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Aspirin for in vitro fertilisation (Review)

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Aspirin for in vitro fertilisation (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	9
Figure 2.	11
Figure 3.	12
Figure 4.	14
Figure 5.	14
DISCUSSION	15
AUTHORS' CONCLUSIONS	16
ACKNOWLEDGEMENTS	17
REFERENCES	18
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	46
Analysis 1.1. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 1 Live birth rate per woman or couple. .	47
Analysis 1.2. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 2 Clinical pregnancy rate per woman or couple.	48
Analysis 1.3. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 3 Ongoing pregnancy rate (beyond 12 weeks).	48
Analysis 1.4. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 4 Multiple pregnancy rate per woman per couple (on ultrasound).	48
Analysis 1.5. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 5 Multiple pregnancy rate per woman per couple at birth.	49
Analysis 1.6. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 6 Miscarriage rate per woman per couple.	49
Analysis 1.7. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 7 Complications during pregnancy per woman per couple - ectopic pregnancy.	49
Analysis 1.8. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 8 Complications during pregnancy per woman/per couple/vaginal bleeding during pregnancy.	50
Analysis 1.9. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 9 Clinical pregnancy rate - subgroup analysis - timing of treatment.	50
Analysis 1.10. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 10 Clinical pregnancy rate - sensitivity analysis.	51
APPENDICES	51
WHAT'S NEW	53
HISTORY	54
CONTRIBUTIONS OF AUTHORS	54
DECLARATIONS OF INTEREST	54
SOURCES OF SUPPORT	54
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	55
NOTES	55
INDEX TERMS	55

[Intervention Review]

Aspirin for in vitro fertilisation

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ABSTRACT

Background

Aspirin is used with the aim of optimising the chance of live birth in women undergoing assisted reproductive technology (ART), despite inconsistent evidence of its efficacy and safety (in terms of intraoperative bleeding during oocyte retrieval and risk of miscarriage). The most appropriate time to commence aspirin therapy and the length of treatment required are also still to be determined. This is the second update of the review first published in 2007.

Objectives

To evaluate the effectiveness and safety of aspirin in women undergoing ART.

Search methods

We searched the Cochrane Gynaecology and Fertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4) in the Cochrane Library (searched 9 May 2016); the databases MEDLINE (1946 to 9 May 2016) and Embase (1974 to 9 May 2016); and trial registers (ClinicalTrials.gov and the [World Health Organization International Clinical Trials Registry Platform search portal](http://www.worldhealthorganization.int/clinical-trials-registry-platform)). We also examined the reference lists of all known primary studies and review articles, citation lists of relevant publications and abstracts of major scientific meetings, combined with the Cochrane Gynaecology and Fertility Group's search strategy.

Selection criteria

Randomised controlled trials on aspirin for women undergoing ART.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted the data. The primary review outcome was live birth. Secondary outcomes included clinical pregnancy, ongoing pregnancy, multiple pregnancy, miscarriage, and other complications associated with IVF/ICSI or with pregnancy and birth. We combined data to calculate risk ratios (RRs) (for dichotomous data) and mean differences (MDs) (for continuous data) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic. We assessed the overall quality of the evidence for the main comparisons using GRADE methods.

Main results

The search identified 13 trials as eligible for inclusion in the review, including a total of 2653 participants with a mean age of 35 years. Ten studies used a dose of 100 mg and three used 80 mg of aspirin per day. In most of them, aspirin was commenced immediately at the start of down-regulation, while the duration of treatment varied widely. Eight studies provided a placebo for the control group.

There was no evidence of a difference between the aspirin group and the group receiving no treatment or placebo in rates of live birth (RR 0.91, 95% CI 0.72 to 1.15, 3 RCTs, $n = 1053$, $I^2 = 15\%$, moderate-quality evidence). In addition, clinical pregnancy rates were also similar for the two groups (RR 1.03, 95% CI 0.91 to 1.17, 10 RCTs, $n = 2142$, $I^2 = 27\%$, moderate-quality evidence); sensitivity analysis, excluding studies at high risk of bias, did not change the effect estimate. There was no evidence of a difference between groups in terms of multiple pregnancy as confirmed by ultrasound (RR 0.67, 95% CI 0.37 to 1.25, 2 RCTs, $n = 656$, $I^2 = 0\%$, low-quality evidence), miscarriage (RR 1.10, 95% CI 0.68 to 1.77, 5 RCTs, $n = 1497$, $I^2 = 0\%$, low-quality evidence), ectopic pregnancy (RR 1.86, 95% CI 0.75 to 4.63, 3 RCTs, $n = 1135$, $I^2 = 0\%$, very low quality evidence) or vaginal bleeding (RR 1.01, 95% CI 0.14 to 7.13, 1 RCT, $n = 487$, very low quality evidence). Data were lacking on other adverse effects.

The overall quality of the evidence ranged from very low to moderate; limitations were poor reporting of study methods and suspected publication bias.

Authors' conclusions

Currently there is no evidence in favour of routine use of aspirin in order to improve pregnancy rates for a general IVF population. This is based on available data from randomised controlled trials, where there is currently no evidence of an effect of aspirin on women undergoing ART, as there is no single outcome measure demonstrating a benefit with its use. Furthermore, current evidence does not exclude the possibility of adverse effects.

PLAIN LANGUAGE SUMMARY

Aspirin for women undergoing assisted reproductive technology (ART).

Review question

Cochrane researchers reviewed the evidence about the effectiveness and safety of aspirin used with the aim of increasing the chance of live birth in women undergoing assisted reproductive technology (ART).

Background

Aspirin has been commonly used in an attempt to increase the chance of live birth in women undergoing ART. However, there is contradictory evidence on the effectiveness of this treatment and on the appropriate time to commence treatment and its duration. Although physiologically aspirin exerts a beneficial effect on some aspects required for a successful pregnancy, aspirin intake has been also associated with miscarriage and vaginal bleeding. It was, therefore, important to evaluate current evidence on the effectiveness of this treatment.

Study characteristics

We found 13 randomised controlled trials with parallel groups, comparing aspirin with placebo or no treatment in a total of 2653 women undergoing ART. Studies were conducted in the USA and a variety of countries in Europe and Asia. One of the included trials was partly funded by a pharmaceutical company relevant to the intervention. In most of the studies, groups were comparable and the mean age of participants in both groups was 32 years. An identical dose of the intervention was administered in most of the studies and most reported a similar timing of the initiation of aspirin intake. The duration of trial varied across the studies, but was sufficient to provide data on the reported outcomes as respectively investigated by each group. The evidence is current to 9 May 2016.

Key results

There was no evidence of a difference between the groups in rates of live birth, clinical pregnancy, ectopic pregnancy, multiple pregnancy, miscarriage or vaginal bleeding. The number of studies was limited and the quality of the evidence ranged from very low to moderate, while data on complication rates, either during the IVF/ICSI procedure or during pregnancy and childbirth were either very limited or missing. At this second update we were not able to add new data from additional studies, as we found no new RCTs reporting on these outcomes in the prespecified comparisons. Based on the available evidence, we reached the same conclusion as the initial version of the review: no single outcome measure demonstrated a benefit with the use of aspirin. Currently, there is no evidence to support the use of aspirin treatment in order to improve pregnancy rates for a general IVF population.

Quality of the evidence

The evidence was of moderate quality for live birth and of very low to moderate quality for other outcomes. The main limitations of the evidence were poor reporting of study methods, publication bias and lack of studies investigating the desired outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Low-dose aspirin compared to placebo or no treatment for women undergoing ART

Low-dose aspirin compared to placebo or no treatment for women undergoing ART

Population: Women with subfertility
Settings: Fertility clinics
Intervention: Low-dose aspirin
Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no treatment	Low-dose aspirin				
Live birth	225 per 1000	204 per 1000 (162 to 258)	RR 0.91 (0.72 to 1.15)	1053 (3 studies)	⊕⊕⊕⊖ moderate ¹	
Clinical pregnancy	337 per 1000	347 per 1000 (307 to 395)	RR 1.03 (0.91 to 1.17)	2142 (10 studies)	⊕⊕⊕⊖ moderate ²	
Multiple pregnancy (on ultrasound)	84 per 1000	56 per 1000 (31 to 105)	RR 0.67 (0.37 to 1.25)	656 (2 studies)	⊕⊕⊖⊖ low ⁴	
Miscarriage rate per woman	43 per 1000	47 per 1000 (29 to 76)	RR 1.1 (0.68 to 1.77)	1497 (5 studies)	⊕⊕⊖⊖ low ³	
Ectopic pregnancy	12 per 1000	23 per 1000 (9 to 56)	RR 1.86 (0.75 to 4.63)	1135 (3 studies)	⊕⊖⊖⊖ very low ⁵	
Vaginal bleeding	8 per 1000	8 per 1000 (1 to 58)	RR 1.01 (0.14 to 7.13)	487 (1 study)	⊕⊖⊖⊖ very low ⁶	
Other adverse events	Other adverse events (such as preterm birth, antepartum haemorrhage, need for operative delivery) were not reported in the included studies					

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 Downgraded one level for serious imprecision with low event rate. Confidence interval compatible with no effect from the intervention or with clinically meaningful benefit in the control group.
- 2 Downgraded one level for serious risk of bias: half of the studies failed to report sufficient detail about study methods.
- 3 Serious imprecision with low event rate: Confidence interval compatible with no effect from the intervention or with clinically meaningful benefit in either group. Failure to report sufficient detail about study methods.
- 4 Very serious imprecision with very low event rate. Confidence interval compatible with no effect from the intervention or with clinically meaningful benefit in the intervention group.
- 5 Very serious imprecision with very low event rate. Confidence interval compatible with no effect from the intervention or with clinically meaningful benefit in either group. Serious risk of bias: failure to describe study methods in sufficient detail.
- 6 Single study. Very serious imprecision with very low event rate. Confidence interval compatible with no effect from the intervention or with clinically meaningful benefit in either group.

BACKGROUND

Description of the condition

Assisted reproduction technologies (ART), and especially in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), have allowed a high degree of intervention in the physiological course of reproduction. The potential of pregnancy requires an embryo with increased implantation potential, a receptive endometrium and highly coordinated signalling and precise crosstalk between these interlinked sides. Unfortunately, success rates remain low. The majority of women undergoing IVF reach the transfer stage with good-quality embryos available for transfer, but only a small proportion of them ever achieve a live birth. More than 85% of the embryos placed into the uterine cavity fail to give a viable pregnancy. Different medical and non-medical strategies have been proposed to prevent this.

Description of the intervention

Aspirin (acetylsalicylic acid) is widely known to reduce fever, pain and inflammation, but may cause stomach ulcers (Flower 2003). Long-term use of aspirin, even at low doses, is associated with bleeding in the digestive tract (Derry 2000). Its main method of action is the inhibition of the synthesis of prostaglandin (a chemical in the body which promotes inflammation, fever and pain) by the enzyme cyclo-oxygenase (Vane 1971); and subsequent reduction of platelet aggregation (making the blood less sticky and hence less likely to clot). There are two main types of cyclo-oxygenase: COX 1 and COX 2. COX 1-generated prostaglandins are required to maintain physiological functions (such as protection of the stomach lining, platelet aggregation) whereas COX 2 is involved in the production of an inflammatory response. Aspirin irreversibly inhibits both types, thus a single aspirin tablet can depress platelet aggregation for many days despite the short amount of time it takes for the body to break the drug down. Aspirin is broken down in the body by freeing the salicylate from the acetyl group, and salicylate may also inhibit cyclo-oxygenase.

As well as reducing fever or pain, aspirin has been used to treat or prevent other diseases including some forms of cancer (Bosetti 2002). How these effects occur is unclear, though production of COX 2 is increased in many tumours and its suppression may restrict cancer cell growth or could activate the destruction of cancer cells (Thun 2002). Aspirin is widely used in the prevention and treatment of cardiovascular disease (ISIS-3 1992); and its use has been linked to a reduction in Alzheimer's disease (Stewart 1997), again possibly by inhibiting COX 2.

How the intervention might work

Within the field of reproductive medicine, aspirin has been used to increase the weight of newborns in pregnant women with foetal growth retardation (Wallenburg 1987), to prevent recurrent unexplained foetal growth retardation (Yamaguchi 1985), and to improve placental and foetal blood flow in women with pre-eclampsia (Jouppila 1985). Historically, aspirin has also been prescribed for women who had suffered recurrent miscarriages in the past, and for women with antiphospholipid antibody syndrome (APS), in combination with heparin (Rai 1997).

The role of aspirin in women with infertility is controversial and the evidence is inconsistent (RCOG 2003). Some papers have demonstrated a beneficial effect of aspirin in women undergoing

assisted conception (Rubinstein 1999); whilst others have not (Urman 2000). Proposed benefits of aspirin include improvement in uterine and ovarian blood flow (Rubinstein 1999); and inhibition of platelet cyclo-oxygenase, thus inhibiting thromboxane synthesis and so preventing thrombosis in the placental vasculature. It may also be a potent stimulator of interleukin-3 (IL-3) in low doses through its ability to raise leukotriene production (proteins associated with pregnancy success) (Fishman 1995). However, the pre-conceptual use of aspirin has been associated with increased miscarriage rates in retrospective studies (Li 2003). As aspirin is thought to increase endometrial thickness, which is purported to increase implantation rates, aspirin therapy is often used to support intracytoplasmic sperm injection treatment cycles in addition to traditional IVF.

