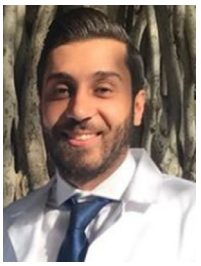
# Aspirin for Endometrial Preparation in Patients Undergoing IVF: A Systematic Review and Meta-analysis



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## ABSTRACT

**Objective:** To investigate the effect of aspirin on IVF success rates when used as an adjuvant treatment for endometrial preparation.

**Data Sources:** Relevant publications were comprehensively selected from PubMed, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to November 15, 2020.

**Study Selection:** Randomized controlled trials (RCTs) and retrospective cohort studies that used aspirin as an adjuvant treatment for endometrial preparation and reported subsequent pregnancy outcomes were included. Studies were excluded if aspirin was used before and/or during ovarian stimulation.

**Data Extraction and Synthesis:** This systematic review and meta-analysis included a total of 7 studies. Risk of bias assessment was based on the methodology and categories listed in the Cochrane Handbook for the RCTs and the Newcastle-Ottawa scale for the retrospective studies. The primary outcome was live birth rate. Summary measures were reported as odds ratios (ORs) with 95% confidence intervals (CIs). There was significant evidence that aspirin for endometrial preparation improved live birth rates (OR 1.52; 95% CI 1.15−2.00). No effect was noted for clinical pregnancy rates (OR 1.37; 95% CI 1.00−1.87); however, aspirin was associated with improved pregnancy rates in a subgroup analysis of patients receiving oocyte donation (OR 2.53; 95% CI 1.30−4.92) and in the sensitivity analysis (OR 1.3; 95% CI 1.02−1.66). No effect of aspirin was found for implantation or miscarriage rates (OR 1.31; 95% CI 0.51−3.36 and OR 0.41; 95% CI 0.02−7.42, respectively).

**Conclusion:** These findings support a beneficial effect of aspirin for endometrial preparation on IVF success rates, mainly live birth rates, outside the context of ovarian stimulation. However, this evidence is based on poor quality data and needs to be confirmed with high-quality RCTs.

**Keywords:** pregnancy; fertilization in vitro; aspirin; live birth; endometrium; embryo

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**Competing interests:** The authors declare they have nothing to disclose.

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## RÉSUMÉ

**Objectif :** Étudier l'effet de l'aspirine sur le taux de réussite de la FIV lorsqu'elle est utilisée comme traitement adjuvant pour la préparation de l'endomètre.

**Sources de données :** Les publications pertinentes publiées jusqu'au 15 novembre 2020 ont été obtenues par une recherche exhaustive dans les bases de données PubMed, Medline, Embase et Cochrane Central Register of Controlled Trials (CENTRAL).

**Sélection des études :** Les essais cliniques randomisés (ECR) et les études de cohorte rétrospectives utilisant l'aspirine comme traitement adjuvant pour la préparation de l'endomètre et faisant état des issues de grossesse subséquentes ont été inclus. Les études ont été exclues lorsque l'aspirine était utilisée avant et/ou pendant la stimulation ovarienne.

**Extraction et synthèse des données :** Cette revue systématique avec méta-analyse porte sur un total de 7 études. L'évaluation du risque de biais a été faite selon la méthodologie et les catégories énumérées dans le *Cochrane Handbook for Systematic Reviews of Interventions*, pour les ECR, et l'échelle de Newcastle-Ottawa, pour les études rétrospectives. Le critère de jugement principal était le taux de naissances vivantes. Les indicateurs synthétiques rapportés sont des rapports de cotes (RC) avec un intervalle de confiance (IC) à 95 %. Des données significatives ont révélé que l'aspirine pour la préparation de l'endomètre améliorait le taux de naissances vivantes (RC : 1,52; IC à 95 % : 1,15-2,00). Aucun effet n'a été observé sur le taux de grossesses cliniques (RC : 1,37; IC à 95 % : 1,00-1,87); cependant, l'aspirine était associée à une amélioration du taux de grossesses dans une analyse des sous-groupes de patientes avec don d'ovocytes (RC : 2,53; IC à 95 % : 1,30-4,92) et dans l'analyse de sensibilité (RC : 1,3; IC à 95 % : 1,02-1,66). L'aspirine s'est révélée n'avoir aucun effet sur les taux

d'implantation et d'avortements spontanés (RC : 1,31; IC à 95 % : 0,51-3,36 et 0,41; IC à 95 % : 0,02-7,42, respectivement).

**Conclusion :** Ces résultats soutiennent l'effet bénéfique de l'aspirine pour la préparation de l'endomètre relativement au taux de réussite de la FIV, en particulier le taux de naissances vivantes, en dehors du contexte de stimulation ovarienne. Toutefois, ces données sont fondées sur des données de faible qualité et doivent être confirmées au moyen d'ECR de qualité élevée.



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## INTRODUCTION

The probability of achieving pregnancy after in vitro fertilization (IVF) has 2 main determinants: an embryo with an implantation potential and a receptive endometrium.[1] The majority of women reach embryo transfer; however, pregnancy rates only range between 29.3% for embryos at day 3 and 44% for blastocysts at day 5.[2] Given the significant risk of miscarriage after a positive pregnancy test, the vast majority of embryos transferred into the uterine cavity fail to result in a viable pregnancy. Thus, different therapeutic modalities known as adjuvant treatments have been proposed to improve the success of IVF.

