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REVIEW

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Role of estradiol level before progesterone start on outcomes of frozen embryo transfer; a systematic review and meta-analysis

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Abstract

Estradiol (E2) levels on the day progesterone starts may negatively impact implantation, ongoing pregnancy, and live birth rates in frozen embryo transfer (FET). Overall, while the picture isn't entirely clear, some evidence suggests maintaining estradiol levels within a specific range before starting progesterone might be beneficial for frozen transfer success. So we performed a systematic review and meta-analysis to find out the rate of pregnancy-related outcomes of frozen embryo transfer in different level of E2. This review was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A multi database search was conducted (PubMed, Web of Science and Scopus) from the earliest date of each database until the 21st of April 2024. Data on the included articles including author, year, type of study, patients number, age, hormones like LH, FSH, successful pregnancy, live birth rate, and miscarriage were retrieved by two independent investigators. We categorized the values of E2 into five groups due to various values reported by studies to understand it better consisting of "Up to 200 pg/mL", "200–500 pg/mL", "500–1000 pg/mL", "1000–2000 pg/mL", "2000–3000 pg/mL" and "more than 3000 pg/mL". A forest plot was used to present the pooled measure. The analysis was performed using Stats version 13. A total of 14 studies containing 16,040 patients were included in the analysis. Studies reported a pooled prevalence of 57% with E2 level up to 200 pg/mL for clinical pregnancy. Also, studies reported a pooled prevalence of 46% with 200–500 pg/mL E2 for live birth rate. The lowest rate of miscarriage (6%) was observed in patients with 1000–2000 pg/mL E2 We found that the best level of E2 for having successful clinical pregnancy is up to 200 pg/mL and live birth rate is 200–500 pg/ml so we can say that E2 less than 500 pg/mL is a suitable value for pregnant.

Keywords Estradiol, IVF, E2, Frozen embryo transfer, Pregnancy, In vitro fertilization

Introduction

Sufficient levels of estrogen are also helpful in improving the endometrium's receptivity for more successful implantation [1]. In relation to the endometrium, luteal estradiol might only have a permissive role [2]. It has no effect on clinical outcomes to have estradiol levels in the middle and late luteal phase < 50 pg/mL [3]. Laufer, in 1982 revealed that in women who did not use assisted reproductive technology, the mid-luteal levels of progesterone and estradiol were essentially similar in both fertile and infertile cycles [4].

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Too little or too much estrogen can have a detrimental effect on the receptivity of the human endometrium, so it can be challenging to find the ideal range. The corpus luteum becomes dysfunctional during in vitro fertilization (IVF) when GnRH-a or GnRH-ant is inhibited in the pituitary gland and a considerable number of granulosa cells are removed during egg retrieval. Consequently, this lowers the synthesis of progesterone and estrogen and stops these hormones from reaching their second peak [5]. Therefore, it has been demonstrated by a number of studies ethat estrogen supplementation at this point can improve clinical outcomes [6, 7].

Nevertheless, additional research has revealed that boosting luteal support with estrogen might not improve clinical results, despite the growing significance of luteal support in IVF [8, 9]. According to certain studies, serum E2 levels measured in the middle and late luteal phases (MllPSE2) may serve as predictive markers for clinical outcomes. Conflicting data, however, exists [10–13], and another study has not been able to substantiate these assertions [14]. Hung et al. demonstrated the lack of a significant relationship between estradiol level and pregnancy rates [15]. Furthermore, Friedler et al. revealed that in good and high responders, there was no correlation between the chance of conception and either the absolute mid-luteal estradiol level [14].

A meta-analysis conducted by Huang et al. in 2015 showed that, even at varying daily dosages, the addition of estradiol during the luteal phase via oral medication does not enhance the success of IVF [16]. Another meta-analysis led by Gelbaya et al. in 2008 revealed that there is no increase in the likelihood of pregnancy when progesterone and estradiol are added for luteal phase support in IVF cycles [9]. We conducted a meta-analysis to address this disagreement, which shows ambiguous effects of E2 on clinical outcomes after IVF.

Methods

This systematic review and meta-analysis was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [17]. The PICO (Patient, Intervention/exposure, Comparison, and outcome) framework was patients undergone frozen embryo transfer, estradiol level, groups with different estradiol level/not taking estradiol supplementation and pregnancy-related outcomes like live birth rate and miscarriage.

Search strategy

A multi database search was conducted (PubMed, Web of Science and Scopus) from the earliest date of each database until the 21st of April 2024. Table 1 gives an overview of our search strategy.

