Table 2 (B) and Supplementary Figure S4).

Women who were pretreated within one cycle prior to FET had better CPR (OR = 1.17, 95% CI: 1.04–1.32,  $I^2 = 61.3\%$ , p = 0.01), IR (OR = 1.16, 95% CI: 1.02–1.32,  $I^2 = 56.7\%$ , p = 0.03), and LBR (OR = 1.28, 95% CI: 1.03–1.60,  $I^2 = 77.8\%$ , p = 0.03). After pituitary suppression, MR did not differ from the non-pretreated group (OR = 0.87, 95% CI: 0.69–1.09,  $I^2 = 53.7\%$ , p = 0.21). Moreover, women who were pretreated more than one cycle prior to FET demonstrated, to a greater extent, improvements in CPR (OR = 2.00, 95% CI: 1.29–3.10,  $I^2 = 66.4\%$ , p = 0.01), IR (OR = 2.07, 95% CI: 0.97–4.43,  $I^2 = 64.4\%$ , p = 0.05), while LBR (OR = 1.42, 95% CI: 0.24–8.39,  $I^2 = 37.9\%$ , p = 0.24) and the rate of miscarriage (OR = 0.50, 95% CI: 0.01–24.11,  $I^2 = 72.6\%$ , p = 0.52) were not significantly different compared with the control. In summary, compared to short-term suppression, prolonged GnRHa administration resulted in better CPR and IR (p < 0.05), though no significant differences were found in LBR or MR (Table 2 (C) and Supplementary Figure S5).

3.3.3. Subset Meta-Analyses of Specific Etiologies among Infertile Women Undergoing FET with Hormonal Endometrial Preparation

In PCOS patients, GnRHa pretreatment promoted higher CPR (OR = 1.24, 95% CI: 1.06–1.44,  $I^2 = 29.1\%$ , p = 0.006) and LBR (OR = 1.22, 95% CI: 1.05–1.42,  $I^2 = 48.9\%$ , p = 0.01), accompanied by a lower MR (OR = 0.75, 95% CI: 0.59–0.95,  $I^2 = 44.9\%$ , p = 0.02) (Figure 4 and Supplementary Figure S6). However, IR (OR = 1.37, 95% CI: 0.46–4.03,  $I^2 = 71.4\%$ , p = 0.35) did not considerably differ from the non-pretreated women.

Outcome	n studies	GnRHa pretreatment	Control		95% Confidence Interval <sup> 2</sup>
CPR			1		
PCOS	11	890/1360	1645/2650		1.24 (1.06 to 1.44)* 29%
Regular Cycle	8	970/2421	329/1227		1.63 (0.96 to 2.71) 77%
			1		
IR			1		
PCOS	3	240/545	225/636 -	<b>B</b>	1.37 (0.46 to 4.03) 71%
Regular Cycle	6	789/3669	276/1724 🕂	•	1.29 (0.82 to 2.04) 61%
			1		
LBR					
PCOS	6	650/1168	1238/2439		1.22 (1.05 to 1.42)* 49%
Regular Cycle	6	711/2298	214/1114 +		2.14 (0.82 to 5.58) 87%
			1		
MR					
PCOS	8	132/854	316/1617 -		0.75 (0.59 to 0.95)* 45%
Regular Cycle	7	171/967	73/327		0.56 (0.19 to 1.63) 73%
			0.51	2 3	_
			←		>
			Favor Control	Favor GnRHa pretreatment	

**Figure 4.** Subset meta-analyses on specific populations: women with PCOS and women with regular menstruation and no ovulation disorders. CPR: clinical pregnancy rate, IR: implantation rate, LBR: live birth rate, MR: miscarriage rate. \*: statistically significant.