Aspirin is a medication used to reduce inflammation and prevent clotting by suppressing the production of thromboxane $A_2$ ($TXA_2$) and prostaglandins (PGs), mainly prostacyclin ($PGI_2$) and $PGE_2$.[3,4] A Cochrane review including 13 randomized controlled trials (RCTs) published in 2016 found that use of aspirin did not improve pregnancy and live birth rates.[5] Another meta-analysis of 13 RCTs published in 2017 reached a similar conclusion.[6] Multiple studies evaluating the effect of aspirin on ovarian stimulation outcomes showed that aspirin has a negative impact on oocyte and embryo quality.[7,8] However, the effect of aspirin on the endometrium seems to be favourable, as demonstrated by significantly decreased resistance of endometrial and uterine artery blood flow in patients with recurrent pregnancy loss.[9,10]

The aim of our review is to evaluate the possible benefits of using aspirin exclusively for endometrial preparation, while eliminating its possible negative effects on the oocyte/embryo. This can be determined by analyzing reports on aspirin used (1) by recipients of oocyte donation, (2) for frozen embryo transfer (FET), and (3) in fresh embryo transfer (ET) in stimulated IVF (sIVF) cycles with aspirin initiated after oocyte retrieval. Thus, in this study, we performed a systematic review and meta-analysis to evaluate the ability of aspirin to improve fertility outcomes of IVF when used exclusively as an adjuvant treatment for endometrial preparation.

## METHODS

### Data Sources and Search Strategy

No approval from an institutional review board was needed for this study because it is a systematic review and meta-analysis with no patient recruitment. We retrieved the literature without any patient interventions.

All published reports describing the use of aspirin for women undergoing embryo transfer were obtained by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, and Embase from database inception to November 15, 2020, without language restrictions. The search terms used were the following: "IVF" or "ICSI" or "ET" or "intracytoplasmic sperm injection" or "in−vitro fertilisation" or "in vitro fertilization" or "Embryo Transfer", and "aspirin" or "acetyl salicylic acid" or "acetylsalicylic" or "low−dose aspirin". Moreover, the reference list in every retrieved study was manually searched to identify potentially eligible publications. The study protocol was registered with PROSPERO: International Prospective Register of Systematic Reviews (CRD42020218724). The systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

### Eligibility Criteria

RCTs and retrospective cohort studies were included. The study population consisted of women undergoing embryo transfer after IVF for oocyte donation, FET, and fresh ET in sIVF. Low-dose aspirin (<150 mg) use was compared to placebo or no treatment. Studies were excluded if aspirin was used before or during ovarian stimulation.

### Data Collection

All collected reports were evaluated for eligibility and data abstraction by 2 independent investigators (A.M. and O. A.), and discrepancies were settled by consensus. For each study, the following data were extracted: first author's name and year of publication; country; patients included (aspirin and control); inclusion criteria; study design; aspirin dose; and day of aspirin initiation.

### Statistical Analysis

All results were merged for meta-analysis using Review Manager Version 5.3 software. For the clinical pregnancy and live birth rate, the generic inverse variance statistical

method was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were either calculated or retrieved from the reviewed article if no calculation was possible. Adjusted ORs with 95% CIs for clinical pregnancy and live birth rates were specified in 1 retrospective study[11] and thus used in the statistical analysis. Otherwise, for the implantation rate, the Mantel-Haenszel random-effects model dichotomous outcomes were summarized by calculating the OR and 95% CI. The number of participants in low-dose aspirin and control groups was entered in all forest plots. A random effect analysis model was used because different populations were included (recipients of oocyte donation, FET, and fresh ET in sIVF).

### Assessment of Risk of Bias

The risk of bias of all included studies was assessed independently (by A.M. and O.A.). Disagreements were resolved by discussion. Description of risk-of-bias categories and study design−specific assessment criteria for RCTs was assessed using the Cochrane Risk of Bias assessment tool.[12] For retrospective studies, the Newcastle-Ottawa scale was used to evaluate methodological quality.[13] A score ≥6 stars was considered high quality.

### Assessment of Heterogeneity

Statistical heterogeneity in the results of different studies was examined by inspecting the data points and CI overlap in the forest plot and statistically by checking the results of the chi-square test for heterogeneity, with $P < 0.1$ indicating significant heterogeneity, and the $I^2$ statistic.

### Subgroup Analysis and Investigation of Heterogeneity

Subgroup analysis was performed if 2 or more studies within the following subgroups were identified: recipients of oocyte donation, FET, fresh ET in sIVF, RCTs, and retrospective studies. If heterogeneity was significant, it was evaluated by performing preplanned subgroup analysis and by conducting a sensitivity analysis. An $I^2$ value above 50% was considered the cut−off for further investigation.