Table 1 A sample search strategy done for PubMed

Database	Keywords and syntax
PubMed	((estradiol [Title/Abstract] OR E2 [Title/Abstract] OR Estrace [Title/Abstract] OR Delestrogen [Title/Abstract] OR Elestrin [Title/Abstract] OR Estradot [Title/Abstract] OR Estrasorb [Title/Abstract] OR Estrogel [Title/Abstract] OR Vivelle [Title/Abstract])) AND ((frozen blastocyst embryo [Title/Abstract] OR frozen embryo transfer [Title/Abstract] OR frozen-thawed embryo transfer [Title/Abstract])) AND ((pregnancy [Title/Abstract] OR live birth [Title/Abstract] OR miscarriage [Title/Abstract] OR abortion [Title/Abstract]))
Link	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28estradiol+%5BTitle%2FAbstract%5D+OR+E2+%5BTitle%2FAbstract%5D+OR+Estrace+%5BTitle%2FAbstract%5D+OR+Delestrogen+%5BTitle%2FAbstract%5D+OR+Elestrin+%5BTitle%2FAbstract%5D+OR+Estradot+%5BTitle%2FAbstract%5D+OR+Estrasorb+%5BTitle%2FAbstract%5D+OR+Estrogel+%5BTitle%2FAbstract%5D+OR+Vivelle+%5BTitle%2FAbstract%5D%29%29+AND+%28%28frozen+blastocyst+embryo+%5BTitle%2FAbstract%5D+OR+frozen+embryo+transfer+%5BTitle%2FAbstract%5D+OR+frozen-thawed+embryo+transfer+%5BTitle%2FAbstract%5D%29%29+AND+%28%28pregnancy+%5BTitle%2FAbstract%5D+OR+live+birth+%5BTitle%2FAbstract%5D+OR+miscarriage++%5BTitle%2FAbstract%5D+OR+abortion+%5BTitle%2FAbstract%5D%29%29+&sort=date

Two authors individually screened and selected studies on the basis of title and abstract. After primary selection, authors reviewed the full text of the selected studies and determined suitability for inclusion, based on the established selection criteria. For further eligible studies, cross-references were screened. Disagreements were solved by discussion with each other and the third/independent author until consensus was reached.

Search strategy was as following:

Inclusion criteria to select studies

- Women undergone frozen embryo transfer
- Women taking estradiol

Exclusion criteria

- Studies investigating pregnancy-related on animals
- Case reports
- Assessing trigger E2

Data extraction

Data on the included articles including author, year, type of study, patients number, age, hormones like LH, FSH,

successful pregnancy, live birth rate, and miscarriage were retrieved by two independent investigators. A third investigator independent from the other two corrected the differences observed in this process. The Newcastle Ottawa Scale was used for the qualitative assessment of studies [18].

Ethical statement

Since this meta-analysis study works with secondary data and only analyzes "published studies", it does not require a code of ethics and patient consent because the study unit in meta-analysis is only published studies, not patients.

Statistical analysis

The main measure of the effect/effect size was pregnancy-related outcomes like live birth rate, miscarriage and successful pregnancies. I^2 (showing the amount of heterogeneity, ranged from 0 to 100%) was used to assess the heterogeneity among the studies. The random-effects model (Der Simonian and Laird) was used for the continuous and frequency outcome under study. Random-effects meta-analysis was performed for estimating the main index, which was the pooled prevalence, at the 95% confidence interval. A forest plot was used to present the pooled measure. The analysis was performed using Stats version 13. Averages of quantitative variables were only reported according to the articles and we just in the meta-analysis process weighted each study by N (sample size). If needed, Hozo's method was used to estimate mean from median [19]. For descriptive purposes, table and figure were used. We categorized the values of E2 into five groups due to various values reported by studies to understand it better consisting of "Up to 200 pg/mL", "200–500 pg/mL", "500–1000 pg/mL", "1000–2000 pg/mL", "2000–3000 pg/mL" and "more than 3000 pg/mL". So different level of E2 used in the various studies could be compared in the forest plot as subgroup analysis while there is final and pooled analysis. *P*-values of < 0.05 were considered statistically significant.

Results

A total of 14 studies [20–32] containing 16,040 patients were included in the analysis (Fig. 1). Study characteristics extracted in systematic review and meta-analysis were presented in Table 2.