On the other hand, subset meta-analysis of normal ovulatory women with regular menstruation as an inclusion criterion demonstrated high heterogeneity with no significant improvements in pregnancy outcomes, including CPR (OR = 1.63, 95% CI: 0.98–2.71,  $I^2 = 76.7\%$ , p = 0.06), IR (OR = 1.29, 95% CI: 0.82–2.04,  $I^2 = 60.7\%$ , p = 0.21), LBR (OR = 2.14, 95% CI: 0.82–5.58,  $I^2 = 86.6\%$ , p = 0.10) and MR (OR = 0.56, 95% CI: 0.19–1.63,  $I^2 = 73.3\%$ , p = 0.23) among those pretreated with GnRHa (Figure 4 and Supplementary Figure S7).

#### 4. Discussion

Successful implantation must be initiated by interaction between a competent embryo and a receptive endometrium. Alongside efforts to improve embryo quality and euploidy rate, sufficient endometrial preparation and synchronization are also essential for successful implantation. Although certain previous studies have compared different endometrial preparation protocols, the optimal strategy for embryo transfer remains conflicting. In this

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work, all included studies employed an artificial cycle protocol for endometrial preparation. Some studies employed a fixed-dose approach [10,18,24,25,39,45], while most authors opted for a step-up regimen. Only the study conducted by Gan et al. used both regimens [51]. Typically, the duration of endothelial preparation with estrogen does not exceed 21 days, and the endometrial thickness must surpass 7 mm prior to embryo transfer to prevent cycle cancellation. The sole variable differentiating the intervention group from the control cohort was the application of GnRHa for pituitary downregulation. Nonetheless, there has been a consensus that pregnancy outcomes were not significantly different between the fixed-dose and step-up regimens utilized for AC-FET [55]. According to the above-mentioned facts, we posit that the AC regimen of endometrial preparation does not exert a significant impact on the treatment outcomes. Thus, this report exclusively focused on evaluating the efficacy of pituitary suppression with GnRHa on the outcomes of AC-FET cycles. We additionally included subgroup analyses of specific infertile populations without evaluating the AC regimen type utilized.

GnRHa, which is widely recognized for its ability to suppress the pituitary gland and exhibit anti-inflammatory effects, has become prevalent in the realm of assisted reproductive technologies. In insemination cycles, this GnRH analog can be used in conjunction with fertility drugs to regulate the menstrual cycle and synchronize ovulation in order to optimize the timing of IUI. During COH, sustained GnRHa administration causes refractoriness of the pituitary, avoiding a premature LH surge, while the high-dose bolus of this medication triggers the final maturation of oocytes [56]. An appropriate dose of GnRHa after embryo transfer could retain its stimulatory effect to preserve LH production, as has been recently postulated in a meta-analysis of the efficacy of GnRHa in luteal-phase support during both fresh and frozen cycles [57]. Some in vitro and in vivo studies have enlightened the mechanisms behind how GnRH agonists improve endometrial receptivity and enhance embryo implantation [8,58]. However, the influence of GnRHa on the uterine endometrium and implantation process remains a subject of ongoing debate, with no consensus having been reached thus far. This systematic review and meta-analysis demonstrates that pituitary suppression using GnRHa prior to artificial embryo transfer cycles significantly enhanced pregnancy outcomes in women undergoing artificial FET cycles.

However, there were discrepancies between subgroup analyses of RCTs and observational cohort studies. Meta-analyses on implantation and pregnancy outcomes failed to demonstrate any significant differences (Table 2 (A) and Figure 3). Nevertheless, the subgroup analysis incorporated randomized controlled trials (RCTs) that had inherent limitations in terms of sample size and study quality. Consequently, the evidence derived from these RCTs did not possess sufficient strength to support a definitive conclusion.