## RESULTS

### Characteristics of Included Studies

The search retrieved 1478 articles. After removing duplicates, 956 articles remained. A total of 932 studies were excluded on the basis of title and abstract, and 24 articles were assessed fully for eligibility. A total of 17 studies were excluded for the following reasons: initiation of aspirin before or during ovarian stimulation (n= 12)[7,14−24]; the dose of aspirin used was >150 mg (n = 1)[25]; and the absence of a control group that did not receive aspirin treatment (n = 4).[26−29] Therefore, 7 studies were included in this meta-analysis, involving a total of 15 417 women (Figure 1, online Appendix).[11,30−35] The studies were published between 1997 and 2019 and written in English. The characteristics of the included studies are listed in the Table.

### Risk of Bias in Included Studies

#### *Randomized Trials*

The process of randomization was adequate in 4 trials. Risk of selection bias owing to allocation concealment was detected in 4 reports. Only 2 studies were blinded for both patients and providers. Incomplete outcome reporting was noted in 2 trials. Outcomes stated in the materials and methods were reported in all RCTs except for 1 trial, in which the risk was deemed unclear. Finally, inclusion and exclusion criteria were clearly described and the treatment and control groups were comparable in 1 study, whereas the remaining reports provided insufficient details.

Assessment of risk of bias for the RCTs is summarized in Figures 2 and 3 (online Appendix).

#### *Retrospective Studies*

The definition and representativeness of cases, the definition of controls, the ascertainment of exposure, and the similarity between methods used for cases and controls were clear in both retrospective studies. The non-response rate in both studies was not clearly stated, and in 1 report,[32] there was no adjustment for possible confounding factors for all outcomes (Table, online Appendix).

### Effect of Aspirin Use

#### *Clinical Pregnancy Rate*

Seven studies reporting clinical pregnancy rate as an outcome were included, with a total of 15 417 participants. The pooled analysis demonstrated that low-dose aspirin use did not improve the clinical pregnancy rate compared with placebo or no treatment, despite a trend in favour of using aspirin (OR 1.37; 95% CI 1.00−1.87; $I^2 = 48\%$) (Figure 1A).

In the subgroup analysis for recipients of oocyte donation, the clinical pregnancy rate improved significantly with the use of aspirin compared to control (OR 2.53; 95% CI 1.30−4.92), with no heterogeneity between studies ($I^2 = 0\%$) (Figure 1B). However, no difference was noted between arms in terms of clinical pregnancy rate for the subgroups of FET, fresh ET in sIVF, RCTs, and retrospective studies ([OR 0.99; 95% CI 0.08−12.50, $I^2 = 82\%$], [OR 1.11; 95%

**Table. The characteristics of included studies**

| Author and year | Country | Design | Patients (no.), aspirin/control | Aspirin dose | Starting day | Inclusion criteria |
|---|---|---|---|---|---|---|
| Weckstein et al. 1997[35] | United States | RCT | 15/13 | 81 mg/d | 1 wk before endometrial preparation | Recipients of oocyte donation |
| Check et al. 1998[30] | United States | RCT | 18/18 | 81 mg/d | From cycle day 2 | FET, previous 1 failed fresh ET |
| Waldenström et al. 2004[34] | Sweden | RCT | 703/677 | 75 mg/d | From the day of ET | Fresh ET on day 3 |
| Duvan et al. 2006[31] | Turkey | RCT | 41/40 | 100 mg/d | From the day of ET | Fresh ET on day 3 |
| Frattarelli et al. 2006[32] | United States | RS | 80/380 | 81 mg/d | During recipients' cycle preparation | Oocyte donation recipients |
| Shirlow et al. 2017[11] | Australia | RS | 431/12 941 | 100 mg/d | From the day of OPU | IVF, ET |
| Madani et al. 2019[33] | Iran | RCT | 30/30 | 100 mg/d | At the time of endometrial preparation | FET |

ET: embryo transfer; FET: frozen embryo transfer; IVF: in vitro fertilization, OPU: ovum pick-up; RCT: randomized controlled trial; RS: retrospective study.

CI 0.66−1.86, $I^2$ = 38%], [OR 1.25; 95% CI 0.65−2.40, $I^2$ = 55%], and [OR 1.58; 95% CI 0.88−2.83, $I^2$ = 60%], respectively) (Figure 1C, D, E, and F). Finally, sensitivity analysis by excluding the studies at risk of bias[30,32] showed a significant increase in the clinical pregnancy rate (OR 1.3; 95% CI 1.02−1.66), with heterogeneity between studies becoming non-significant ($I^2$ = 28%; $P$ = 0.23; Figure 1G).

### *Live Birth Rate*

Five studies reporting live birth rate as an outcome were included, with a total of 15 300 participants. Pooled analysis demonstrated that low-dose aspirin use improved the live birth rate compared with placebo or no treatment (OR 1.52; 95% CI 1.15−2.00), with acceptable heterogeneity between studies ($I^2$ = 37%; $P$ = 0.17; Figure 2A).