The anti-platelet effect of aspirin lasts for about seven days after discontinuation and so consideration to excessive bleeding risk at the egg collection stage should be given, especially for empirical reasons. For women who are on anticoagulants for genuine reasons such as proven thrombophilias, previous thrombo-embolic events and cardiac patients (Fatemi 2013), a bridging plan should be established with their haematologist so as to minimise bleeding risk at egg collection versus thrombotic risk from their predisposed state and the hyperoestrogenic — and so hypercoagulable — state induced by the gonadotrophins used in assisted conception.

If indicated at all, when aspirin should be prescribed in an IVF treatment cycle is unclear. Possible times are: during down-regulation of the woman's own reproductive hormones; before administration of drugs to stimulate ovulation; after egg collection; or after confirmation of pregnancy either by a pregnancy test or when confirmed by ultrasound. Also unclear is when aspirin should be stopped, for example after 12 weeks gestation, at 34 weeks or at delivery.

Why it is important to do this review

Couples may feel desperate enough to try anything that may help in assisted conception. They may be aware of the use of aspirin in some assisted conception units but may also have heard of the association between aspirin use and risk of miscarriage and bleeding. It is essential that any medically prescribed drug is fully tested under rigorous trial conditions so that the potential benefits and risks are clear to both clinicians and the couples undergoing assisted conception treatment cycles. We updated a systematic review of the randomised controlled trial evidence on the use of aspirin in assisted conception. We intend that this will help guide both healthcare providers and consumers in their decision-making processes.

OBJECTIVES

To evaluate the effectiveness and safety of aspirin in women undergoing ART.

METHODS

Criteria for considering studies for this review

Types of studies

All parallel-design randomised controlled trials (RCTs), published or unpublished, which addressed the objectives of the review. Non-randomised and quasi-randomised trials were excluded as they

are not randomised and are therefore more prone to bias. From crossover trials, only data from the first phase were included in meta-analyses.

Types of participants

Women undergoing in vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI), or both, and their partners.

Types of interventions

Aspirin, versus placebo, any other active intervention or no treatment, taken either pre-conceptually or at different stages of the treatment cycle (for example during down-regulation, during stimulation of ovulation, after oocyte collection or after confirmation of pregnancy by a pregnancy test or ultrasound). Aspirin treatment given for varying lengths of time was considered (for example up to different points in the treatment cycle; until confirmation of pregnancy; up to 12 weeks' gestation, 34 weeks' gestation or delivery). We defined low dose as a dose of 150 mg or less taken once per day. Trials reporting on the synchronous use of aspirin with any other treatment were excluded from the review.

Types of outcome measures

These were divided into primary and secondary outcomes.

Primary outcomes

Live birth rate (defined as delivery of a live foetus after 20 completed weeks of gestational age) per woman or couple randomised.

Secondary outcomes

1. Clinical pregnancy rate (confirmed by ultrasound at seven gestational weeks) per woman or couple randomised.
2. Ongoing pregnancy rate (number of pregnancies which continued beyond 12 gestational weeks) per woman or couple randomised.
3. Multiple pregnancy rate per woman or couple:
 - (a) confirmed by ultrasound;
 - (b) on delivery.
4. Miscarriage rate (confirmed by ultrasound and pregnancy test, or histology) per woman or couple randomised.
5. Complications with the IVF or ICSI procedure:
 - (a) intra-operative haemorrhage (bleeding);
 - (b) vaginal or pelvic haematoma (painful swelling caused by the collection of blood between tissues);
 - (c) hospital admission;
 - (d) blood transfusion;
 - (e) ovarian hyperstimulation syndrome;
 - (f) gastritis (inflammation of the stomach lining);
 - (g) haematemesis (vomiting blood).
6. Gestational age of baby.
7. Complications during pregnancy or birth:
 - (a) threatened miscarriage;
 - (b) antepartum haemorrhage (bleeding during late pregnancy);
 - (c) need for operative delivery;
 - (d) postpartum haemorrhage (bleeding after delivery);
 - (e) ectopic pregnancy;

(f) preterm birth.

Search methods for identification of studies

We searched for all published and unpublished RCTs on aspirin in ART, without language restriction and in consultation with the Gynaecology and Fertility Group Information Specialist.

Electronic searches

All reports which appeared to describe RCTs of aspirin for women undergoing IVF were obtained using the following search strategies (from the inception of the databases to 9 May 2016):

- (1) The Cochrane Gynaecology and Fertility Group Specialised Register of controlled trials was searched for any trials ([Appendix 1](#)).
- (2) The Cochrane Central Register of Controlled Trials (CENTRAL CRSO) was searched in all fields ([Appendix 2](#)).
- (3) The electronic databases MEDLINE ([Appendix 3](#)), Embase ([Appendix 4](#)), and PsycINFO ([Appendix 5](#)) were searched using search terms that included "(aspirin OR acetylsalicylic acid) AND (in-vitro fertilisation OR intracytoplasmic sperm injection)". The MEDLINE search was combined with the Cochrane Menstrual Disorders and Subfertility Group's Highly Sensitive Search Strategy for identifying randomised controlled trials which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.0.2 chapter 6, 6.4.11).
- (4) Published or ongoing trials in the trial registers for ongoing and registered trials: 'ClinicalTrials.gov', a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home) and www.controlled-trials.com, as well as the World Health Organization International Trials Registry Platform search portal (who.int/trialsearch/Default.aspx) ([Appendix 6](#)).

The latest search was run on 9 May 2016. All searches have been date limited from 1 January 2014 to 9 May 2016, following the same search strategy as mentioned above.

Searching other resources

The citation lists of any relevant publications identified (including review articles and included studies) were searched for further potentially eligible studies; as were articles in books identified through the citation lists of any relevant publications together with internal reports and conference proceedings.

Data collection and analysis

Selection of studies

During the update of this review, the search was largely supported by the Gynaecology and Fertility Group Information Specialist. C Siristatidis and P Vogiatzi independently selected trials among all potentially eligible studies and disagreements were resolved by discussion. The same two authors independently examined these full-text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the update of the review. Further information was sought from the authors of studies where insufficient information was included in the papers to make a decision about eligibility; e-mails were sent seeking the necessary clarifications. In order to allow an intention-to-treat analysis for binary outcome measures, data were sought on the number of participants with each outcome event by allocated

treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up.

During the initial version, from the trials identified by the above search strategies, V Poustie and A Drakeley independently selected trials which were eligible for inclusion based on the criteria for considering studies for the review (as detailed above). Disagreements were resolved by discussion or through arbitration by S Dodd. As a large number of studies were identified, V Poustie and A Drakeley independently screened the titles and discarded those studies that were clearly ineligible. The abstracts of the remaining studies were reviewed independently by V Poustie and A Drakeley. The full papers of any studies which appeared to be eligible, or for which we could not confirm eligibility, were obtained and reviewed independently. Further information was sought from the authors of studies where insufficient information was included in the papers to make a decision about eligibility. During the current update of the review, the same strategy was followed, performed by C Siristatidis and P Vogiati.

Data extraction and management

Data were extracted independently by C Siristatidis and P Vogiati using a data extraction form designed and pilot-tested by the authors and disagreements between the two aforementioned authors were resolved by consensus with G Basios. Where studies had multiple publications, the authors collated multiple reports of the same study, so that each study rather than each report is the unit of interest in the review, and such studies have a single study ID with multiple references. We sought additional information on trial methodology or actual original trial data from the principal author of trials which appeared to meet the eligibility criteria when aspects of methodology were unclear, or where the data were unpublished or in a form unsuitable for meta-analysis. The following quality criteria and methodological details are presented in the table '[Characteristics of included studies](#)' and help provide a context for discussing the reliability of the results.

Analysis was carried out using Review Manager 5 software.

Where rates were reported, such that women may be counted more than once (for example 'per embryo transfer' or 'per cycle'), or reporting in percentages, rates 'per woman or couple' were calculated and reported if sufficient data were available, either extracted from papers or obtained from the trial authors. Binary outcome measures for each study were expressed and pooled using relative risks (RR) with 95% confidence intervals (CI). We presented relative risks in preference to odds ratios (OR) as they are more easily understood where event rates are high, as may have been the case in these studies.

Assessment of risk of bias in included studies

The risk of bias of all studies that were deemed eligible for the review was assessed independently by C Siristatidis and G Basios.

The Cochrane 'Risk of bias' assessment tool (handbook.cochrane.org) was used to assess: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias. Disagreements were resolved by discussion. All

judgements were fully described and presented in the conclusions through the 'Risk of bias' table.

Measures of treatment effect

Risk ratios (RR) and 95% confidence intervals (CIs) were calculated for all outcomes.

Unit of analysis issues

The primary analysis was per woman/couple randomised. Multiple live births (e.g. twins or triplets) were counted as one live birth event.

Only first-phase data from crossover trials were included.

Dealing with missing data

Only the available data were analysed. In the cases that missing data were considered significant, the original investigators were contacted by e-mail to request missing data or information. Live births were assumed not to have occurred in participants without a reported outcome. For other outcomes, we analysed only the available data.

Assessment of heterogeneity

Statistical heterogeneity between the results of different studies was examined by inspecting the scatter in the data points and the overlap in their confidence intervals in the forest plot and, more formally, by checking the results of the Chi² test for heterogeneity and the I² statistic.

Assessment of reporting biases

Funnel plots were used to explore the possibility of small study effects. A funnel plot was not presented due to the small number of studies reporting the primary outcome.

Data synthesis

Low-dose aspirin was compared to placebo or no treatment and data for each outcome were pooled using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If sufficient studies had been identified (five or more), we would have performed subgroup analyses on the results to look at the possible contribution of:

1. Differences in duration and timing of treatment.
2. Couples with/without infertility.
3. Aspirin dose – higher or lower than 150 mg.

If heterogeneity was evident, it was investigated by carrying out the pre-planned subgroup and sensitivity analyses stated below. If unexplained heterogeneity remained, it was incorporated by using random-effects modelling. An I² value greater than 50% was predefined as the cut-off for further exploration.

Exploratory subgroup analyses were undertaken to assess the effect of timing of treatment (started pre-conceptually or at first confirmation of pregnancy). Further subgroup analysis would have been undertaken to assess the effects of duration of treatment, had sufficient studies been identified to allow this.

Sensitivity analysis

If sufficient studies had been identified (five or more), we intended to perform sensitivity analysis to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis, according to study risk of bias, including only studies at low risk of bias related to:

- (1) sequence generation;
- (2) allocation concealment;
- (3) loss to follow-up;
- (4) blinding.

Overall quality of the body of evidence: Summary of findings table

For the assessment of the quality of evidence we prepared a 'Summary of findings' table using GRADEpro and Cochrane methods. This table evaluated the overall quality of the body of evidence for the main review outcomes (live birth, clinical pregnancy, multiple pregnancy, miscarriage, ectopic pregnancy, vaginal bleeding and other adverse events) for the main review

comparison. We assessed the quality of the evidence using GRADE criteria. Two review authors (C Siristatidis and P Vagiati) independently conducted judgements about evidence quality, and resolved disagreements by discussion. Judgements were justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The search retrieved 1450 articles. Eighty-six studies were potentially eligible and were retrieved in full text. Fifty-six studies met our inclusion criteria. We excluded 41 studies, there were no studies awaiting further assessment and two studies are ongoing. Complete characteristics of the studies can be found in the respective tables, [Characteristics of included studies](#), [Characteristics of excluded studies](#), [Characteristics of ongoing studies](#), while a complete flow diagram of study selection process is presented in [Figure 1](#).

Figure 1. Study flow diagram

Included studies

Thirteen studies involving a total of 2653 women met the criteria for inclusion in the review (Bordes 2003; Check 1998; Dirckx 2009; Duvan 2006; Haapsamo 2010; Hung Lok 2004; Lambers 2009a; Lentini 2003; Moini 2007; Pakilla 2005; Rubinstein 1997-1999; Urman 2000; Van Dooren 2004).

Study design and setting

Thirteen RCTs were included, with parallel groups. Studies were conducted in ART clinics in the USA, the Netherlands, Finland, France, Belgium, Turkey, Iran and Hong Kong; four studies did not report the setting of the trial (Lentini 2003; Rubinstein 1997-1999; Urman 2000; Van Dooren 2004). Three studies were large: one included 487 participants (Haapsamo 2010), another 374 participants (Pakilla 2005), one 300 (Urman 2000) and one 298 participants (Rubinstein 1997-1999).

The other studies were smaller, including 36 (Check 1998), 84 (Lentini 2003), 62 (Hung Lok 2004), 138 (Bordes 2003), 145 (Moini 2007), 169 (Lambers 2009a), 170 (Van Dooren 2004), 193 (Dirckx 2009) and 197 (Duvan 2006) participants, respectively. One trial was partly funded by a pharmaceutical company that produces aspirin (Haapsamo 2010).