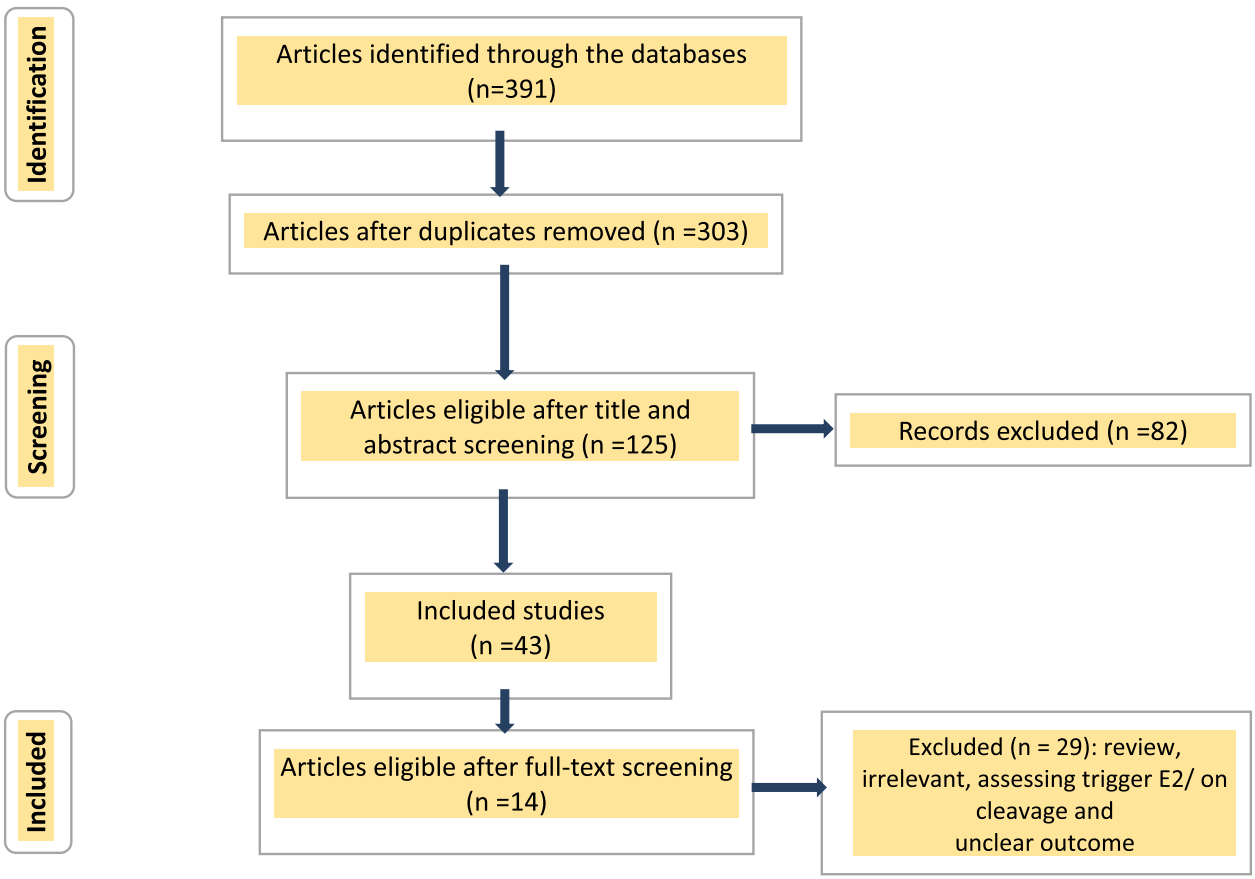

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 2 Baseline characteristics of the included studies in the systematic review and meta-analysis

Author	N*	Design	Age	Groups	BMI	Basis FSH_IU.L	Basis LH_IU.L	Basic.E2	Clinical pregnancy	Preeclampsia	Gestational diabetes	Abortion	Live birth	Endometrium mm
Huang et al., 2024a [3]	500	Retro**	34.18 ± 4.62	Group A < 50 pg/mL	-	6.49 ± 3.00	3.84 ± 2.87	40.96 ± 32.16	276	-	-	44	232	11.75 ± 5.51
Huang et al., 2024b [3]	2545	Retro	34.23 ± 4.75	Group B 50 pg/mL ≤ E2 < 150 pg/mL	-	6.24 ± 2.93	3.94 ± 2.34	43.62 ± 19.74	1451	-	-	232	1219	11.36 ± 3.03
Huang et al., 2024c [3]	1327	Retro	34.26 ± 4.49	Group C 150 pg/mL ≤ E2 < 250 pg/mL	-	5.81 ± 2.66	3.55 ± 2.48	36.11 ± 21.53	766	-	-	108	658	11.46 ± 4.13
Huang et al., 2024d [3]	925	Retro	34.26 ± 4.89	Group D 250 pg/mL ≤ E2 < 500 pg/mL	-	5.89 ± 2.43	3.56 ± 2.54	35.87 ± 17.55	523	-	-	76	447	11.35 ± 3.15
Huang et al., 2024e [3]	668	Retro	34.35 ± 4.70	Group E ≥ 500 pg/mL	-	5.92 ± 2.24	3.55 ± 2.90	36.67 ± 22.73	368	-	-	59	309	11.17 ± 3.35
Alsbjerg et al., 2024a [20]	260	Cohort	30.9 ± 4.3	Group A ≥ 292 pg/mL	25.2 ± 3.6	-	-	715 ± 223	102	-	-	-	101	-
Alsbjerg et al., 2024b [20]	102	Cohort	30.7 ± 4.7	Group B 292–409 pg/mL	24.8 ± 3.4	-	-	1243 ± 113	63	-	-	-	60	-
Alsbjerg et al., 2024c [20]	50	Cohort	31.8 ± 4.0	Group C ≥ 409 pg/mL	25.2 ± 3.3	-	-	1749 ± 298	14	-	-	-	10	-
Hsieh et al., 2023 [21]	888	Retro	36.5 ± 5.1	459.7 ± 218.5	26.6 ± 4.9	-	-	459.7 ± 218.5	-	95	-	-	-	10.7 ± 1.93
Lin et al., 2024 [22]	229	Retro	-	149.62 ± 14.58	-	-	-	149.62 ± 14.58	-	9	22	-	-	-
Vyas et al., 2023a [23]	41	Retro	36.7 ± 3.8	Group A < 300 pg/mL	26 ± 8.7	-	-	104.3 ± 118.6	4	-	-	4	17	9.8 ± 1.9

Table 2 (continued)