In the subgroups of recipients of oocyte donation and retrospective studies, the live birth rate improved significantly with the use of aspirin compared to control (OR 1.85 [95% CI 1.09−3.12] and OR 1.56 [95% CI 1.19−2.04], respectively), with no heterogeneity between studies ($I^2$ = 0%; Figure 2B and D). However, in the subgroup of RCTs, no difference was noted for live birth rate, with high heterogeneity (OR 2.04; 95% CI 0.78−5.34, $I^2$ = 60%). Finally, the sensitivity analysis excluding the study at risk of bias[32] showed a significant increase in the clinical pregnancy rate (OR 1.48; 95% CI 1.06−2.06, $I^2$ = 45%; Figure 2E).

### *Implantation Rate*

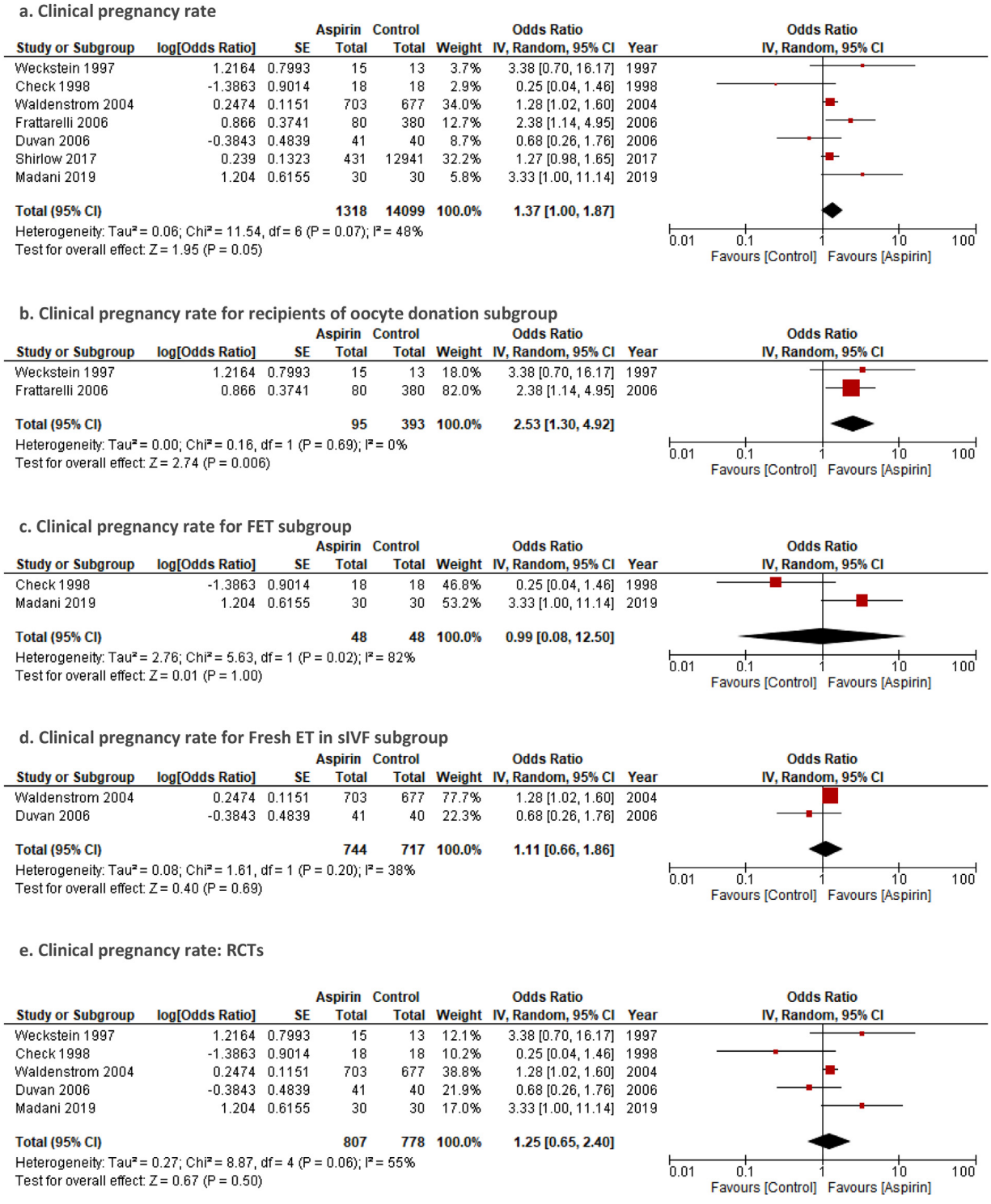
Four studies reporting implantation rate as an outcome were included. Pooled analysis demonstrated that low-dose aspirin use did not improve the implantation rate in the aspirin group compared to placebo or no treatment (OR 1.31; 95% CI 0.51−3.36), with substantial heterogeneity between studies ($I^2$ = 71%; $P$ = 0.02; Figure 3A).

In the subgroup analysis for FET, the implantation rate did not improve with the use of aspirin compared to control (OR 0.92; 95% CI 0.08−10.25), given considerable heterogeneity between studies ($I^2$ = 85%; $P$ = 0.01; Figure 3B). The sensitivity analysis excluding the study at risk of bias[30] did not show a significant difference in the implantation rate (OR 1.83; 95% CI 0.77−4.36; $I^2$ = 64%; Figure 3C).