Participants

In most of the studies, the mean age of participants in both groups was 32 years. Two studies did not state the age of the participants (Bordes 2003; Check 1998). One study (Van Dooren 2004) described the overall age of study participants regardless of group allocation (median of 32 years, range 22 to 44 years).

Cause and duration of subfertility was not described in three of the studies (Bordes 2003; Check 1998; Lentini 2003).

Four studies stated whether the participants had previously undergone IVF or ICSI treatment. In one, 56.7% of the treatment group had undergone previous treatment, as had 60% of the control group (Hung Lok 2004); and in another the rates were reported as 40% and 42%, respectively (Haapsamo 2010). All participants in the third and fourth studies had previously undergone IVF treatment (Check 1998; Lambers 2009a).

One study involved only women undergoing their first IVF or ICSI cycle (Van Dooren 2004), ICSI cycle only (Duvan 2006), and one undergoing either their first or second IVF or ICSI cycle (Dirckx 2009).

Interventions

Ten studies used a dose of 100 mg of aspirin per day (Bordes 2003; Dirckx 2009; Duvan 2006; Haapsamo 2010; Lambers 2009a; Lentini 2003; Moini 2007; Pakilla 2005; Rubinstein 1997-1999; Van Dooren 2004); two used 80 mg per day (Hung Lok 2004; Urman 2000); and in one the dose was 81 mg per day (Check 1998). In most of the studies aspirin was commenced immediately at the start of down-regulation of the women's own reproductive hormones, or a short time before down-regulation. The exception was a study commenced with frozen embryo cycles, where aspirin intake was initiated on the second day of the frozen cycle (Check 1998); while in another study, aspirin intake was initiated at the day of embryo transfer (Duvan 2006). Eight studies provided a placebo for the control group (Bordes 2003; Haapsamo 2010; Hung Lok 2004; Lambers 2009a; Moini 2007; Pakilla 2005; Rubinstein 1997-1999; Van

Dooren 2004). Duration of treatment varied from study to study and according to whether pregnancy was achieved. In one study aspirin was stopped prior to egg collection (Hung Lok 2004). In the other studies aspirin was continued in women with a positive pregnancy outcome until the pregnancy was confirmed (Dirckx 2009; Duvan 2006; Urman 2000); for 10 weeks after embryo transfer (Van Dooren 2004); until the pregnancy reached 12 weeks (Lambers 2009a; Rubinstein 1997-1999) or for the duration of the pregnancy (Check 1998; Haapsamo 2010; Pakilla 2005). The remaining studies did not state the duration of the aspirin treatment (Bordes 2003; Lentini 2003; Moini 2007).

Outcomes

Only three studies provided data on live birth rate per woman or couple (Dirckx 2009; Haapsamo 2010; Pakilla 2005). All studies provided data on clinical pregnancy rate per woman or couple, except from one that provided data per embryo transfer (Moini 2007), and another two that gave data as percentages (Bordes 2003; Lentini 2003).

Five studies provided data on chemical pregnancy rate (Check 1998; Haapsamo 2010; Lentini 2003; Rubinstein 1997-1999; Urman 2000). However, only two provided the data as per woman or couple (Haapsamo 2010; Lentini 2003); the remainder presented data as per embryo transferred. Multiple pregnancy rate was presented in four studies (Dirckx 2009; Haapsamo 2010; Lambers 2009a; Rubinstein 1997-1999); and miscarriage rate was presented in five studies (Dirckx 2009; Haapsamo 2010; Lambers 2009a; Pakilla 2005; Urman 2000). Only three studies provided details of any complications during the pregnancies by presenting ectopic pregnancy rate (Haapsamo 2010; Pakilla 2005; Urman 2000); and only one by presenting hypertensive complications, vaginal bleeding, intrauterine growth restriction in singletons and blood loss at delivery (Haapsamo 2010). One study reported incidence of ovarian hyperstimulation syndrome (Moini 2007).

All other outcomes relevant to this review were either not investigated or not reported.

Excluded studies

Forty-one studies were excluded from the review. Twelve of these investigated the use of aspirin alongside prednisone, heparin or terbutaline therapy (Geva 2000; Grandone 2014; Guan 2007; Hanevik 2012; Mollo 2002; Revelli 2008; Sher 1994; Stern 2001; Stern 2003; Strehler 2002; Ubaldi 2002; Zhu 2013), thirteen were not randomised studies (Akhtar 2013; Frattarelli 2008; Gizzo 2014; Hatasaka 2000; Hurst 2005; Kuo 1997; Kutteh 1997; Sher 1998; Stoval 1999; Villani 2015; Wada 1994; Wallace 2003; Ying 2012), four were quasi-randomised, while in two studies participants were allocated to treatment group according to which day of the week they attended the clinic (Waldenström 2004); or on a weekly basis (Pergolini 2013). In another two, allocation was based on the paired or unpaired status of participants' social security number (Várnagy 2010; Weckstein 1997). Rabiee 2011 compared different regimens of aspirin in IVF. Haapsamo 2009 measured uterine artery haemodynamics after aspirin treatment; Lambers 2009 described the results after a questionnaire given to participants of the original study; and two studies did not refer to IVF or ICSI (Hsieh 2000; Kosar 2011). Another study was excluded because researchers investigated the impact of low-dose aspirin on patients undergoing ovulation induction with a Chinese patent medicine and, thus, the outcomes were not relevant to IVF (Zhao 2014). Four studies

were excluded as the authors failed to respond to our request for additional information concerning their study (Matassa 2001; Madani 2014; Lee 2001; Vandana 2014); two studies were conducted in the framework of an oocyte donation programme (Rubinstein 1999; Weckstein 1997); while in Zolghadr 2011 the outcomes investigated were number of follicles, serum estradiol and ovarian size, thus greatly differing from the outcomes of this analysis.

Two ongoing studies have been registered as clinical trials: one has completed recruitment with no results published to date (Gourabi 2012), and the second was due in December 2014 (Vandana 2013); however, to date, the authors have not provided their results. The

authors of both studies have been contacted in order to provide some preliminary results to assess whether these are eligible to be included in the analysis, but no information is available to date.

Studies awaiting assessment

No studies are awaiting further classification.

Risk of bias in included studies

See the 'Characteristics of included studies' table Figure 2 and Figure 3

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bordes 2003	?	-	?	-	?	?
Check 1998	?	-	?	-	?	?
Dirckx 2009	+	+	+	+	+	?
Duvan 2006	+	?	+	-	?	?
Haapsamo 2010	+	+	+	+	+	-
Hung Lok 2004	+	?	+	-	?	?
Lambers 2009a	+	+	+	-	+	+
Lentini 2003	?	-	?	-	?	?
Moini 2007	+	-	?	-	?	?
Pakilla 2005	?	?	+	+	+	?
Rubinstein 1997-1999	+	+	+	-	?	?
Urman 2000	+	?	+	-	?	?
Van Dooren 2004	?	-	+	-	?	?

Allocation

Sequence generation

All studies were stated to be randomised trials, although five did not provide details of how the randomisation schedule was prepared (Bordes 2003; Check 1998; Lentini 2003; Pakilla 2005; Van Dooren 2004). The remaining studies used computer-generated randomisation schedules.

Allocation concealment

Allocation concealment was assessed at low risk in four out of 13 studies, as it was stated that it was performed by an independent pharmacist in the hospital pharmacy (Lambers 2009a), performed by the central pharmacy of the hospital (Dirckx 2009), or opaque sealed envelopes were used (Rubinstein 1997-1999; Haapsamo 2010).

In four studies risk of bias associated with allocation concealment was assessed as unclear, as sealed envelopes were used in two (Duvan 2006; Pakilla 2005), but it was unclear who prepared the envelopes and whether they were opaque and serially numbered; while in two, participants were randomised by a research nurse but it was unclear whether the nurse was involved in the study (Hung Lok 2004; Urman 2000).

Blinding

Nine out of 13 studies were double blind, with both the participants and treatment providers reported as blinded (Dirckx 2009; Duvan 2006; Haapsamo 2010; Hung Lok 2004; Lambers 2009a; Pakilla 2005; Rubinstein 1997-1999; Van Dooren 2004; Moini 2007); one was at least single blind as the assessors were blinded (Check 1998); one reported to be double blind but no further information was given (Bordes 2003); and one study was single blind as the treatment providers were unaware of which group the participants belonged to (Urman 2000).

Eight trials were reported as placebo controlled (Bordes 2003; Haapsamo 2010; Hung Lok 2004; Lambers 2009a; Moini 2007; Pakilla 2005; Rubinstein 1997-1999; Van Dooren 2004); in one study tablets of aspirin or placebo of identical appearance were given (Haapsamo 2010); in another a similar dose of 100 mg of placebo was reported (Lambers 2009a).

Incomplete outcome data

Three studies were assessed as at low risk of attrition bias, as they provided rates of the primary outcome (Dirckx 2009; Haapsamo 2010; Pakilla 2005). Three others provided pregnancy rates as a percentage rather than actual numbers (Bordes 2003; Lentini 2003; Moini 2007). These studies did not state how many women completed the study or withdrew from treatment, so that it is unknown whether the rates were calculated per woman, per transfer or per cycle. They have not been included in the analysis.

Intention-to-treat analysis was clearly stated in three studies (Haapsamo 2010; Lambers 2009a; Rubinstein 1997-1999). Three of the studies did not specifically state that an intention-to-treat analysis was undertaken; however they presented results on all recruited participants and reported no withdrawals (Check 1998; Duvan 2006; Rubinstein 1997-1999).

Withdrawals were reported in eight studies: they were stated either as none (Rubinstein 1997-1999); or they represented less than 10% of the study population (Dirckx 2009; Haapsamo 2010; Hung Lok 2004; Lambers 2009a; Pakilla 2005; Urman 2000), while in one study cancellation rates were stated as more than this percentage at 16.7% and 23.3% of the study and control groups, respectively (Moini 2007).

Selective reporting

Four out of 13 studies were at low risk of reporting bias (Dirckx 2009; Haapsamo 2010; Lambers 2009a; Pakilla 2005), while the other nine were at unclear risk (Bordes 2003; Check 1998; Duvan 2006; Hung Lok 2004; Lentini 2003; Moini 2007; Rubinstein 1997-1999; Urman 2000; Van Dooren 2004).

Other potential sources of bias

Inclusion and exclusion criteria were clearly described and treatment and control group participants appeared to be comparable in eight studies (Dirckx 2009; Check 1998; Duvan 2006; Haapsamo 2010; Hung Lok 2004; Lambers 2009a; Pakilla 2005; Urman 2000). The remaining studies provided insufficient detail to reach a decision on these factors. In most of the studies the general care programmes in the treatment and control groups were identical, although one study failed to provide this information (Lentini 2003).

Compliance to aspirin treatment was not assessed in all but one of the studies (Hung Lok 2004).

We found no other potential sources of within-study bias in the 13 included studies.

Effects of interventions

See: [Summary of findings for the main comparison](#) Low-dose aspirin compared to placebo or no treatment for women undergoing ART

Primary outcome measure

(1) Live birth rate per woman or couple

This outcome was reported in three studies involving 1053 participants (Dirckx 2009; Haapsamo 2010; Pakilla 2005).

No evidence of a difference was found (Analysis 1.1) between the treatment and control groups (RR 0.91, 95% CI 0.72 to 1.15, 3 RCTs, $n = 1053$, $I^2 = 0\%$, moderate-quality evidence) (Figure 4).

Figure 4. Forest plot of comparison: 1 Low-dose aspirin versus placebo or no treatment, outcome: 1.1 Live birth rate per woman or couple.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)
- (F) Other bias

Secondary outcome measures

(1) Clinical pregnancy rate (confirmed by ultrasound) per woman or couple

This outcome was reported in all of the included studies. Three studies provided pregnancy rates as a percentage rather than actual numbers (Bordes 2003; Lentini 2003; Moini 2007). These studies did not state how many women completed the study or withdrew from treatment, so that it is unknown whether the rates

were calculated per woman, per transfer or per cycle. They have not been included in the analysis.

Based on data from 2142 participants in 10 studies (Analysis 1.2), no evidence of a difference was found in clinical pregnancy rate between the treatment and control groups (RR 1.03, 95% CI 0.91 to 1.17, 10 RCTs, n = 2142, I² = 27%, moderate-quality evidence) (Figure 5).

Figure 5. Forest plot of comparison: 1 Low-dose aspirin versus placebo or no treatment, outcome: 1.2 Clinical pregnancy rate per woman or couple.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding (performance bias and detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)
- (F) Other bias

Subgroup analysis of nine studies on the timing of starting treatment showed no evidence of a difference in clinical pregnancy rates whether treatment started before, at or after down-regulation

(RR 1.03, 95% CI 0.90 to 1.17, 9 RCTs, n = 1972, I² = 35%, moderate-quality evidence).

Sensitivity analysis by including only studies with low risk of bias in all domains listed ended up with three trials (Dirckx 2009; Haapsamo 2010; Lambers 2009a). Based on data from 849 participants no evidence of a difference was found in clinical pregnancy rate between the treatment and control groups (RR 1.01, 95% CI 0.82 to 1.23, 3 RCTs, $n = 849$, $I^2 = 0\%$, high-quality evidence) (Analysis 1.10).