Author	N*	Design	Age	Groups	BMI	Basis FSH_IU.L	Basis LH_IU.L	Basic.E2	Clinical pregnancy	Preeclampsia	Gestational diabetes	Abortion	Live birth	Endometrium mm
Vyas et al., 2023b [23]	192	Retro	36.2 ± 4.1	Group B 300–500 pg/mL	24.1 ± 8.1	-	-	269.3 ± 176.3	9	-	-	17	118	9.8 ± 2.2
Vyas et al., 2023c [23]	517	Retro	35.7 ± 4.1	Group C > 500 pg/mL	22.4 ± 5.9	-	-	611.5 ± 425	47	-	-	45	238	9.6 ± 2.2
Liu et al., 2022a [24]	112	Case–control	-	Group High 1560.4 pg/mL	-	-	-	-	58	-	-	14	44	-
Liu et al., 2022b [24]	60	Case–control	-	Group ultr-high2420.9 pg/mL	-	-	-	-	24	-	-	-	24	-
[24] [25]	746	Retro	-	281 pg/mL	-	-	-	-	-	14	56	-	-	-
Zhou et al., 2021a [26]	1676	Retro	30.59 ± 4.49	< 200 pg/ml	21.65 ± 2.88	-	-	167.61 ± 26.02	1151	-	-	-	960	9.20 ± 1.47
Zhou et al., 2021b [26]	1296	Retro	30.80 ± 4.52	200–399 pg/ml	21.70 ± 3.06	-	-	270.79 ± 58.87	901	-	-	-	748	9.15 ± 1.56
Zhou et al., 2021c [26]	885	Retro	30.74 ± 4.73	≥ 400 pg/ml	21.70 ± 2.93	-	-	1061.87 ± 575.83	564	-	-	-	446	8.82 ± 1.53
Goldman et al., 2022a [27]	90	Retro	35.3 (4.0)	212 pg/ml	25.4 (6.8)	-	-	-	-	-	-	10	52	9.7 (2.5)
Goldman et al., 2022b [27]	92	Retro	35.0 (3.9)	274 pg/ml	26.1 (6.4)	-	-	-	-	-	-	11	40	10.0 (2.7)
Goldman et al., 2022c [27]	91	Retro	34.5 (4.0)	340 pg/ml	26.5 (6.2)	-	-	-	-	-	-	11	49	9.6 (2.1)
Goldman et al., 2022d [27]	90	Retro	35.2 (3.8)	528 pg/ml	25.0 (5.5)	-	-	-	-	-	-	5	35	9.1 (2.6)

Table 2 (continued)

Author	N*	Design	Age	Groups	BMI	Basis FSH_IU.L	Basis LH_IU.L	Basic.E2	Clinical pregnancy	Preeclampsia	Gestational diabetes	Abortion	Live birth	Endometrium mm
[27] [28]	45	Retro	32.38 ± 3.81	1838.75 ± 425.25 pg/ml	21.35 ± 3.35	-	-	1700.0 (1127.0–2828.5)	26	-	-	1	15	9.71 ± 1.77
[29] [29]	110	Historical cohort	32.1 ± 0.6	-	-	-	-	234.1 ± 16.6	-	-	-	-	36	-
Garimella et al., 2021a [30]	11	Retro	30 ± 4.95	< 100 pg/ml	24.6 ± 2.5	-	-	59.3 ± 22.61	7	-	-	3	-	9.57 ± 1.58
Garimella et al., 2021b [30]	86	Retro	32.1 ± 4.4	100–200 pg/ml	25.71 ± 3.72	-	-	161.48 ± 25.61	56	-	-	12	-	9.89 ± 1.51
Garimella et al., 2021c [30]	160	Retro	31.7 ± 3.99	200–300 pg/ml	26.01 ± 3.70	-	-	253.38 ± 28.16	104	-	-	21	-	9.66 ± 1.42
Garimella et al., 2021d [30]	153	Retro	31.9 ± 3.71	300–400 pg/ml	26.72 ± 3.72	-	-	343.49 ± 27.83	90	-	-	21	-	9.39 ± 1.3
Garimella et al., 2021e [30]	67	Retro	31.3 ± 3.76	400–500 pg/ml	26.03 ± 3.32	-	-	441.9 ± 29.4	44	-	-	9	-	9.44 ± 1.23
Garimella et al., 2021f [30]	32	Retro	32.3 ± 4.4	> 500 pg/ml	27.56 ± 4.07	-	-	593.18 ± 97.6	17	-	-	13	-	9.43 ± 0.73
Mackens et al., 2020a [31]	124	Retro	31.0 ± 5.3	52–144 pg/ml	25.9 ± 5.0	-	14.0 ± 7.5	-	-	-	-	-	31	8.3 ± 1.7
Mackens et al., 2020b [31]	977	Retro	32.3 ± 4.6	145–438 pg/ml	25.1 ± 5.1	-	14.0 ± 9.2	-	-	-	-	-	207	8.8 ± 2.0

Table 2 (continued)

Author	N*	Design	Age	Groups	BMI	Basis FSH_IU.L	Basis LH_IU.L	Basic.E2	Clinical pregnancy	Preeclampsia	Gestational diabetes	Abortion	Live birth	Endometrium mm
Mackens et al., 2020c [31]	121	Retro	34.0 ± 5.1	439–1010 pg/ml	24.6 ± 5.0	-	13.4 ± 11.7	-	-	-	-	-	21	8.7 ± 2.1
Miao et al., 2021a [32]	126	Retro	30.7 ± 4.3	-	22.6 ± 3	-	-	115.32 ± 25.07	70	-	-	-	45	9.8 ± 1.3
Miao et al., 2021b [32]	318	Retro	31.7 ± 4.4	-	22.0 ± 3.4	-	-	224.57 ± 40.29	185	-	-	-	145	9.7 ± 1.4
Miao et al., 2021c [32]	154	Retro	31.9 ± 4.4	-	21.9 ± 2.8	-	-	357.33 ± 42.41	88	-	-	-	72	9.3 ± 1.3
Miao et al., 2021d [32]	115	Retro	32.4 ± 4.3	-	22.4 ± 3.1	-	-	604.64 ± 127.97	67	-	-	-	52	8.8 ± 1.3
Miao et al., 2021e [32]	59	Retro	32.4 ± 4.8	-	22.8 ± 3.3	-	-	1357.63 ± 373.28	33	-	-	-	21	8.7 ± 1.3

* N = sample size, Retro** = Retrospective

Table 3 Mean age, BMI and main hormones of the patients

Variable	Minimum	Maximum	Mean	Standard deviation
Age (year)	30.00	36.7	32.96	1.92
Baseline BMI	21.35	31.7	24.60	2.25
FSH (IU.L)	5.81	7.90	6.37	0.78
LH (IU.L)	3.00	14.00	6.98	5.12
E2 (pg/mL)	35.87	1749	469.07	408.33

Mean age of the patients was 23.96 with mean BMI of 24.60 kg/m^2. Mean FSH, LH and E2 was 6.37 IU.L, 6.98 IU.L and 469.07 pg/mL (Table 3).