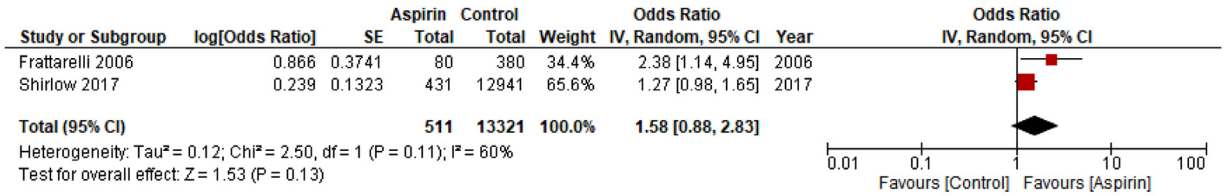
### *Miscarriage Rate*

Two studies reporting the miscarriage rate were included in the analysis. No significant difference was noted between the arms (OR 0.41; 95% CI 0.02−7.42; $I^2$ = 70%; Figure 4, online Appendix).

**Figure 1. Forest plot of comparison: Low−dose aspirin versus placebo or no treatment, outcome: a. clinical pregnancy rate, b. clinical pregnancy rate for recipients of oocyte donation subgroup, c. clinical pregnancy rate for FET subgroup, d. clinical pregnancy rate for Fresh ET in sIVF subgroup, e. clinical pregnancy rate: RCTs, f. clinical pregnancy rate: Retrospective studies, g. clinical pregnancy rate: Sensitivity analysis.**



f. Clinical pregnancy rate: Retrospective studies




g. Clinical pregnancy rate: Sensitivity analysis

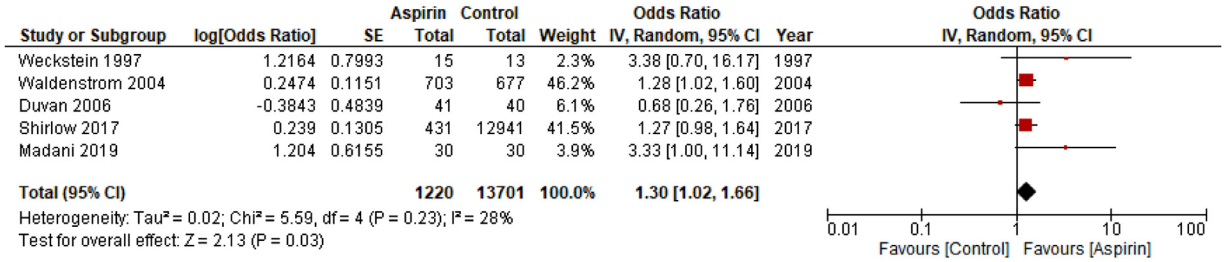



**Figure 1.** Continued

## DISCUSSION

This review included 7 studies that assessed the use of low-dose aspirin exclusively for endometrial preparation in women undergoing embryo transfer. We found significant evidence that aspirin can improve live birth rates when used for endometrial preparation. These results can be explained by the pharmacological properties of aspirin. The main role of aspirin stems from the irreversible inhibition of cyclooxygenase, which reduces the activity of $TXA_2$ and PGs.[3] This function leads to a decrease in vascular tone by preventing vasoconstriction, and thus it can improve tissue perfusion, including uterine blood flow velocity.[36] A lower dose of aspirin seemed to be more effective than higher doses, which can be explained by the fact that low doses yield a better $TXA_2/PGI_2$ ratio and hence lead to a greater reduction in vascular resistance and better perfusion.[37] The effect of aspirin on endometrial receptivity was investigated at the molecular level in female mice; aspirin significantly increased the expression of cell adhesion molecules, such as integrins and leukemia inhibitory factor, which may explain the enhanced receptivity.[38]

An optimal state of balance between proinflammatory and anti-inflammatory factors plays an essential role in implantation.[39] Aspirin, with its anti-inflammatory proprieties, might be able to counteract and modulate excessive inflammation by inhibiting chronically upregulated inflammatory pathways.[40] Aspirin has been shown to decrease the inflammatory marker high-sensitivity C-reactive protein,[41] which is associated with lower IVF success rates.[42]

The number of studies included in this review was limited, and most were at risk of bias. Furthermore, the number of patients included in the analyzed reports differed significantly across subgroups. More participants were included in retrospective studies than in RCTs, which might be a limiting factor. Moreover, the heterogeneity among studies in terms of inclusion criteria (oocyte donation, FET, and fresh ET in sIVF) and the use of different doses of aspirin are essential limiting factors. However, we tried to address these limitations by conducting subgroup and sensitivity analyses.

The quality of evidence ranges between low and moderate, which can limit the interpretation of the results. Regarding prevention of risk of bias, one strength of this review was the assessment of reports by 2 independent investigators. Nevertheless, a limiting factor was the inclusion of retrospective studies. However, the risk of bias was evaluated for both RCTs and retrospective studies using appropriate assessment tools, and a subgroup analysis for RCTs and retrospective studies was conducted. Finally, to the best of our knowledge, this is the first meta-analysis to date to investigate this specific method of aspirin use, which can change practice in fertility treatments by favouring aspirin exclusively for endometrial preparation. This meta-analysis highlights the need for more high-quality RCTs to examine this area of interest in IVF.