(2) Ongoing pregnancy rate (number of pregnancies which continued beyond 12 weeks) per woman or couple

This outcome was reported in only two of the included studies (Lambers 2009a; Van Dooren 2004). No evidence of a difference was found between the intervention and control groups (RR = 0.94, 95% CI 0.69 to 1.27, 2 RCTs, $n = 339$, $I^2 = 0\%$, low-quality evidence).

(3) Multiple pregnancy rate per woman or couple

This outcome was reported in three of the included studies (Dirckx 2009; Haapsamo 2010; Lambers 2009a). There was no evidence of a difference in the number of multiple pregnancies found at ultrasound (RR 0.67, 95% CI 0.37 to 1.25, 2 RCTs, $n = 656$, $I^2 = 0\%$, low-quality evidence) (Haapsamo 2010; Lambers 2009a), or in the number of multiple births (RR 0.74, 95% CI 0.38 to 1.46, 2 RCTs, $n = 680$, $I^2 = 0\%$, low-quality evidence) (Dirckx 2009; Haapsamo 2010), between the treatment and control groups.

(4) Miscarriage rate (confirmed by ultrasound and pregnancy test, or histology) per woman or couple

This outcome was reported in five of the included studies (Dirckx 2009; Haapsamo 2010; Lambers 2009a; Pakilla 2005; Urman 2000). There was no evidence of a difference between the treatment and control groups (RR 1.10, 95% CI 0.68 to 1.77, 5 RCTs, $n = 1497$, $I^2 = 0\%$, low-quality evidence).

(5) Complications with the IVF or ICSI procedure

In one study ovarian hyperstimulation syndrome (OHSS) was reported as occurring in 5.6% of the intervention group and 23.3% of the control group (Moini 2007). No further analysis was possible given that neither the numerators nor denominators were provided, so that we could not add the necessary data into the analysis. No studies reported outcomes related to intra-operative haemorrhage, formation of haematoma or the need for blood transfusion during the procedure. No cases of gastritis or haematemesis were reported.

(6) Gestational age of baby

This outcome was reported in one of the studies (Haapsamo 2010): 38 (31 to 42) versus 38 (28 to 41) in the study and control groups, respectively.

(7) Complications during pregnancy or birth

One study involving 487 participants reported the rate of vaginal bleeding during pregnancy (Haapsamo 2010). There was no evidence of a difference between the treatment and control groups (RR 1.01, 95% CI 0.14 to 7.13, 1 RCT, $n = 487$, very low quality evidence).

Three studies reported the rate of ectopic pregnancies (Haapsamo 2010; Pakilla 2005; Urman 2000). There was no evidence of a difference between the treatment and control groups (RR 1.86, 95% CI 0.75 to 4.63, 3 RCTs, $n = 1135$, $I^2 = 0\%$, very low quality evidence).

Other potential adverse effects, including preterm birth, antepartum haemorrhage and need for operative delivery were not reported in any included study.

DISCUSSION

Summary of main results

This review included a total of 2653 participants that were recruited in randomised controlled trials assessing aspirin versus control (no intervention) in women undergoing ART. We found no evidence that aspirin had an effect on live birth rate in this population. We also found no evidence that aspirin intake can influence rates of clinical or ongoing or multiple pregnancy or miscarriage. However, the number of studies was limited and the quality of the evidence ranged from very low to moderate. Furthermore, data on complication rates, either during the IVF/ICSI procedure (intra-operative bleeding, vaginal/pelvic haematoma, blood transfusion, ovarian hyperstimulation syndrome, gastritis, haematemesis) or during pregnancy and childbirth (threatened miscarriage, antepartum haemorrhage, need for operative delivery, postpartum haemorrhage, ectopic pregnancy) were either very limited or missing; therefore, to date, definitive conclusions are precluded.

Medical personnel involved in ART are mostly committed to offering couples adequate management towards achieving a successful clinical outcome: a pregnancy and the birth of a healthy baby. It is imperative that before treatments become embedded in unit protocols they are subjected to rigorous, properly designed and adequately powered randomised controlled clinical trials. We must first do 'no harm', but it is also essential that purported treatments do actually convey benefit. Treatment with aspirin for IVF is one such treatment.

In an attempt to reassess whether aspirin administration is useful in increasing pregnancy rates in IVF and ICSI cycles, we performed a second update of a previously published Cochrane review on this issue. We were not able to add new data from additional studies, as we found no new RCTs reporting on these outcomes based on the desired comparisons. We have excluded 17 new studies. Based on the available evidence, we reached the same conclusion as the initial version of the review: no single outcome measure demonstrated a benefit with the use of aspirin.

Currently, there is no evidence to support the use of aspirin treatment in order to improve pregnancy rates for a general IVF population. Women undergoing IVF treatment are often prepared to undertake any number of measures to improve their chances of conceiving; therefore, recruitment targets in clinical trials of this treatment are likely to be achievable. Such women should be given the opportunity to participate in adequately powered, high-quality studies which aim to improve the evidence base for all couples requiring IVF treatment.

Overall completeness and applicability of evidence

The relevance of the evidence sourcing from the identified studies to the review question was borderline. Very few of them reported on all the objectives of the review question, especially live birth rate, which is ultimately the outcome all couples undergoing IVF are most interested in. The difficulty of collecting data at birth and the possible reporting bias of outcomes could justify such a lack. The small number of eligible studies identified and variations

across studies in dose of treatment provided, stage of treatment in terms of commencement and cessation and use of placebo was not adequate. Lack of sufficient data on miscarriage rates associated with aspirin treatment is also a concern, particularly in light of evidence suggesting that higher doses of aspirin can result in increased miscarriage rates in pregnancy. Finally, a limitation of this second update of the review was the difficulty in identifying the full text of three new possibly eligible RCTs, while in two cases there was difficulty in assessing the risk of bias, whereas no new data were obtained in our correspondence effort.

Quality of the evidence

For the primary outcome, live birth, the evidence was of moderate quality. For clinical pregnancy, the evidence was of moderate quality: three studies failed to provide specifications on randomisation methods; two studies did not specify how allocation concealment was performed; one study was performed with inadequate blinding. In ongoing pregnancy the evidence was of low quality, as one study failed to provide specifications on the method of randomisation and allocation concealment.

For other outcomes the quality of the evidence was low or very low. The main limitations were failure to report study methods in sufficient detail and imprecision.

Potential biases in the review process

The strength of the review in terms of preventing bias was maintained by having two independent review authors. The methods established to conduct the current review were agreed by all authors and any potential bias that could have been introduced was bypassed through independent screening, assessment, selection and data extraction with discrepancies resolved through team consensus. The search was supported by the CGFG Information Specialist. Importantly, relevant data were obtained by discussion between the three authors.

Agreements and disagreements with other studies or reviews

The conclusions of the second update of this Cochrane review are in agreement with the current literature.

The first published systematic review and meta-analysis involved six trials ([Gelbaya 2007](#)). That review found no difference between patients who received aspirin and those who received placebo or no treatment in clinical pregnancy rate per embryo transfer (RR 1.09, 95% CI 0.92 to 1.29); and there were no differences in a variety of outcome measures studied, including live births. The authors concluded that aspirin had no substantial positive effect on likelihood of pregnancy and, therefore, it should not be routinely recommended for women undergoing IVF and ICSI.

Similarly, another meta-analysis of randomised trials evaluating the effects of aspirin in IVF ([Ruopp 2008](#)), including 10 trials, found no difference between women taking aspirin and those who did not with regards to implantation and miscarriage rates but the clinical pregnancy rate per embryo transfer was reported to be significantly higher in the aspirin group (RR 1.15, 95% CI 1.03 to 1.27). This study commented on the difference in findings on the clinical pregnancy rate, as compared with the previous review ([Gelbaya 2007](#)), attributing the "divergent findings to different

approaches to statistical modelling, study selection, and statistical inference" ([Ruopp 2008](#)).

In this second update of our review, we found two further systematic reviews ([Groeneveld 2011](#); [Dentali 2012](#)).

The first group of authors performed an individual patient data (IPD) meta-analysis; whereas the conventional meta-analysis limited to studies that could provide IPD showed an OR of 0.89 (95% CI 0.69 to 1.2), the conventional meta-analysis limited to the eight studies of which method of randomisation could be confirmed showed an OR of 0.94 (95% CI 0.76 to 1.17) and the conventional meta-analysis including all 10 eligible RCTs identified changed the OR to 1.07 (95% CI 0.81 to 1.41): authors concluded that aspirin does not improve pregnancy rates after IVF.

The second group of authors using pooled odds ratios (ORs) and 95% confidence intervals (CIs), included 17 studies with 6403 patients: authors found that the use of aspirin did not improve live birth pregnancy rate compared with placebo or no treatment (OR 1.08, 95% CI 0.90 to 1.29), but pregnancy rates were significantly increased in patients randomised to low-dose aspirin (OR 1.19, 95% CI 1.01 to 1.39), while miscarriage rates were not (OR 1.18, 95% CI 0.82 to 1.68); on the contrary, results of sensitivity analyses including high-quality studies did not show statistically significant differences in all considered endpoints. The conclusion reached was that there was not a substantial efficacy of aspirin in women undergoing IVF/ICSI and does not support the use of low-dose aspirin to improve the success of IVF/ICSI in terms of pregnancy outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is no evidence to support the routine use of aspirin in order to improve pregnancy rates for a general IVF population. This is based on available data from randomised controlled trials, where there is currently no evidence of an effect of aspirin on women undergoing ART, as there is no single outcome measure which demonstrated a benefit with its use: there is no evidence of a difference in live birth rates associated with use of aspirin compared to placebo or no treatment in women undergoing ART, nor is there evidence of any difference in rates of pregnancy, miscarriage, ectopic or vaginal bleeding rates. Furthermore, the possibility of adverse events cannot be excluded as data in the field remain limited.

Implications for research

One of the largest studies included in this review reported on 298 women and showed some benefit in clinical pregnancy rate ([Rubinstein 1997-1999](#)). Twenty-eight per cent of the control population obtained a clinical pregnancy compared to 45% using aspirin, giving a 17% improvement. Using these data, an appropriately powered trial would need a similar sample size of 125 women in each group, at a 5% significance level and 80% power and assuming a similar control success rate in order to replicate this improvement. To demonstrate a 10% improvement, a sample size of 350 women in each group would be required.

A major drawback was that only three studies reported on live birth rate, which we consider to be the most important outcome measure.

Since the last update on aspirin for IVF ([Siristatidis 2011](#)), no randomised trials have been published in the field. This contradicts current clinical practice, as many women that undergo IVF are treated with low-dose aspirin. Given the fact that, to date, aspirin has not proved to be beneficial, we urge researchers in the field of reproductive medicine to use this review and its outcome parameters to construct well-designed clinical trials that are adequately powered to the outcome measure of live birth rate.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bordes 2003

Methods	Study design: randomised, double-blind placebo controlled trial No. of centres involved: two centres Method of randomisation: NS Method of allocation concealment: NS Blinding: it was not clearly stated whether the individuals who administered the intervention were blinded, or the assessors of the outcomes (abstract) Sample size: NS Intention-to-treat analysis: NS Overall risk of bias rating: high risk
Participants	Inclusion criteria: unselected women undergoing IVF cycles Exclusion criteria: NS No. eligible for randomisation: NS No. enrolled in the trial: 138 No. randomised to intervention group at the start of the trial: 69 No. randomised to control group at the start of the trial: 69 No. in the treatment group at the end of the trial: NS No. in the control group at the end of the trial: NS No. (%) in the treatment group who were lost to follow-up/withdrew: NS No. (%) in the control group who were lost to follow-up/withdrew: NS Age of intervention group at the start of the trial: NS Age of control group at the start of the trial: NS No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: NS Cause/duration of subfertility of control group: NS Other relevant demographic information: none
Interventions	Dose of aspirin given to intervention group: 100 mg per day Control treatment: placebo Concomitant treatment given to intervention group: controlled ovarian hyperstimulation (COH) with a long protocol Concomitant treatment given to control group: controlled ovarian hyperstimulation (COH) with a long protocol Time of commencement of treatment: co-treatment on the 21st day of the menstrual cycle preceding the introduction of the GnRH analogue Duration of treatment: NS Length of study follow-up: NS

Bordes 2003 (Continued)

Outcomes

PRIMARY OUTCOME MEASURES

Live birth rate (per woman/couple) in intervention group: NS

Live birth rate (per woman/couple) in control group: NS

SECONDARY OUTCOME MEASURES

Clinical pregnancy rate (per woman/couple) in intervention group: 21.4%

Clinical pregnancy rate (per woman/couple) in control group: 39.3%

Chemical pregnancy rate (per woman/couple) in intervention group: NS

Chemical pregnancy rate (per woman/couple) in control group: NS

Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS

Multiple pregnancy rate on delivery (per woman/couple) in control group: NS

Miscarriage rate in intervention group: NS

Miscarriage rate in control group: NS

Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS

Complications with IVF/ICSI procedure (per woman/couple) in control group: NS

Preterm birth: NS

Complications during pregnancy/birth (per woman/couple) in intervention group: NS