According to Fig. 2, pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 51%, i.e. 51 out of every 100 patients experience clinical pregnancy in different levels of E2 level in which up to 200 pg/mL was the best level with 0.57 prevalence of clinical pregnancy as well as 54% for 1000–2000 pg/ml.

According to Fig. 3, pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 9%, i.e. 9 out of every 100 patients experience miscarriage in different levels of E2 level and 1000–2000 pg/mL showed less miscarriage rate (6%).

According to Fig. 4, pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 43%, i.e. 43 out of every 100 patients experience live birth in different levels of E2 level in which 200–500 pg/mL was the best level with 0.46 prevalence of live birth.

Figure 5 shows that bias publication did not have an influence on the creation of negative results, which is shown as symmetry in the funnel plot. Meanwhile, no evidence of publication bias was detected ($P=0.520$, $t=0.65$). Indeed, publication of bias due to affecting by sample size is not a powerful test.

Discussion

In this study, we examined the effects of different levels of estradiol on FET-related outcomes, because according to the results of different studies, various findings of estradiol levels have been reported, which are not consistent and required a meta-analysis to reach a pooled result. In summary, we found that pregnant women with estradiol levels up to 200 pg/mL had the highest success rates in terms of clinical pregnancy as well as 200–500 pg/mL for delivering live birth. It's important to note that these results need further confirmation through larger studies that follow women over a longer period.

In a study by Alsbjerg et al. [20] that the primary outcome was the live birth rate in relation to E2 levels, it was shown a significant association between serum E2 levels and the optimal serum E2 levels correlating with ongoing pregnancy were ≥ 292 pg/mL and < 409 pg/mL. Totally this study was about consistent with our study by the levels are different in which we found 200–500 pg/mL as premium level of live birth rate.

Lin et al. [21] revealed that there were no significant differences in obstetric complications and perinatal outcomes based on the estradiol level and they stated that the hormonal environment around implantation did not appear to be the primary cause of differences in obstetric and perinatal outcomes between the two EM preparation methods used in FET. Vyas et al. performed a study on live birth rate when estradiol levels more closely mimic physiology. In this study, negative impact of higher peak E2 on the live birth rate was found using regression. They reported serum E2 levels to 300–500 pg/mL following FET to obtain high live birth rate compared with E2 levels of < 300 pg/mL or > 500 pg/mL [22].

Vyas et al. [22] showed about same results with Alsbjerg et al. [20] reporting serum E2 levels to ≥ 292 pg/mL and < 409 pg/mL to improve live birth rate but our study suggests higher levels of E2 to improve live birth rate. Deng et al. reported different results and showed that a high serum E2 level before progesterone administration does not adversely affect the pregnancy outcomes [27]. Also, Choi et al. [28] reported results consistent with the results of Deng et al. [27] and showed that Ongoing pregnancy rate in frozen embryo transfer cycles is not negatively impacted by elevated estradiol levels but at estradiol levels > 3000 pg/mL, a statistically significant ongoing pregnancy rate was observed. This study was consistent with our results indicating more than 5000 pg/mL for E2 level to increase clinical pregnancy and live birth rate. Larger sample sizes have more powerful results to generable for others so we must focus on larger sample size of studies to make decision considering the correct methodology of the study.

Liu et al. [23] showed that all of abortions occurred in the high estradiol level group (1560.4 pg/mL) and embryo implantation rate of the ultra-high estradiol group (2420.9 pg/mL) was the highest. The pregnancy outcome of the three groups was as follows: the clinical pregnancy rate of the three groups was 37.9% in the control group, 51.8% in the high estradiol group and 40.0% in the ultra-high estradiol group shows that higher level compared to normal level resulted in high clinical pregnancy and in this regard this study was consistent with our results. Additionally, Goldman et al. [26] demonstrated the same results consistent with our study and reported that high levels of serum estradiol on the day of progesterone start may be detrimental to implantation, pregnancy, and live birth following frozen blastocyst