**Figure 2. Forest plot of comparison: Low−dose aspirin versus placebo or no treatment, outcome: a. live birth rate, b. live birth rate for recipients of oocyte donation subgroup, c. live birth rate: RCTs, d. live birth rate: Retrospective studies, e. live birth rate: Sensitivity analysis.**

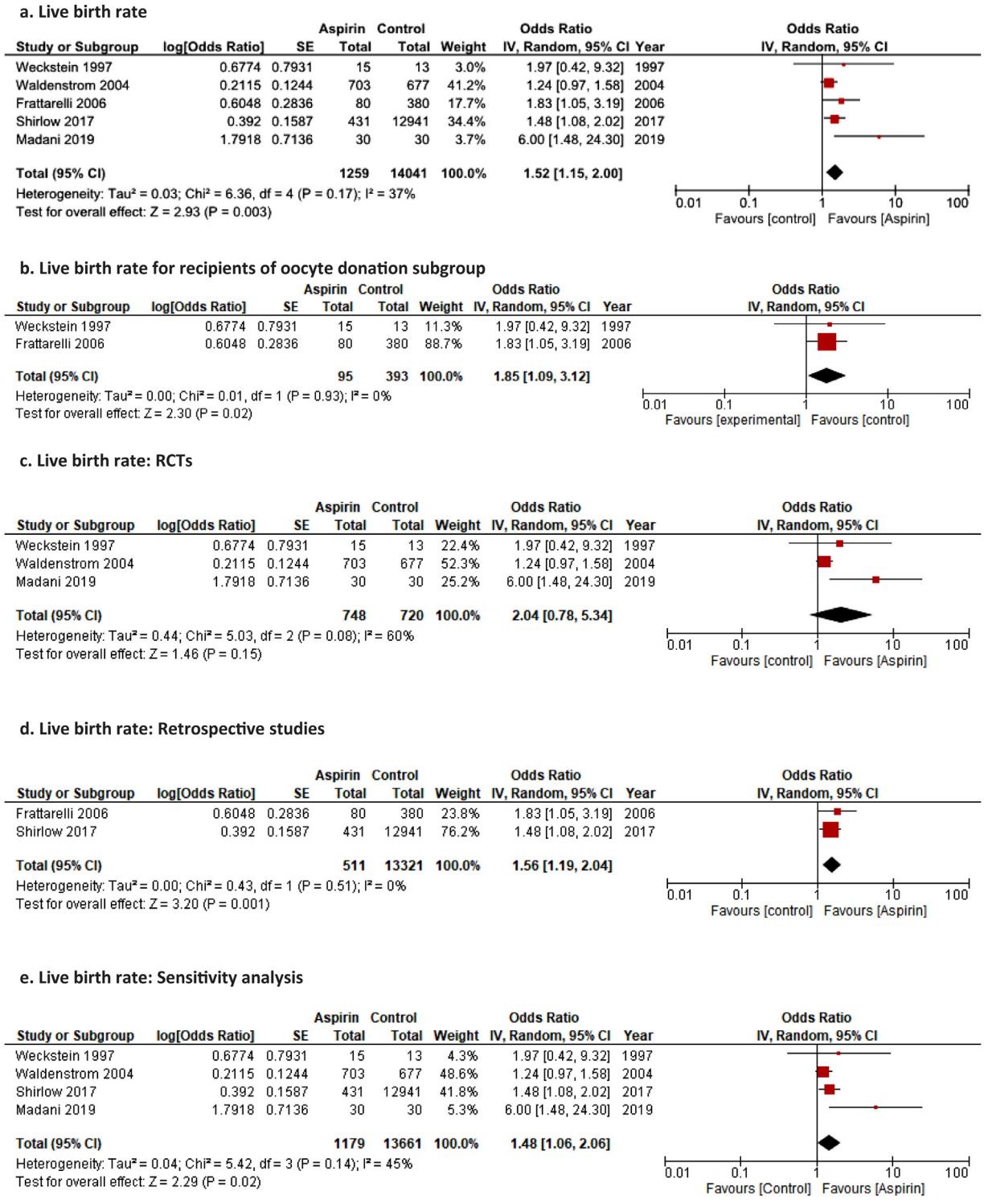
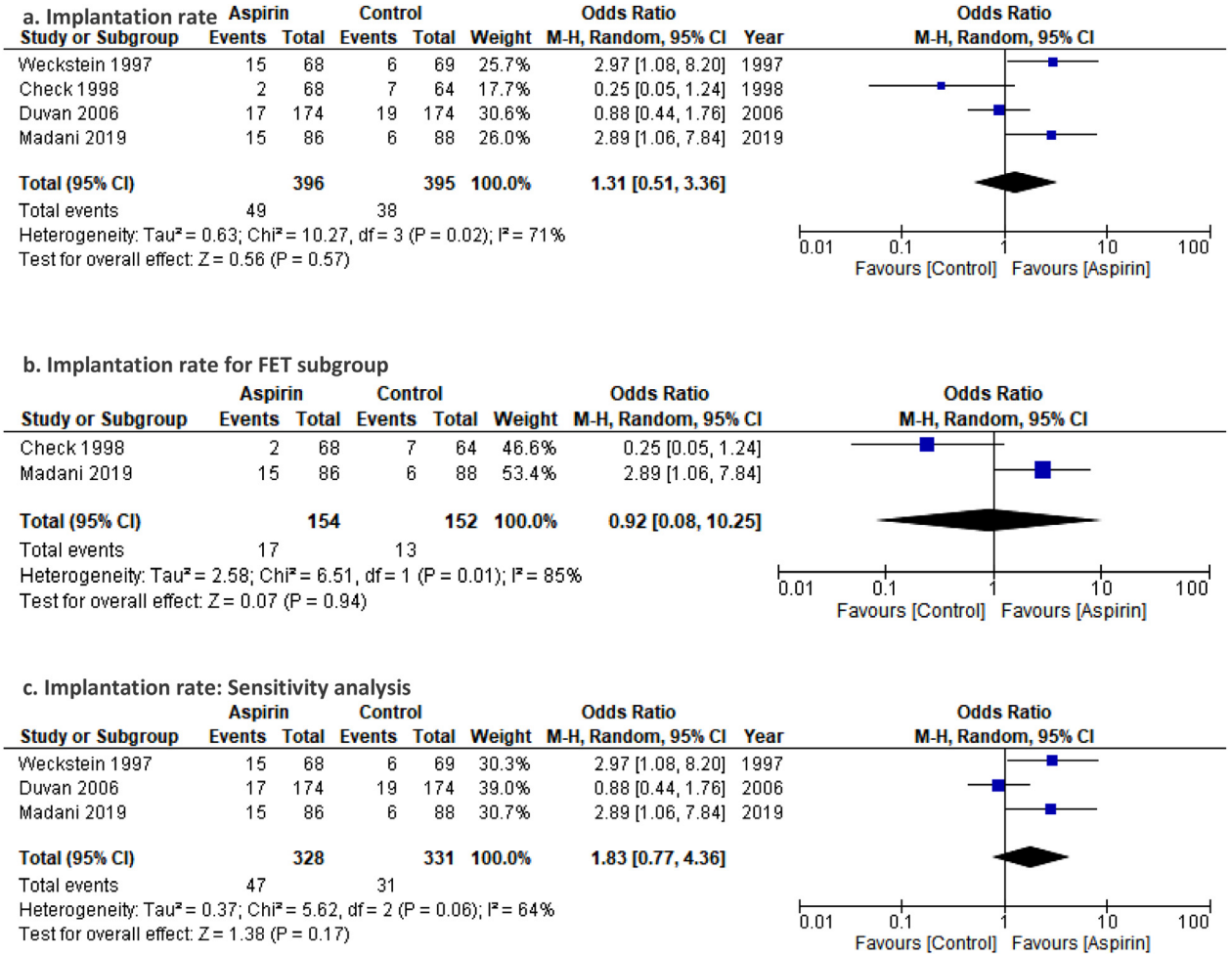