Complications during pregnancy/birth (per woman/couple) in control group: NS

Notes

Setting of trial: Hôpital Edouard Herriot, Médecine de la Reproduction, Lyon and Institut Rhônalpin, Bron, France
Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	High risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Clinical pregnancy rates are reported as percentages
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Check 1998

Methods

Study design: parallel randomised controlled trial

No. of centres involved: single centre

Method of randomisation: NS

Method of allocation concealment: NS

Blinding: participants were not blinded, it was not stated whether the individuals who administered the intervention were blinded, assessors of the outcomes were blinded

Sample size: calculation provided

Check 1998 (Continued)

Intention-to-treat analysis: NS
Overall risk of bias rating: high risk

Participants	<p>Inclusion criteria: women undergoing a frozen embryo cycle, using their own oocytes Exclusion criteria: over 42 years of age and/or taking concomitant medications which would increase blood flow No. eligible for randomisation: NS No. enrolled in the trial: NS No. randomised to intervention group at the start of the trial: NS No. randomised to control group at the start of the trial: NS No. in the treatment group at the end of the trial: 18 No. in the control group at the end of the trial: 18 No. (%) in the treatment group who were lost to follow-up/withdrew: NS No. (%) in the control group who were lost to follow-up/withdrew: NS Age of intervention group at the start of the trial: NS Age of control group at the start of the trial: NS No. (%) in intervention group who had previous IVF treatment: 18 (100%) No. (%) in control group who had previous IVF treatment: 18 (100%) Cause/duration of subfertility of intervention group: NS Cause/duration of subfertility of control group: NS Other relevant demographic information: none</p>
Interventions	<p>Dose of aspirin given to intervention group: 81 mg per day Control treatment: no treatment Concomitant treatment given to intervention group: standard protocol Concomitant treatment given to control group: standard protocol Time of commencement of treatment: day 2 of frozen cycle Duration of treatment: until birth Length of study follow-up: NS</p>
Outcomes	<p>PRIMARY OUTCOME MEASURES Live birth rate (per woman/couple) in intervention group: NS Live birth rate (per woman/couple) in control group: NS</p> <p>SECONDARY OUTCOME MEASURES Clinical pregnancy rate (per woman/couple) in intervention group: 2/18 (11.1%) Clinical pregnancy rate (per woman/couple) in control group: 6/18 (33.3%) Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS Multiple pregnancy rate on delivery (per woman/couple) in control group: NS Miscarriage rate in intervention group: NS Miscarriage rate in control group: NS Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Complications with IVF/ICSI procedure (per woman/couple) in control group: NS Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS</p>
Notes	<p>Setting of trial: Assisted Conception Unit, Cooper Hospital University Medical Centre, USA Source of funding: NS</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

Check 1998 (Continued)

Allocation concealment (selection bias)	High risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants were not blinded; it was not stated whether the individuals who administered the intervention were blinded; assessors of the outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Reporting clinical pregnancy rates only
Selective reporting (reporting bias)	Unclear risk	No reports
Other bias	Unclear risk	Unclear

Dirckx 2009

Methods	Study design: randomized, double-blind placebo controlled trial No. of centres involved: single centre Method of randomisation: computerized Method of allocation concealment: by the central pharmacy of the hospital Blinding: stated as being double-blind Sample size: calculation provided Intention-to-treat analysis: NS Overall risk of bias rating: low risk
Participants	Inclusion criteria: Dutch-speaking women starting a first or second IVF/ICSI cycle Exclusion criteria: women who were suffering from platelet dysfunction, thrombopenia, gastrointestinal ulcers, recurrent gastritis, aspirin hypersensitivity or who were on treatment with anticoagulants or aspirin No. eligible for randomisation: 201 couples No. enrolled in the trial: 193 No. randomised to intervention group at the start of the trial: 97 No. randomised to control group at the start of the trial: 96 No. in the treatment group at the end of the trial: 93 No. in the control group at the end of the trial: 88 No. (%) in the treatment group who were lost to follow-up/withdrew: 4/97 (4.1%) No. (%) in the control group who were lost to follow-up/withdrew: 8/96 (8.33%) Age of intervention group at the start of the trial: 31.1 (3.9) Age of control group at the start of the trial: 31.3 (3.8) No. (%) in intervention group who had previous IVF treatment: 18 (100%) No. (%) in control group who had previous IVF treatment: 18 (100%) Cause/duration of subfertility of intervention group: primary subfertility 66 (68%) Cause/duration of subfertility of control group: primary subfertility 72 (75%) Other relevant demographic information: cycle number, subfertility status, use of different gonadotrophins, the variable starting dose of gonadotrophins and the use of different forms of luteal support, mean dose of stimulation and mean total dose of gonadotrophins
Interventions	Dose of aspirin given to intervention group: 100 mg per day Control treatment: no treatment Concomitant treatment given to intervention group: standard short agonist protocol Concomitant treatment given to control group: standard short agonist protocol Time of commencement of treatment: together with the oral contraceptive pill prior to stimulation Duration of treatment: until confirmation of pregnancy by detection of foetal heart activity Length of study follow-up: NS

Dirckx 2009 (Continued)

Outcomes

PRIMARY OUTCOME MEASURES

Live birth rate (per woman/couple) in intervention group: 24/97 (25%)

Live birth rate (per woman/couple) in control group: 27/96 (28%)

SECONDARY OUTCOME MEASURES

Clinical pregnancy rate (per woman/couple) in intervention group: 31/97 (32%)

Clinical pregnancy rate (per woman/couple) in control group: 30/96 (31%)

Chemical pregnancy rate (per woman/couple) in intervention group: NS

Chemical pregnancy rate (per woman/couple) in control group: NS

Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: 3/97 (3.09%)

Multiple pregnancy rate on delivery (per woman/couple) in control group: 4/96 (4.16%)

Miscarriage rate in intervention group: 5/97 (5.15%)

Miscarriage rate in control group: 1/96 (1.04%)

Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS

Complications with IVF/ICSI procedure (per woman/couple) in control group: NS

Preterm birth: NS

Complications during pregnancy/birth (per woman/couple) in intervention group: NS

Complications during pregnancy/birth (per woman/couple) in control group: NS

Notes

Setting of trial: Centre for Reproductive Medicine of the University Hospital of Ghent, Belgium

Source of funding: One of the authors is holder of a fundamental clinical research mandate by the National Fund for Scientific Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized
Allocation concealment (selection bias)	Low risk	By the central pharmacy of the hospital
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as being double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reporting of primary and some of the secondary measures of the review
Selective reporting (reporting bias)	Low risk	No reports
Other bias	Unclear risk	Unclear

Duvan 2006

Methods

Study design: randomized study

No. of centres involved: single centre

Method of randomisation: lottery randomization

Method of allocation concealment: envelopes and initial letters of the groups

Blinding: participants and the individuals providing the intervention were blinded

Sample size: calculation provided

Intention-to-treat analysis: NS

Duvan 2006 (Continued)

Overall risk of bias rating: moderate risk

Participants	<p>Inclusion criteria: nonselected infertile patients who were undergoing their first ICSI cycle</p> <p>Exclusion criteria: women with systemic diseases in which anti-aggregants and/or steroid administrations were contraindicated and during the trial further reasons for exclusion included poor response to ovulation induction or premature LH surge (LH levels > 10 IU/mL), or the onset of severe ovarian hyperstimulation syndrome</p> <p>No. eligible for randomisation: NS</p> <p>No. enrolled in the trial: 197 couples</p> <p>No. randomised to intervention group at the start of the trial: 41</p> <p>No. randomised to control group at the start of the trial: 40</p> <p>No. in the treatment group at the end of the trial: NS</p> <p>No. in the control group at the end of the trial: NS</p> <p>No. (%) in the treatment group who were lost to follow-up/withdrew: NS</p> <p>No. (%) in the control group who were lost to follow-up/withdrew: NS</p> <p>Age of intervention group at the start of the trial: 31 (5.6)</p> <p>Age of control group at the start of the trial: 30 (5.6)</p> <p>No. (%) in intervention group who had previous IVF treatment: none</p> <p>No. (%) in control group who had previous IVF treatment: none</p> <p>Cause/duration of subfertility of intervention group: duration: 6.1 ± 4.1 years; causes: male 46.3%, tubal 22%, unexplained 24.4%, ovulatory 4.9%, endometriosis 2.4%</p> <p>Cause/duration of subfertility of control group: 6.4 ± 4.8; causes: male 57.5%, tubal 10%, unexplained 32.5%, ovulatory 0%, endometriosis 0%</p> <p>Other relevant demographic information: mean basal FSH and LH levels, cycle characteristics (mean gonadotropin doses, number of follicles, oocytes, M2 oocytes)</p>
Interventions	<p>Dose of aspirin given to intervention group: 100 mg per day</p> <p>Control treatment: no treatment</p> <p>Concomitant treatment given to intervention group: standard long-luteal GnRH agonist stimulation protocol, vaginal micronised progesterone 3×200 mg/day</p> <p>Concomitant treatment given to control group: standard long-luteal GnRH agonist stimulation protocol, vaginal micronised progesterone 3×200 mg/day</p> <p>Time of commencement of treatment: at the day of embryo transfer</p> <p>Duration of treatment: until confirmation of pregnancy clinically</p> <p>Length of study follow-up: NS</p>
Outcomes	<p>PRIMARY OUTCOME MEASURES</p> <p>Live birth rate (per woman/couple) in intervention group: NS</p> <p>Live birth rate (per woman/couple) in control group: NS</p> <p>SECONDARY OUTCOME MEASURES</p> <p>Clinical pregnancy rate (per woman/couple) in intervention group: 11/41 (27%)</p> <p>Clinical pregnancy rate (per woman/couple) in control group: 14/40 (35%)</p> <p>Chemical pregnancy rate (per woman/couple) in intervention group: NS</p> <p>Chemical pregnancy rate (per woman/couple) in control group: NS</p> <p>Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS</p> <p>Multiple pregnancy rate on delivery (per woman/couple) in control group: NS</p> <p>Miscarriage rate in intervention group: NS</p> <p>Miscarriage rate in control group: NS</p> <p>Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS</p> <p>Complications with IVF/ICSI procedure (per woman/couple) in control group: NS</p> <p>Preterm birth: NS</p> <p>Complications during pregnancy/birth (per woman/couple) in intervention group: NS</p> <p>Complications during pregnancy/birth (per woman/couple) in control group: NS</p>
Notes	<p>Setting of trial: Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara University, Turkey</p> <p>Source of funding: Not stated</p>

Duvan 2006 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Lottery randomisation
Allocation concealment (selection bias)	Unclear risk	Envelopes and initial letters of the groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and the individuals providing the intervention were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Not addressing live birth rate, intention to treat or withdrawals
Selective reporting (reporting bias)	Unclear risk	No reports
Other bias	Unclear risk	Unclear

Haapsamo 2010

Methods	<p>Study design: randomized placebo-controlled trial</p> <p>No. of centres involved: four centres</p> <p>Method of randomisation: by means of computer-generated random numbers in blocks of four by the pharmacist (third-party administrator)</p> <p>Method of allocation concealment: by using opaque sealed envelopes</p> <p>Blinding: blinding of the participants and investigators was ensured by treating the women with tablets of aspirin or placebo of identical appearance</p> <p>Sample size: calculation provided</p> <p>Intention-to-treat analysis: provided</p> <p>Overall risk of bias rating: moderate risk</p>
Participants	<p>Inclusion criteria: (i) age < 40 years (ii) < 4 previous ovarian stimulations and (iii) no contraindications for aspirin</p> <p>Exclusion criteria: described in previous studies/no pre-existing medical condition</p> <p>No. eligible for randomisation: 487 couples</p> <p>No. enrolled in the trial: 487 couples</p> <p>No. randomised to intervention group at the start of the trial: 242</p> <p>No. randomised to control group at the start of the trial: 245</p> <p>No. in the treatment group at the end of the trial: 227</p> <p>No. in the control group at the end of the trial: 229</p> <p>No. (%) in the treatment group who were lost to follow-up/withdrew: 15/242 (6.1%)</p> <p>No. (%) in the control group who were lost to follow-up/withdrew: 16/245 (6.5%)</p> <p>Age of intervention group at the start of the trial: 31.4 (3.4)</p> <p>Age of control group at the start of the trial: 31.3 (4.2)</p> <p>No. (%) in intervention group who had previous IVF treatment: 21 (40%)</p> <p>No. (%) in control group who had previous IVF treatment: 23 (42%)</p> <p>Cause/duration of subfertility of intervention group: 3.8 (1.9) – stated</p> <p>Cause/duration of subfertility of control group: 4.1 (2.5) – stated</p> <p>Other relevant demographic information: provided</p>
Interventions	<p>Dose of aspirin given to intervention group: 100 mg per day</p> <p>Control treatment: placebo</p>

Aspirin for in vitro fertilisation (Review)

Haapsamo 2010 (Continued)