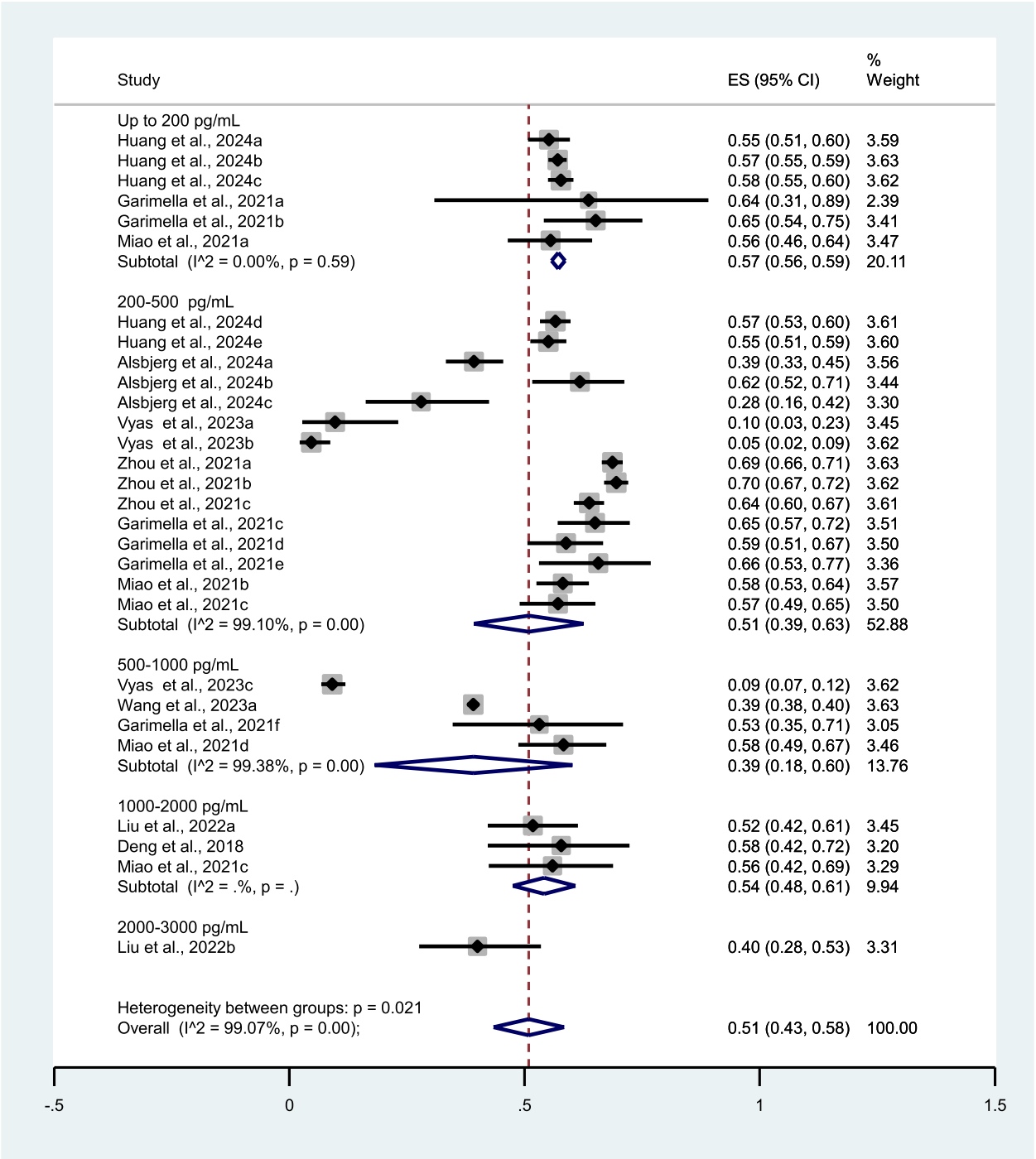

Fig. 2 Forest plot showing the clinical pregnancy rate

transfer. They showed that the estradiol with a mean of 528 pg/mL were associated with lower risks of implantation, ongoing pregnancy, and live birth compared with those with the estradiol with a mean of 212 pg/mL. Miao et al. in 2021 [32] divided the patients into 5 groups based on their estradiol level on the day of endometrial transformation as follows: Group A (< 150 pg/ml). Group B (150 ≤ estradiol < 300 pg/ml); Group C (300 ≤ estradiol < 450 pg/ml); Group D (450 ≤ estradiol < 900 pg/ml); Group E (estradiol > 900 pg/ml). They found that there