**Figure 3. Forest plot of comparison: Low–dose aspirin versus placebo or no treatment, outcome: a. implantation rate, b. implantation rate for FET subgroup, c. implantation rate: Sensitivity analysis.**




## CONCLUSION

Aspirin use exclusively for endometrial preparation without interference in ovarian stimulation seems to be beneficial for pregnancy outcomes. However, this conclusion is based on low-quality studies and needs high-quality, properly designed, adequately powered RCTs to be confirmed.

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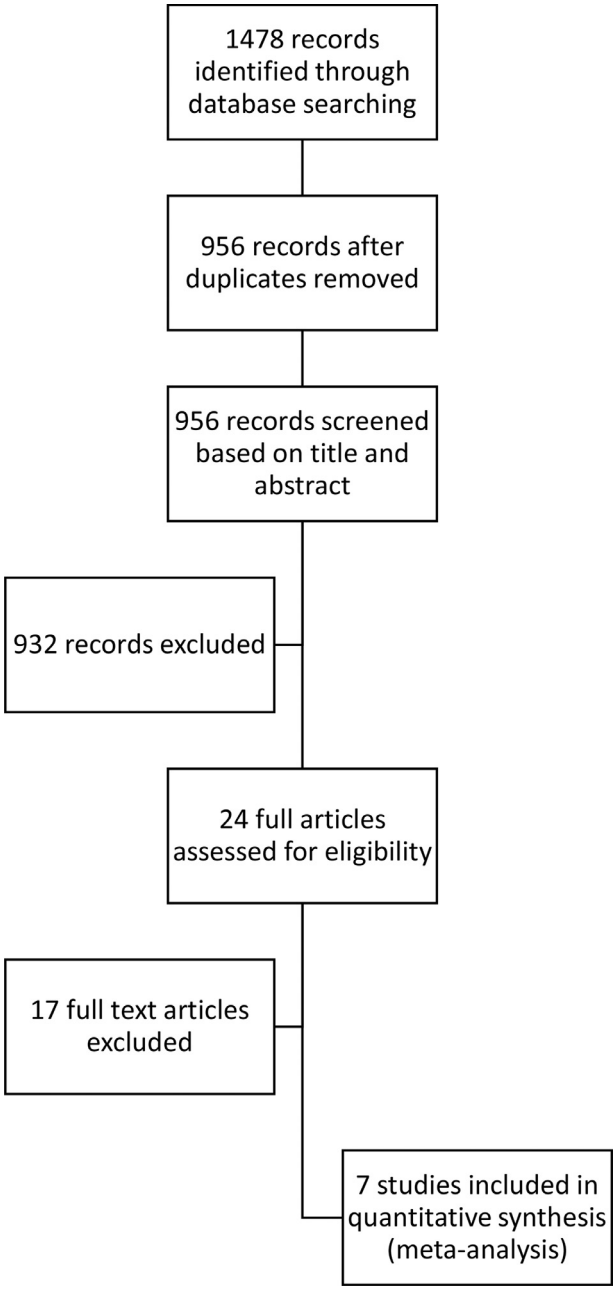
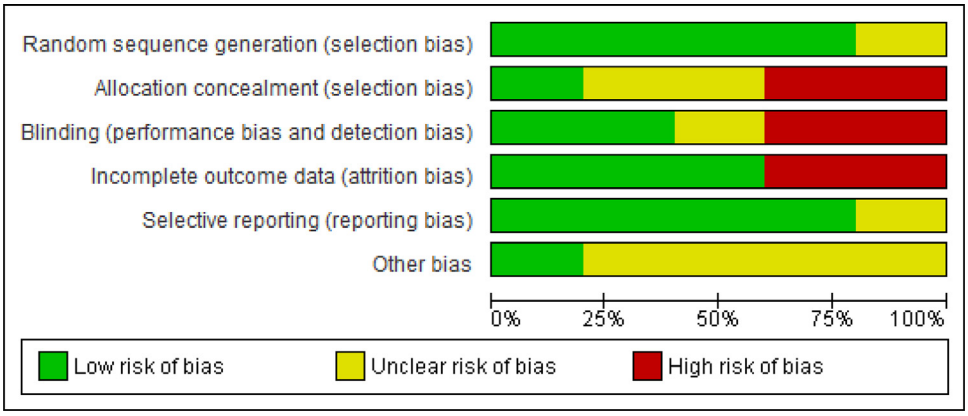
**Supplemental Table. Newcastle-Ottawa scale risk of bias summary: review authors' judgments about each risk of bias item for each included study**

| | Selection | | | Comparability | | | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Case definition adequate | Representativeness of the cases | Selection of controls | Definition of controls | Main factor | Additional factor | Ascertainment of exposure | Same method | Non-response rate | Final score |
| Frattarelli et al., 2006[32] | * | * | | * | | | * | * | | 5/9 |
| Shirlow et al., 2017[11] | * | * | * | * | * | * | * | * | | 8/9 |

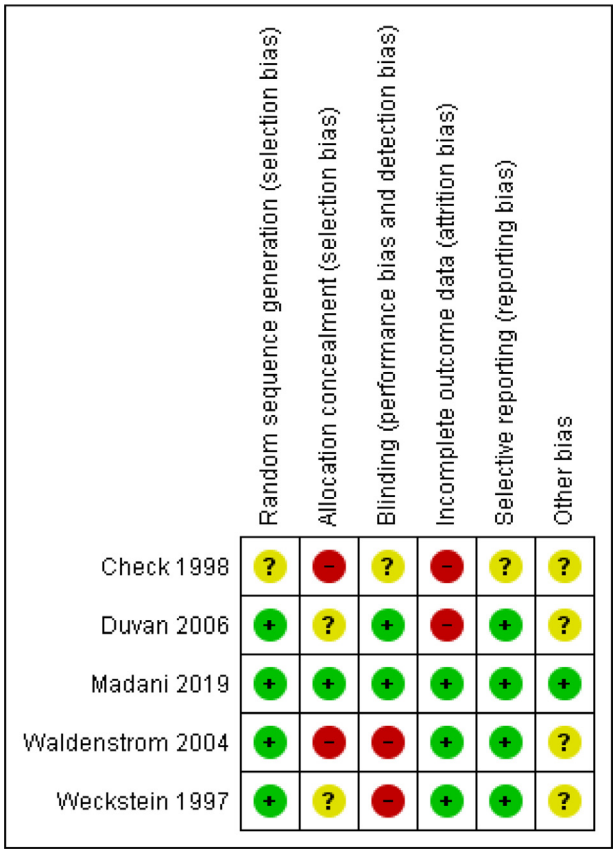
**Supplemental Figure 1. Study flow diagram.**



**Supplemental Figure 2. Risk of bias graph for randomized controlled trials. Review authors' judgments about each risk of bias item presented as percentages across all included studies.**




**Supplemental Figure 3. Risk of bias summary of the randomized controlled trials. Review authors' judgments about each risk of bias item for each included study.**




**Supplemental Figure 4. Forest plot comparison: low−dose aspirin versus placebo or no treatment. Outcome: miscarriage rate.**