Concomitant treatment given to intervention group: standard long-luteal GnRH agonist stimulation protocol, vaginal progesterone 3 × 200 mg/day
 Concomitant treatment given to control group: standard long-luteal GnRH agonist stimulation protocol, vaginal progesterone 3 × 200 mg/day
 Time of commencement of treatment: on the first day of gonadotrophin stimulation
 Duration of treatment: until menstruation or a negative pregnancy test; and for those who became pregnant, until delivery.
 Length of study follow-up: until delivery

Outcomes	<p>PRIMARY OUTCOME MEASURES</p> <p>Live birth rate (per woman/couple) in intervention group: 52/242 (21.4%) Live birth rate (per woman/couple) in control group: 55/245 (22.4%)</p> <p>SECONDARY OUTCOME MEASURES</p> <p>Clinical pregnancy rate (per woman/couple) in intervention group: 64/242 (26.4%) (28.2% – per embryo transfer) Clinical pregnancy rate (per woman/couple) in control group: 67/245 (27.3%) (29.3% – per embryo transfer) Chemical pregnancy rate (per woman/couple) in intervention group: 3/242 (1.3%) Chemical pregnancy rate (per woman/couple) in control group: 5/245 (2.1%) Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: 11/242 (4.5%) Multiple pregnancy rate on delivery (per woman/couple) in control group: 15/245 (6.1%) Miscarriage rate in intervention group: 8/242 (3.67%) Miscarriage rate in control group: 9/245 (3.67%)</p> <p>Ectopic rate in intervention group: 4/242 (1.6%) Miscarriage rate in control group: 3/245 (1.2%) Complications with IVF/ICSI procedure (per woman/couple) in intervention group: 13/242 (5.3%) Complications with IVF/ICSI procedure (per woman/couple) in control group: 15/245 (6.1%) Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: hypertensive complications 8/242, vaginal bleeding 2/242, IUGR in singletons 2/242, blood loss at delivery 682 (478) Complications during pregnancy/birth (per woman/couple) in control group: 10/245, vaginal bleeding 2/245, IUGR in singletons 3/245, blood loss at delivery 633 (499)</p>
Notes	<p>Setting of trial: Four fertility centres situated in Finland: Oulu University Hospital; The Family Federation of Finland, Oulu; Tampere University Hospital; and Kuopio University Hospital.</p> <p>Source of funding: stated (supported by the University of Oulu, Bayer AG, The Academy of Finland, Si-grid Jusélius Foundation, Maud Kuistila Foundation and Paavo Ilmari Ahvenainen Foundation)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By means of computer-generated random numbers in blocks of four by the pharmacist (third-party administrator)
Allocation concealment (selection bias)	Low risk	By using opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of the participants and investigators was ensured by treating the women with tablets of aspirin or placebo of identical appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reporting of the primary outcome/clinical pregnancy as rates – percentages per embryo transfer

Haapsamo 2010 (Continued)

Selective reporting (re-reporting bias)	Low risk	No reports to suggest selective reporting
Other bias	High risk	Trial was partly funded by a pharmaceutical company producing aspirin

Hung Lok 2004

Methods	<p>Study design: double blind, parallel randomised controlled trial</p> <p>No. of centres involved: single centre</p> <p>Method of randomisation: computer-generated randomisation schedule</p> <p>Method of allocation concealment: coordinated by a research nurse</p> <p>Blinding: participants and the individuals providing the intervention were blinded</p> <p>Sample size: calculation provided</p> <p>Intention-to-treat analysis: not performed – 1 participant from each group dropped out and were not included in the final analysis</p> <p>Overall risk of bias rating: moderate risk</p>
Participants	<p>Inclusion criteria: women undergoing IVF who were described as poor responders due to either poor response in previous cycles, or high basal levels of FSH (> 10 IU/L)</p> <p>Exclusion criteria: women over 40 years, and/or with polycystic ovarian syndrome or ovarian cysts or endometrioma. Those who were heavy smokers, had cardiovascular disorders or on medication that could affect the circulation were also excluded</p> <p>No. eligible for randomisation: 69</p> <p>No. enrolled in the trial: 62</p> <p>No. randomised to intervention group at the start of the trial: 31</p> <p>No. randomised to control group at the start of the trial: 31</p> <p>No. in the treatment group at the end of the trial: 30</p> <p>No. in the control group at the end of the trial: 30</p> <p>No. (%) in the treatment group who were lost to follow-up/withdrew: 1 (3.2%)</p> <p>No. (%) in the control group who were lost to follow-up/withdrew: 1 (3.2%)</p> <p>Age of intervention group at the start of the trial: median 36.0 years, inter-quartile range 33.8 to 37.3</p> <p>Age of control group at the start of the trial: median 36.9 years, inter-quartile range 33.0 to 38.8</p> <p>No. (%) in intervention group who had previous IVF treatment: 17 (56.7%)</p> <p>No. (%) in control group who had previous IVF treatment: 18 (60.0%)</p> <p>Cause/duration of subfertility of intervention group: median duration 10.0 years, inter-quartile range 8.7 to 12.0. Causes: tubal disease = 11 (36.7%), endometriosis = 12 (40%), male factor = 1 (3.3%), unexplained = 5 (16.7%), anovulation or other = 1 (3.3%)</p> <p>Cause/duration of subfertility of control group: median duration 10.9 years, inter-quartile range 9.7 to 12.0. Causes: tubal disease = 12 (40%), endometriosis = 10 (33.3%), male factor = 3 (10%), unexplained = 4 (13.3%), anovulation or other = 1 (3.3%)</p> <p>Other relevant demographic information: intervention group had a median basal FSH level of 10.7 IU/L (inter-quartile range 8.1 to 12.3), 17 had previously cancelled a cycle due to poor response (56.7%) and 15 participants had a history of ovarian surgery (50%). The control group had a median basal FSH level of 10.5 IU/L (inter-quartile range 7.3 to 11.1), 18 (60%) had previously cancelled a cycle due to poor response, and 11 (36.7%) had a history of ovarian surgery</p>
Interventions	<p>Dose of aspirin given to intervention group: 80 mg per day</p> <p>Control treatment: placebo</p> <p>Concomitant treatment given to intervention group: standard protocol</p> <p>Concomitant treatment given to control group: standard protocol</p> <p>Time of commencement of treatment: start of GnRHα</p> <p>Duration of treatment: until administration of hCG or cancellation</p> <p>Length of study follow-up: until confirmation of clinical pregnancy</p>
Outcomes	<p>PRIMARY OUTCOME MEASURES</p> <p>Live birth rate (per woman/couple) in intervention group: NS</p> <p>Live birth rate (per woman/couple) in control group: NS</p>

Hung Lok 2004 (Continued)

SECONDARY OUTCOME MEASURES

Clinical pregnancy rate (per woman/couple) in intervention group: 1/30 (3.3%)
 Clinical pregnancy rate (per woman/couple) in control group: 2/30 (6.7%)
 Chemical pregnancy rate (per woman/couple) in intervention group: NS
 Chemical pregnancy rate (per woman/couple) in control group: NS
 Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS
 Multiple pregnancy rate on delivery (per woman/couple) in control group: NS
 Miscarriage rate in intervention group: NS
 Miscarriage rate in control group: NS
 Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS
 Complications with IVF/ICSI procedure (per woman/couple) in control group: NS
 Preterm birth: NS
 Complications during pregnancy/birth (per woman/couple) in intervention group: NS
 Complications during pregnancy/birth (per woman/couple) in control group: NS

Notes	Setting of trial: Assisted Conception Unit, Hong Kong Source of funding: NS
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Coordinated by a research nurse
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and the individuals providing the intervention were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Only reporting of clinical pregnancy rates
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	No data

Lambers 2009a

Methods	Study design: double blind, placebo controlled trial for patients with previous failed conception No. of centres involved: single centre Method of randomisation: computerized tables Method of allocation concealment: performed by an independent pharmacist of the hospital pharmacy Blinding: participants and the individuals providing the intervention were blinded Sample size: calculation provided Intention-to-treat analysis: performed Overall risk of bias rating: low risk
Participants	Inclusion criteria: patients < 39 years of age at the start of treatment, with serum FSH level ≤ 10 IU/L on cycle day 3 and with at least one previous IVF or intracytoplasmic sperm injection (ICSI) treatment with failed conception. Patients did not have a previous ongoing pregnancy, both ovaries were present, and there was no contraindication for aspirin

Lambers 2009a (Continued)

Exclusion criteria: women with tubal pathology, ovarian hyperstimulation syndrome in a previous treatment cycle, body mass index > 30 kg/m², smoking habit of more than 5 cigarettes per day, untreated endocrinopathy, systemic disease, hypertension, previous allergic reaction to study medication, or contraindication for pregnancy

No. eligible for randomisation: 171

No. enrolled in the trial: 169

No. randomised to intervention group at the start of the trial: 84

No. randomised to control group at the start of the trial: 85

No. in the treatment group at the end of the trial: 73

No. in the control group at the end of the trial: 76

No. (%) in the treatment group who were lost to follow-up/withdrew: 4 (4.7%)

No. (%) in the control group who were lost to follow-up/withdrew: 1 (1.1%)

Age of intervention group at the start of the trial: 33.04

Age of control group at the start of the trial: 32.96

No. (%) in intervention group who had previous IVF treatment: 84 (100%)

No. (%) in control group who had previous IVF treatment: 85 (100%)

Cause/duration of subfertility of intervention group: causes — primary subfertility 76.5%; male factor = 64.7%; idiopathic = 28.2%; other = 7.1%

Cause/duration of subfertility of control group: causes — primary subfertility 76.2%, male factor = 66.7%, idiopathic = 23.8%, other = 9.5%

Other relevant demographic information: intervention group had a median basal FSH level of 6.16 IU/L, a BMI of 22.94, and previous cycles characteristics are described (duration of stimulation, daily FSH dosage, number of follicles on the day of Pregnyl (hCG) injection, endometrial thickness, serum level of E₂, number of oocytes retrieved, fertilization rate, number of embryos available for transfer, number of embryos transferred, the cumulative embryo score (CES) of the morphologically most optimal embryo, percentage of patients with possibility of cryopreservation, and number of embryos cryopreserved). The control group had a median basal FSH level of 5.96 IU/L, a BMI of 23 and previous cycles characteristics are described as above

Interventions	Dose of aspirin given to intervention group: 100 mg per day Control treatment: placebo 100 mg Concomitant treatment given to intervention group: standard protocol (long GnRH-agonist protocol with oral contraceptives as pretreatment) Concomitant treatment given to control group: standard protocol (long GnRH-agonist protocol with oral contraceptives as pretreatment) Time of commencement of treatment: start of the oral contraceptive pill Duration of treatment: until day of pregnancy test or until 12 weeks' gestational age Length of study follow-up: until 12 weeks of gestation at least
Outcomes	PRIMARY OUTCOME MEASURES Live birth rate (per woman/couple) in intervention group: NS Live birth rate (per woman/couple) in control group: NS SECONDARY OUTCOME MEASURES Clinical pregnancy rate (per woman/couple) in intervention group: 35/84 (41.8%) Clinical pregnancy rate (per woman/couple) in control group: 33/85 (39.3%) Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: 10/84 (12.1%) Multiple pregnancy rate on delivery (per woman/couple) in control group: 28.1% (24/85) Miscarriage rate in intervention group: 5/84 (6%) Miscarriage rate in control group: 6/85 (7%) Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Complications with IVF/ICSI procedure (per woman/couple) in control group: NS Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS
Notes	Setting of trial: University Fertility Clinic, Department of Obstetrics, Gynecology and Reproductive Medicine Free University Medical Center, Amsterdam, The Netherlands

Lambers 2009a (Continued)

Source of funding: NS

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized tables
Allocation concealment (selection bias)	Low risk	Performed by an independent pharmacist of the hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and the individuals providing the intervention were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No reporting of live birth rate
Selective reporting (reporting bias)	Low risk	No reports for selective reporting
Other bias	Low risk	Free from other problems

Lentini 2003

Methods	Study design: parallel randomised controlled trial No. of centres involved: NS Method of randomisation: NS Method of allocation concealment: NS Blinding: NS Sample size: NS Intention-to-treat analysis: NS Overall risk of bias rating: high risk
Participants	Inclusion criteria: women undergoing IVF Exclusion criteria: NS No. eligible for randomisation: NS No. enrolled in the trial: NS No. randomised to intervention group at the start of the trial: 42 No. randomised to control group at the start of the trial: 42 No. in the treatment group at the end of the trial: NS No. in the control group at the end of the trial: NS No. (%) in the treatment group who were lost to follow-up/withdrew: NS No. (%) in the control group who were lost to follow-up/withdrew: NS Age of intervention group at the start of the trial: mean 34.6 years, standard deviation 3.5 Age of control group at the start of the trial: mean 34.2 years, standard deviation 4.6 No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: NS Cause/duration of subfertility of control group: NS Other relevant demographic information: none
Interventions	Dose of aspirin given to intervention group: 100 mg per day Control treatment: no treatment Concomitant treatment given to intervention group: standard protocol

Aspirin for in vitro fertilisation (Review)