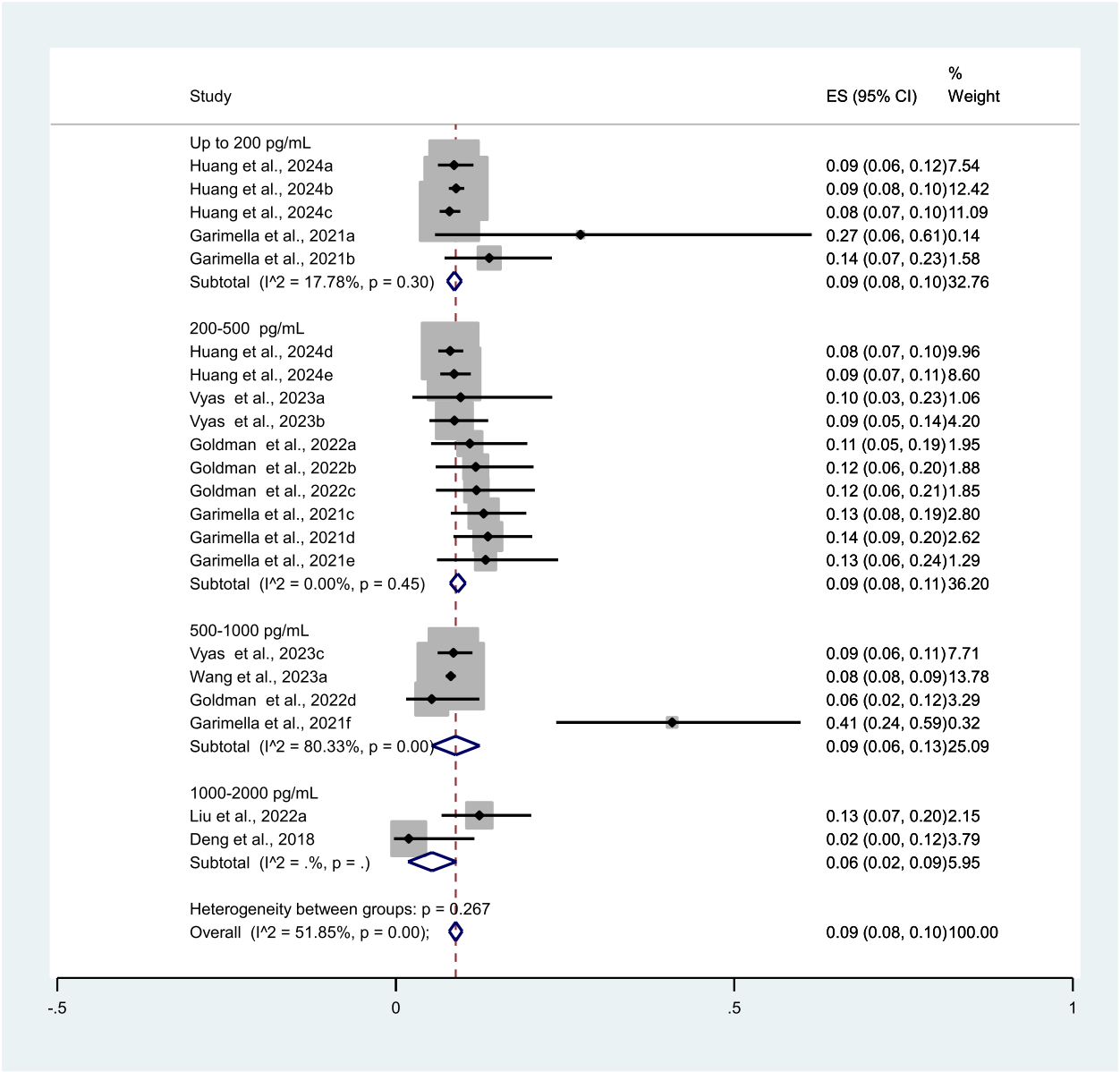

Fig. 3 Forest plot showing the miscarriage rate

were no statistically significant differences between the five groups in clinical pregnancy rates. They reported that high estradiol levels (>900 pg/mL) may be associated with first trimester abortion. Furthermore, the live birth rate was relatively high when the estradiol level was in the range of 150–900 pg/ml on the day of endometrial transformation [32]. But we found that 200–500 pg/mL was the best level of E2 with %46 prevalence of live birth. Fritz et al. in 2017 [29] indicated that average E2 levels were significantly lower in cycles resulting in patients with live birth (234.1 ± 16.6 pg/ml). Although increasing E2, decreases live birth rate. As200-500 pg/mL was the best level of E2 for higher live birth rate in our study, the results of Fritz et al. [29] is close to our results.

In a study by Garimella et al. in 2021 [30], the results showed that miscarriage rate was high when E2 was less than 100 pg/mL (28.5%) and when E2 was more than 500 pg/mL (41.1%) while we found that prevalence of miscarriage is similar in different levels (6–9%). Garimella et al. reported that clinical pregnancy did not influenced by E2 levels while our results demonstrated that up to 200 pg/mL was the best level