GnRHa can be administered in short-acting form as daily low-dose shots or through a single long-acting depot injection. The utilization of depot GnRHa during COH results in a more robust suppression effect, necessitating a higher dose of gonadotropins and an extended period of administration. This may lead to an increase in overall treatment cost as compared with daily low-doses of GnRHa [59]. On the other hand, the depot GnRH-a protocol appeared to offer a significantly higher LBR in normogonadotropic women without discernible differences in luteal function or offspring health, as recently reported by Zhang et al. in a large-scale matched cohort study [60]. The eutopic expression levels of endometrial receptivity markers, such as HOXA10, MEIS1, and LIF, were significantly greater with the depot GnRHa protocol compared to GnRH antagonist or long GnRHa protocols in fresh embryo transfer cycles [61]. In the context of endometrial preparation for FET, daily injections for the GnRHa pretreatment protocol require more visits and injections, thereby potentially increasing the cost of treatment. In this meta-analysis, we documented the beneficial effects of both protocols on pregnancy outcomes (Table 2 (B) and Supplementary Figure S4). Notably, GnRHa depot had an impact on live birth outcomes (OR = 1.19, 95% CI: 1.04–1.37,  $l^2$  = 72.1%, p = 0.02), whereas no significant improvement was found in women pretreated with a daily GnRHa regimen (OR = 1.14, 95% CI: 0.86–1.52,  $l^2 = 26.8\%$ , p = 0.18). The result postulates that the use of depot GnRHa could be a superior option for pituitary down-regulation prior to FET cycles compared to daily low-dose administration in terms of cost efficiency, patient convenience, and treatment efficacy.

The choice between short-term or long-term down-regulation with GnRHa in assisted reproductive technology (ART) procedures has been a subject of ongoing debate among reproductive endocrinologists. Sustained GnRHa administration has been specifically considered for women who possess particular medical conditions. GnRHa taken for 3-4 months before fibroid surgery can decrease the size of fibroids and the volume of the uterus, as well as address pre-operative iron deficiency anemia and minimize blood loss during myomectomy or hysterectomy [62]. Conservation treatment for adenomyosis or fibroid has also been considered with long-term GnRH analogues [63], while a post-operative approach with this protocol could reduce the risk of endometriosis recurrence [64]. Longer GnRHa treatment ( $\geq$ 3 months) ameliorates the inflammatory microenvironment [65], thus improving the quality and quantity of retrieved oocytes in IVF cycles among women with endometriosis [66]. We reported herein better pregnancy outcomes after FET with prolonged pituitary suppression (Table 2 (C) and Supplementary Figure S5) when compared with those undergoing GnRHa pretreatment within one cycle. It is essential to emphasize that the therapeutic benefits of GnRHa are intertwined with its associated consequences [67]. Temporary symptoms such as hot flashes, fatigue, and loss of libido typically subside shortly after discontinuing GnRHa. Other detrimental consequences, such as osteoporosis or gynecomastia, usually persist longer but have been suggested to occur only with extremely extended usage of GnRH analogs [68]. In this meta-analysis, only a limited number of studies were found that utilized GnRHa in a multi-cycle manner. Those studies that reported GnRH pretreatment for more than one month exclusively used the depot form and limited the number of depot GnRHa doses to less than six, thus reducing the risk of detrimental side effects. Due to insufficient data, we were unable to compare the effectiveness of different treatment durations on the pregnancy outcomes of FET cycles. Nevertheless, the findings herein support the use of GnRHa for more than one cycle but not exceeding six months. Since the evidence on this protocol remains limited, routine application to all women could non-beneficially increase the time and cost of treatment. More rigorous and well-designed studies are necessary to determine the most effective pituitary suppression protocol before embryo transfer.

In women suffering PCOS, endometrial receptivity has been postulated to be affected via several mechanisms: (1) sustained androgenic exposure due to the abberant hormonal milieu [69,70], (2) metabolic alterations that regulate decidualization [71], (3) compromised PR functions led to total failure of the uterus in supporting embryo implantation [72], and (4) altered intrauterine microenvironment via deregulation of local inflammatory mediators [73,74]. In clinical practice, PCOS is related to a higher risk of miscarriage and adverse pregnancy outcomes [75], though its effect on IVF and FET cycles remains controversial. The advantages of GnRHa administration include its ability to ameliorate hyperandrogenism and inhibit the function of the GnRH-HCG axis while also reducing endometrial inflammation and enhancing the expression of endometrial adhesion molecules [76]. We found herein substantial improvements in CPR, LBR, and MR (Figure 4 and Supplementary Figure S6) among PCOS women pretreated with GnRHa prior to transfer, though the difference in implantation rate did not reach significance. Our findings support the hypothesis that pituitary suppression may effectively alleviate the detrimental effects on implantation in females diagnosed with this syndrome, particularly in cases where metabolic syndrome or hyperandrogenism is present [25].