Lentini 2003 (Continued)

Concomitant treatment given to control group: standard protocol
Time of commencement of treatment: one month prior to starting IVF cycle
Duration of treatment: NS
Length of study follow-up: NS

Outcomes	<p>PRIMARY OUTCOME MEASURES</p> <p>Live birth rate (per woman/couple) in intervention group: NS Live birth rate (per woman/couple) in control group: NS</p> <p>SECONDARY OUTCOME MEASURES</p> <p>Clinical pregnancy rate (per woman/couple) in intervention group: 30.9% Clinical pregnancy rate (per woman/couple) in control group: 23.8% Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS Multiple pregnancy rate on delivery (per woman/couple) in control group: NS Miscarriage rate in intervention group: NS Miscarriage rate in control group: NS Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Complications with IVF/ICSI procedure (per woman/couple) in control group: NS</p> <p>Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS</p>
Notes	<p>Setting of trial: NS Source of funding: NS</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women undergoing IVF/not stated
Allocation concealment (selection bias)	High risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No reporting of live birth or clinical pregnancy rate per woman
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Moini 2007

Methods	<p>Study design: randomised, double-blind placebo-controlled study No. of centres involved: Two centres Method of randomisation: randomised block design Method of allocation concealment: NS</p>
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Moini 2007 (Continued)

Blinding: NS
Sample size: NS
Intention-to-treat analysis: NS
Overall risk of bias rating: high risk

Participants	<p>Inclusion criteria: women undergoing conventional IVF randomly referred to the Institute Exclusion criteria: the patients with history of endocrine disorders No. eligible for randomisation: NS No. enrolled in the trial: 145 No. randomised to intervention group at the start of the trial: 72 No. randomised to control group at the start of the trial: 73 No. in the treatment group at the end of the trial: 60 No. in the control group at the end of the trial: 56 No. (%) in the treatment group who were lost to follow-up/withdrew: cancellation rate 12 (16.7%) No. (%) in the control group who were lost to follow-up/withdrew: cancellation rate 17 (23.3%) Age of intervention group at the start of the trial: mean 29 years, range 25 to 33 Age of control group at the start of the trial: mean 30 years, range 25 to 35 No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: duration NS Causes: tubal, male or unexplained factors Cause/duration of subfertility of control group: duration NS Causes: tubal, male or unexplained factors Other relevant demographic information: None Previous history of intervention group (n): NS Previous history of control group (n): NS</p>
Interventions	<p>Dose of aspirin given to intervention group: 100 mg per day Control treatment: placebo Concomitant treatment given to intervention group: standard protocol Concomitant treatment given to control group: standard protocol Time of commencement of treatment: on the 21st of their preceding menstrual cycle Duration of treatment: until menstruation or a negative pregnancy test or until 12 weeks of pregnancy Length of study follow-up: until 12 weeks of pregnancy</p>
Outcomes	<p>PRIMARY OUTCOME MEASURES Live birth rate (per woman/couple) in intervention group: NS Live birth rate (per woman/couple) in control group: NS</p> <p>SECONDARY OUTCOME MEASURES Clinical pregnancy rate (per woman/couple) in intervention group: per embryo transfer 33/72 (45.5%) Clinical pregnancy rate (per woman/couple) in control group: 24/73 (33.3%) Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS Multiple pregnancy rate on delivery (per woman/couple) in control group: NS Miscarriage rate in intervention group: NS Miscarriage rate in control group: NS Complications with IVF/ICSI procedure (per woman/couple) in intervention group: OHSS 5.6% Complications with IVF/ICSI procedure (per woman/couple) in control group: OHSS 23.3% Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS</p>
Notes	<p>Setting of trial: Department of Endocrinology and Female Infertility (Moini, Zafarani, Haddadian, Ahmadi), Royan Institute, and the Department of Obstetrics and Gynecology (Honar, Riazi), Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Source of funding: NS</p>

Risk of bias
Aspirin for in vitro fertilisation (Review)

Moini 2007 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised block design
Allocation concealment (selection bias)	High risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Reporting of clinical pregnancy rate per embryo transfer
Selective reporting (reporting bias)	Unclear risk	No data
Other bias	Unclear risk	Unclear

Pakilla 2005

Methods	Study design: parallel randomised controlled trial No. of centres involved: Four centres Method of randomisation: NS Method of allocation concealment: sealed envelopes prepared by pharmacist Blinding: participants and the individuals providing the intervention were blinded Sample size: calculation provided Intention-to-treat analysis: NS Overall risk of bias rating: moderate risk
Participants	Inclusion criteria: women less than 40, with fewer than four previous ovarian stimulations and no contraindications for aspirin. Exclusion criteria: NS No. eligible for randomisation: NS No. enrolled in the trial: NS No. randomised to intervention group at the start of the trial: 186 No. randomised to control group at the start of the trial: 188 No. in the treatment group at the end of the trial: 186 No. in the control group at the end of the trial: 187 No. (%) in the treatment group who were lost to follow-up/withdrew: 0 (0%) No. (%) in the control group who were lost to follow-up/withdrew: 1 (0.5%) Age of intervention group at the start of the trial: mean 32 years, range 24-39 Age of control group at the start of the trial: mean 31.3 years, range 22-39 No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: duration NS Causes: male factor 28%; tubal 13%; endometriosis 22%; other female 9%; unexplained 23%; mixed 5% Cause/duration of subfertility of control group: duration NS Causes: male factor 29%; tubal 15%; endometriosis 19%; other female 11%; unexplained 19%; mixed 7% Other relevant demographic information: None Previous history of intervention group (n); previous pregnancy 63; total number of pregnancies 101; live births 49; spontaneous abortion 52

Pakilla 2005 (Continued)

Previous history of control group (n); previous pregnancy 71; total number of pregnancies 122; live births 57; spontaneous abortion 65

Interventions	Dose of aspirin given to intervention group: 100 mg per day Control treatment: placebo Concomitant treatment given to intervention group: standard protocol Concomitant treatment given to control group: standard protocol Time of commencement of treatment: first day of gonadotrophin stimulation Duration of treatment: until birth Length of study follow-up: until birth
Outcomes	<p>PRIMARY OUTCOME MEASURES</p> Live birth rate (per woman/couple) in intervention group: 32/186 (17.2%) Live birth rate (per woman/couple) in control group: 37/187 (19.7%)
	<p>SECONDARY OUTCOME MEASURES</p> Clinical pregnancy rate (per woman/couple) in intervention group: 44/186 (23.7%) Clinical pregnancy rate (per woman/couple) in control group: 48/187 (25.7%) Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS Multiple pregnancy rate on delivery (per woman/couple) in control group: NS Miscarriage rate in intervention group: 8/186 (4.3%) Miscarriage rate in control group: 8/187 (4.3%) Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Ectopic pregnancy in 4/186 (2.2%) Complications with IVF/ICSI procedure (per woman/couple) in control group: NS Ectopic pregnancy in 3/187 (1.6%)
	Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Complications with IVF/ICSI procedure (per woman/couple) in control group: NS Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS
Notes	Setting of trial: Four fertility centres situated in Finland: Oulu University Hospital; The Family Federation of Finland, Oulu; Tampere University Hospital; and Kuopio University Hospital Source of funding: Academy of Finland, University of Oulu.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No data
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes prepared by pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and the individuals providing the intervention were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reporting most of the outcome measures of the review
Selective reporting (reporting bias)	Low risk	No data for selective reporting

Aspirin for in vitro fertilisation (Review)

Pakilla 2005 (Continued)

Other bias	Unclear risk	Unclear
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Rubinstein 1997-1999

Methods	<p>Study design: double blind, parallel, randomised placebo-controlled trial</p> <p>No. of centres involved: single centre</p> <p>Method of randomisation: computer-generated randomisation schedule</p> <p>Method of allocation concealment: sealed, opaque envelopes</p> <p>Blinding: both participants and individuals who provided the treatment were blinded</p> <p>Sample size: power calculation provided</p> <p>Intention-to-treat analysis: yes</p> <p>Overall risk of bias rating: low risk</p>
Participants	<p>Inclusion criteria: Women undergoing IVF with tubal factor infertility</p> <p>Exclusion criteria: NS</p> <p>No. eligible for randomisation: NS</p> <p>No. enrolled in the trial: 298</p> <p>No. randomised to intervention group at the start of the trial: 149</p> <p>No. randomised to control group at the start of the trial: 149</p> <p>No. in the treatment group at the end of the trial: 149</p> <p>No. in the control group at the end of the trial: 149</p> <p>No. (%) in the treatment group who were lost to follow-up/withdrew: 0</p> <p>No. (%) in the control group who were lost to follow-up/withdrew: 0</p> <p>Age of intervention group at the start of the trial: mean 35.9 years, standard deviation 4.2</p> <p>Age of control group at the start of the trial: mean 35.4 years, standard deviation 3.9</p> <p>No. (%) in intervention group who had previous IVF treatment: NS</p> <p>No. (%) in control group who had previous IVF treatment: NS</p> <p>Cause/duration of subfertility of intervention group: tubal infertility – duration NS</p> <p>Cause/duration of subfertility of control group: tubal infertility – duration NS</p> <p>Other relevant demographic information: NS</p>
Interventions	<p>Dose of aspirin given to intervention group: 100 mg per day</p> <p>Control treatment: placebo</p> <p>Concomitant treatment given to intervention group: standard protocol</p> <p>Concomitant treatment given to control group: standard protocol</p> <p>Time of commencement of treatment: start of GnRHa</p> <p>Duration of treatment: until 12 weeks pregnant</p> <p>Length of study follow-up: until 12 weeks pregnant</p>
Outcomes	<p>PRIMARY OUTCOME MEASURES</p> <p>Live birth rate (per woman/couple) in intervention group: NS</p> <p>Live birth rate (per woman/couple) in control group: NS</p> <p>SECONDARY OUTCOME MEASURES</p> <p>Clinical pregnancy rate (per woman/couple) in intervention group: 67/149 (45.0%)</p> <p>Clinical pregnancy rate (per woman/couple) in control group: 42/149 (28.2%)</p> <p>Chemical pregnancy rate (per woman/couple) in intervention group: NS</p> <p>Chemical pregnancy rate (per woman/couple) in control group: NS</p> <p>Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS</p> <p>Multiple pregnancy rate on delivery (per woman/couple) in control group: NS</p> <p>Miscarriage rate in intervention group: NS</p> <p>Miscarriage rate in control group: NS</p> <p>Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS</p> <p>Complications with IVF/ICSI procedure (per woman/couple) in control group: NS</p> <p>Preterm birth: NS</p> <p>Complications during pregnancy/birth (per woman/couple) in intervention group: NS</p> <p>Complications during pregnancy/birth (per woman/couple) in control group: NS</p>

Rubinstein 1997-1999 (Continued)

Notes Setting of trial: NS
Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Both participants and individuals who provided the treatment were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reporting live birth rate
Selective reporting (reporting bias)	Unclear risk	No data
Other bias	Unclear risk	No data

Urman 2000

Methods	Study design: single blind, parallel randomised controlled trial No. of centres involved: NS Method of randomisation: computer-generated randomisation schedule Method of allocation concealment: coordinated by a research nurse Blinding: only the individuals providing the treatment were blinded Sample size: power calculation provided Intention-to-treat analysis: not performed Overall risk of bias rating: moderate risk
Participants	Inclusion criteria: couples undergoing ICSI for male factor infertility Exclusion criteria: female factor infertility No. eligible for randomisation: NS No. enrolled in the trial: 300 No. randomised to intervention group at the start of the trial: 150 No. randomised to control group at the start of the trial: 150 No. in the treatment group at the end of the trial: 139 No. in the control group at the end of the trial: 136 No. (%) in the treatment group who were lost to follow-up/withdrew: 11 (7.3%) No. (%) in the control group who were lost to follow-up/withdrew: 14 (9.3%) Age of intervention group at the start of the trial: mean 32.5 years, standard deviation 4.8 Age of control group at the start of the trial: mean 32.4 years, standard deviation 4.7 No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: male factor infertility, mean duration 8.6 years, standard deviation 5.4 Cause/duration of subfertility of control group: male factor infertility, mean duration 9.1 years, standard deviation 5.5 Other relevant demographic information: NS

Aspirin for in vitro fertilisation (Review)

Urman 2000 (Continued)

Interventions	Dose of aspirin given to intervention group: 80 mg per day Control treatment: no treatment Concomitant treatment given to intervention group: standard protocol + tetracycline 200mg/day and methylprednisolone 16 mg/day administered for 5 days from day of oocyte retrieval Concomitant treatment given to control group: standard protocol + tetracycline 200mg/day and methylprednisolone 16 mg/day administered for 5 days from day of oocyte retrieval Time of commencement of treatment: start of GnRH α Duration of treatment: until confirmation of clinical pregnancy Length of study follow-up: until confirmation of clinical pregnancy
Outcomes	PRIMARY OUTCOME MEASURES Live birth rate (per woman/couple) in intervention group: NS. Live birth rate (per woman/couple) in control group: NS SECONDARY OUTCOME MEASURES Clinical pregnancy rate (per woman/couple) in intervention group: 55/139 (39.6%) Clinical pregnancy rate (per woman/couple) in control group: 59/136 (43.4%) Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS Multiple pregnancy rate on delivery (per woman/couple) in control group: NS Miscarriage rate in intervention group: 8/139 (5.8%) Miscarriage rate in control group: 7/136 (5.1%) Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Complications with IVF/ICSI procedure (per woman/couple) in control group: NS Ectopic pregnancy in 1/136 (0.7%) Ectopic pregnancy in 5/139 (3.6%) Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS
Notes	Setting of trial: NS Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Coordinated by a research nurse / no further data
Blinding (performance bias and detection bias) All outcomes	Low risk	Only the individuals providing the treatment were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No reporting of live birth rate
Selective reporting (reporting bias)	Unclear risk	No data
Other bias	Unclear risk	Unclear