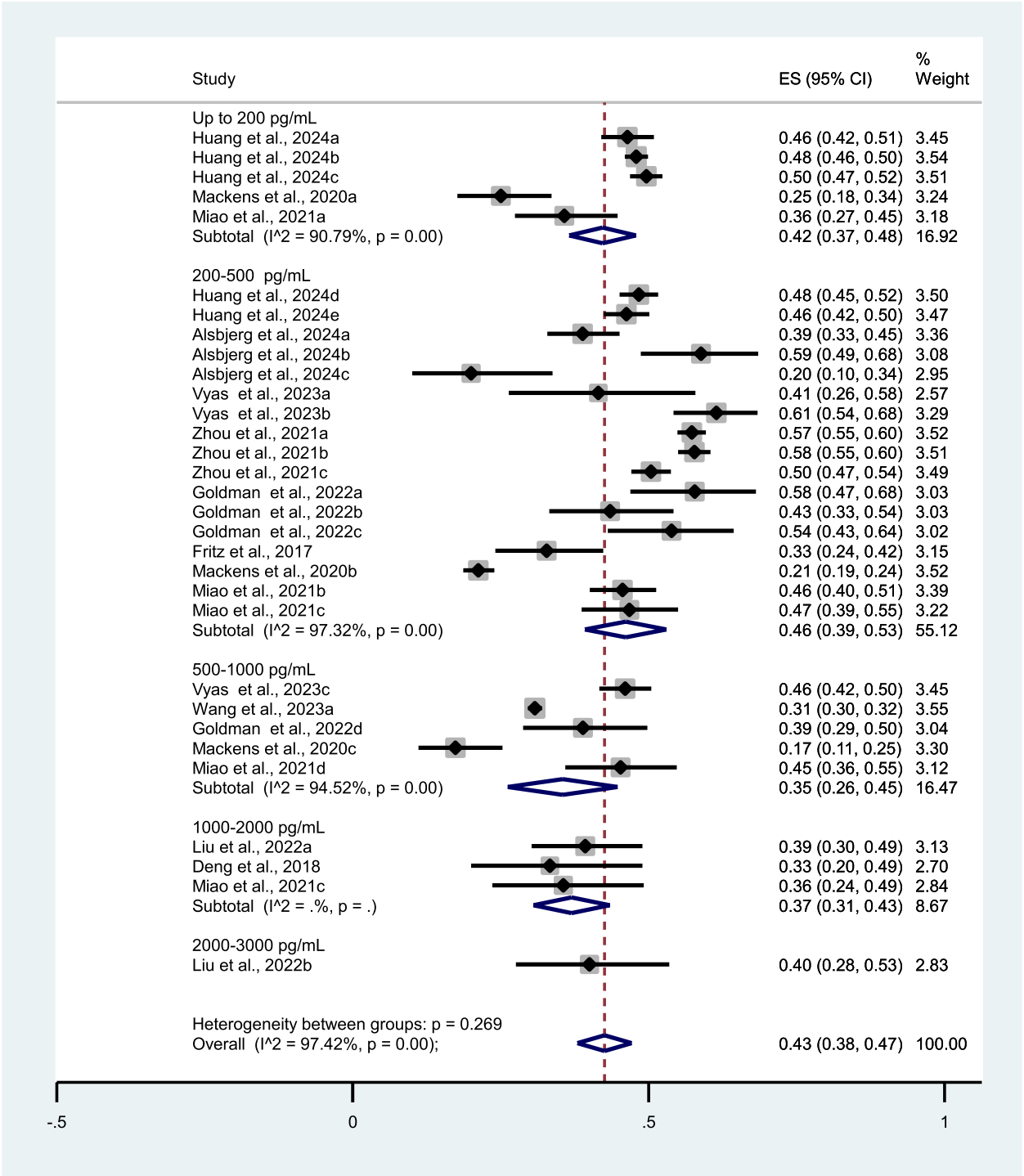

Fig. 4 Forest plot showing the live birth rate

with 0.57 prevalence of clinical pregnancy. In another study, Mackens et al. in 2020 [31] included a large sample size ($N=1222$) in three groups (E2 ≤ 144 pg/ml, 145 to 438 pg/ml and > 439 pg/ml). They reported no association between serum E2 levels and live birth rate. Finally, as we found, it is not necessary to increase E2 levels more than 500 pg/ml using supplementations. While our findings suggest optimal E2

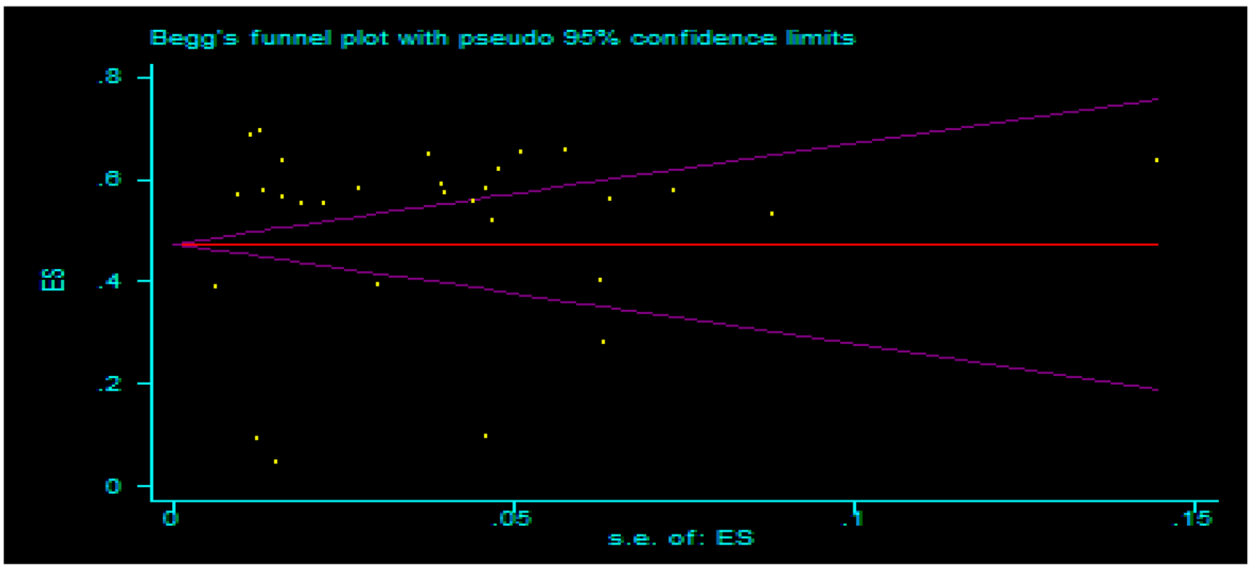

Fig. 5 Funnel plot assessing publication bias by Egger's test

ranges for different outcomes, but these results should be confirmed through prospective studies before being widely implemented in clinical practice. Long-term follow up can be performed as a long-term prospective cohort study.

Conclusion

In conclusion, the study suggests that E2 levels up to 200 pg/mL might be associated with the highest rates of clinical pregnancy (57%) and 200–500 pg/mL for live birth (46%) so we can say that E2 less than 500 pg/mL is a suitable value for pregnant. The lowest miscarriage rate (6%) was seen in the group with estradiol levels between 1000 and 2000 pg/mL. It's important to note that these findings require further confirmation with clinical trials and longitude prospective cohorts.

Authors' contributions

BNJ, FP, ME and EG prepared the primary draft by. First edition was done by SA, AZ, NN and SD. All authors helped for data extraction. Manuscript finalized by BNJ and FP both equally. All authors read and signed the final paper.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable because no primary data were collected.

Competing of interest

There is no conflict of interest in this study.

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