However, it is important to note that the effects of GnRHa on the immune and endocrine systems remain unclear and may vary depending on the individual and their specific condition. In women with ovulatory disorders, pituitary down-regulation can facilitate the restoration of a normal endometrial cycle by reverting the endometrium to its original status. Additionally, it provides temporary relief from associated abnormalities like hyperandrogenism or excessive inflammation caused by overexposure to estrogen. However, these problems are usually absent in women who experience regular menstrual periods and do not have an ovulatory disorder. Therefore, from a pathophysiological perspective, GnRHa may not have a beneficial effect on this particular group of patients. In line with the above hypothesis, no significant differences in pregnancy outcomes were found among normo-ovulatory women with regular menstruation in our subset meta-analysis (Figure 4 and Supplementary Figure S7). In women with normal functioning ovaries, the use of GnRHa has not been able to demonstrate sufficient efficacy and should be considered with caution since pretreatment may result in a doubling of expenditures [11] without a commensurate improvement in pregnancy outcomes. The choice of GnRHa, as well as the dosage and duration of treatment, should be carefully assessed according to each patient's characteristics and medical history.

Interestingly, in addition to GnRH agonists, the use of oral contraceptive pills (OCPs) and GnRH antagonists in artificial reproductive technology (ART) has been reported as being more patient-friendly, although their efficacy remains controversial [77,78]. Additional research is imperative to ascertain the impact of various down-regulation approaches on the success of infertility treatments in subpopulations of women with diverse underlying medical conditions.

#### 5. Conclusions

Pituitary suppression with GnRHa during AC-FET cycles could demonstrate a beneficial role in certain patient settings, in which long-term suppression and the use of depot GnRHa protocols supposedly provide better pregnancy outcomes. Individuals with PCOS benefit from GnRHa pretreatment, while this FET protocol should be carefully considered in ovulatory women with regular menstruation. The discrepancies between RCTs and real-world data are the main limitation of this study and call for a more rigorous investigation.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www. mdpi.com/article/10.3390/biomedicines12040760/s1, Table S1: PRISMA 2020 checklist [79]; Table S2: Detailed search strategy for electronic database searches (Searches performed on 30 August 2022). Table S3: Inclusion and exclusion criteria of the studies in the systematic review and meta-analysis; Table S4: Sensitive analysis for outcomes with publication biases; Figure S1: Baujat plot for sources of heterogeneity in overall infertile population (Clinical Pregnancy Rate); Figure S2: Baujat plot for sources of heterogeneity in overall infertile population (Miscarriage Rate); Figure S3: Baujat plot for sources of heterogeneity in overall infertile population (Live Birth Rate); Figure S4: Forest plots of meta-analysis for pregnancy outcomes following AC-FET cycles with and without GnRHa pretreatment: subgroups of daily and depot GnRHa protocols; Figure S5: Forest plots of meta-analysis for pregnancy outcomes following AC-FET cycles with and without GnRHa pretreatment: subgroups of daily and depot GnRHa protocols; Figure S5: Forest plots of meta-analysis for pregnancy outcomes following AC-FET cycles with and without GnRHa pretreatment: subgroups of daily and depot GnRHa pretreatment in PCOS patients; Figure S7: Forest plots of meta-analysis for pregnancy outcomes following AC-FET cycles with and without GnRHa pretreatment in ovulatory women with regular cycles.

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