Aspirin for in vitro fertilisation (Review)

Van Dooren 2004

Methods	<p>Study design: double blind, parallel randomised controlled trial</p> <p>No. of centres involved: multicentre</p> <p>Method of randomisation: NS (stratified according to primary/secondary infertility)</p> <p>Method of allocation concealment: NS</p> <p>Blinding: participants and providers of treatment were blinded</p> <p>Sample size: NS</p> <p>Intention-to-treat analysis: NS</p> <p>Overall risk of bias rating: high risk</p>
Participants	<p>Inclusion criteria: women less than 39 years old with regular cycles undergoing first IVF/ICSI cycle</p> <p>Exclusion criteria: NS</p> <p>No. eligible for randomisation: NS</p> <p>No. enrolled in the trial: NS</p> <p>No. randomised to intervention group at the start of the trial: NS</p> <p>No. randomised to control group at the start of the trial: NS</p> <p>No. in the treatment group at the end of the trial: 85</p> <p>No. in the control group at the end of the trial: 85</p> <p>No. (%) in the treatment group who were lost to follow-up/withdrew: NS</p> <p>No. (%) in the control group who were lost to follow-up/withdrew: NS</p> <p>Age of intervention group at the start of the trial: median age of all participants entered into both treatment and control groups was 32 years (range 22 to 44)</p> <p>Age of control group at the start of the trial: see above</p> <p>No. (%) in intervention group who had previous IVF treatment: NS</p> <p>No. (%) in control group who had previous IVF treatment: NS</p> <p>Cause/duration of subfertility of intervention group: described as similar in both groups, with median duration of 3 years (range 1 to 14 years)</p> <p>Cause/duration of subfertility of control group: see above</p> <p>Other relevant demographic information: none</p>
Interventions	<p>Dose of aspirin given to intervention group: 100 mg per day</p> <p>Control treatment: placebo</p> <p>Concomitant treatment given to intervention group: standard protocol</p> <p>Concomitant treatment given to control group: standard protocol</p> <p>Time of commencement of treatment: day 16 of cycle</p> <p>Duration of treatment: until 10 weeks or start of menstruation</p> <p>Length of study follow-up: unclear but beyond 12 weeks</p>
Outcomes	<p>PRIMARY OUTCOME MEASURES</p> <p>Live birth rate (per woman/couple) in intervention group: NS</p> <p>Live birth rate (per woman/couple) in control group: NS</p> <p>SECONDARY OUTCOME MEASURES</p> <p>Clinical pregnancy rate (per woman/couple) in intervention group: 31/85 (36.5%)</p> <p>Clinical pregnancy rate (per woman/couple) in control group: 29/85 (34.1%)</p> <p>Chemical pregnancy rate (per woman/couple) in intervention group: NS</p> <p>Chemical pregnancy rate (per woman/couple) in control group: NS</p> <p>Ongoing pregnancy rate in intervention group: 24/85 (28.3%)</p> <p>Ongoing pregnancy rate in control group: 25/85 (29.4%)</p> <p>Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS</p> <p>Multiple pregnancy rate on delivery (per woman/couple) in control group: NS</p> <p>Miscarriage rate in intervention group: NS</p> <p>Miscarriage rate in control group: NS</p> <p>Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS</p> <p>Complications with IVF/ICSI procedure (per woman/couple) in control group: NS</p> <p>Preterm birth: NS</p> <p>Complications during pregnancy/birth (per woman/couple) in intervention group: NS</p> <p>Complications during pregnancy/birth (per woman/couple) in control group: NS</p>

Van Dooren 2004 (Continued)

Notes Setting of trial: NS
Source of funding: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified according to primary/secondary infertility
Allocation concealment (selection bias)	High risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and providers of treatment were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No reporting of live birth rate
Selective reporting (reporting bias)	Unclear risk	No data for selective reporting
Other bias	Unclear risk	No data

NS = not stated

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Akhtar 2013	Retrospective cohort study
Frattarelli 2008	Retrospective cohort analysis
Geva 2000	ASP and prednisone; not RCT
Gizzo 2014	Not RCT
Grandone 2014	Not RCT; ASP and heparin
Guan 2007	ASP and growth hormone
Haapsamo 2009	Uterine artery haemodynamics was the primary outcome after aspirin treatment
Hanevik 2012	Combination of ASP and terbutaline
Hatasaka 2000	Not RCT
Hsieh 2000	Not IVF or ICSI
Hurst 2005	Not RCT
Kosar 2011	Not RCT, no IVF

Aspirin for in vitro fertilisation (Review)

Study	Reason for exclusion
Kuo 1997	Not RCT
Kutteh 1997	Not RCT
Lambers 2009	Follow-up through a questionnaire/original study Lambers 2008
Lee 2001	No reply to consecutive emails sent. Not enough information to determine eligibility
Madani 2014	No reply to consecutive emails sent. No available data (presented in conference proceedings) to perform analysis.
Matassa 2001	No reply to emails sent. Not enough information to determine eligibility
Mollo 2002	ASP and prednisone
Pergolini 2013	Quasi-randomised study
Rabiee 2011	Compared different regimens of aspirin in IVF
Revelli 2008	ASP and prednisone
Rubinstein 1999	Oocyte donation programme
Sher 1994	ASP and heparin
Sher 1998	Not RCT
Stern 2001	ASP and heparin; cross-over trial
Stern 2003	ASP and heparin
Stoval 1999	Not RCT
Strehler 2002	ASP and prednisone
Ubaldi 2002	ASP and prednisone
Vandana 2014	No reply to consecutive emails sent. No available data (presented in conference proceedings) to perform analysis
Villani 2015	Not RCT
Várnagy 2010	Quasi-randomised study
Wada 1994	Not RCT
Waldenström 2004	Quasi-RCT
Wallace 2003	Not RCT
Weckstein 1997	Oocyte donation programme, quasi-randomised study
Ying 2012	Retrospective analysis
Zhao 2014	Ovulation induction, not IVF

Study	Reason for exclusion
Zhu 2013	Retrospective analysis, ASP and prednisone
Zolghadr 2011	Not investigating outcome of interest. E-mail sent to verify this.

ASP = aspirin treatment

RCT = randomised controlled trial

IVF = in vitro fertilisation

ICSI = intracytoplasmic sperm injection

Characteristics of ongoing studies *[ordered by study ID]*

[Gourabi 2012](#)

Trial name or title	The Effect of Low Dose Aspirin in Increasing the Chance of Pregnancy
Methods	Study design: randomised-controlled clinical trial No. of centres involved: single centre Method of randomisation: NS Method of allocation concealment: NS Blinding: double Blind (subject, caregiver, investigator, outcomes assessor) Sample size: NS Intention-to-treat analysis: NS Overall risk of bias rating: unclear risk
Participants	Inclusion criteria: women 18 to 40 years, undergoing IVF with long or antagonist protocol, who did not achieve a pregnancy following a fresh embryo transfer or women whose embryos had not been transferred due to OHSS, or had frozen embryos available for another transfer Exclusion criteria: patients with history of recurrent abortion No. eligible for randomisation: NS No. enrolled in the trial: 60 No. randomised to intervention group at the start of the trial: NS No. randomised to control group at the start of the trial: NS No. in the treatment group at the end of the trial: NS No. in the control group at the end of the trial: NS No. (%) in the treatment group who were lost to follow-up/withdrew: NS No. (%) in the control group who were lost to follow-up/withdrew: NS Age of intervention group at the start of the trial: NS Age of control group at the start of the trial: NS No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: NS Cause/duration of subfertility of control group: NS Other relevant demographic information: NS
Interventions	Dose of aspirin given to intervention group: 100 mg per day Control treatment: placebo Concomitant treatment given to intervention group: standard protocol Concomitant treatment given to control group: standard protocol Time of commencement of treatment: with the onset of endometrial preparation and oestrogen treatment Duration of treatment: a further 5 weeks following a positive β HCG Length of study follow-up: until 20 weeks of gestation
Outcomes	PRIMARY OUTCOME MEASURES Live birth rate (per woman/couple) in intervention group: NS Live birth rate (per woman/couple) in control group: NS

Gourabi 2012 (Continued)

SECONDARY OUTCOME MEASURES

Clinical pregnancy rate (per woman/couple) in intervention group: NS
 Clinical pregnancy rate (per woman/couple) in control group: NS
 Chemical pregnancy rate (per woman/couple) in intervention group: NS
 Chemical pregnancy rate (per woman/couple) in control group: NS
 Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS
 Multiple pregnancy rate on delivery (per woman/couple) in control group: NS
 Miscarriage rate in intervention group: NS
 Miscarriage rate in control group: NS
 Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS
 Complications with IVF/ICSI procedure (per woman/couple) in control group: NS

 Preterm birth: NS

 Complications during pregnancy/birth (per woman/couple) in intervention group: NS
 Complications during pregnancy/birth (per woman/couple) in control group: NS

Starting date	May 2012 to October 2012
Contact information	gourabi@royaninstitute.org
Notes	http://clinicaltrials.gov/show/NCT01633528 Setting of trial: Royan Institute, Tehran, Iran Source of funding: NS

Vandana 2013

Trial name or title	
Methods	Study design: randomised-controlled clinical trial No. of centres involved: single centre Method of randomisation: NS Method of allocation concealment: NS Blinding: single blind (subject) Sample size: NS Intention-to-treat analysis: NS Overall risk of bias rating: unclear risk
Participants	Inclusion criteria: Women 19 to 35 years undergoing IVF, with FSH levels of ≤ 8 IU/l and BMI between 19 kg/m ² and 25 kg/m ² , with presence of both ovaries; ≥ 2 previous IVF failures, good-quality embryos for transfer and endometrial thickness between 10 mm and 14 mm Exclusion criteria: women with polycystic ovary syndrome and/or endometriosis No. eligible for randomisation: NS No. enrolled in the trial: estimated enrolment is 400 participants No. randomised to intervention group at the start of the trial: NS No. randomised to control group at the start of the trial: NS No. in the treatment group at the end of the trial: NS No. in the control group at the end of the trial: NS No. (%) in the treatment group who were lost to follow-up/withdrew: NS No. (%) in the control group who were lost to follow-up/withdrew: NS Age of intervention group at the start of the trial: NS Age of control group at the start of the trial: NS No. (%) in intervention group who had previous IVF treatment: NS No. (%) in control group who had previous IVF treatment: NS Cause/duration of subfertility of intervention group: NS Cause/duration of subfertility of control group: NS Other relevant demographic information: NS

Vandana 2013 (Continued)

Interventions	Dose of aspirin given to intervention group: 75 mg per day Control treatment: placebo (sodium chloride) Concomitant treatment given to intervention group: NS Concomitant treatment given to control group: NS Time of commencement of treatment: NS Length of study follow-up: NS
Outcomes	PRIMARY OUTCOME MEASURES Live birth rate (per woman/couple) in intervention group: NS. Live birth rate (per woman/couple) in control group: NS SECONDARY OUTCOME MEASURES Clinical pregnancy rate (per woman/couple) in intervention group: NS Clinical pregnancy rate (per woman/couple) in control group: NS Chemical pregnancy rate (per woman/couple) in intervention group: NS Chemical pregnancy rate (per woman/couple) in control group: NS Multiple pregnancy rate on ultrasound (per woman/couple) in intervention group: NS Multiple pregnancy rate on delivery (per woman/couple) in control group: NS Miscarriage rate in intervention group: NS Miscarriage rate in control group: NS Complications with IVF/ICSI procedure (per woman/couple) in intervention group: NS Complications with IVF/ICSI procedure (per woman/couple) in control group: NS Preterm birth: NS Complications during pregnancy/birth (per woman/couple) in intervention group: NS Complications during pregnancy/birth (per woman/couple) in control group: NS
Starting date	
Contact information	
Notes	http://clinicaltrials.gov/show/NCT01924104 Setting of trial: Jeevan Jyoti Hospital, India Source of funding: NS

NS = not stated

DATA AND ANALYSES

Comparison 1. Low-dose aspirin versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman or couple	3	1053	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.15]
2 Clinical pregnancy rate per woman or couple	10	2142	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.17]
3 Ongoing pregnancy rate (beyond 12 weeks)	2	339	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.69, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Multiple pregnancy rate per woman per couple (on ultrasound)	2	656	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.37, 1.25]
5 Multiple pregnancy rate per woman per couple at birth	2	680	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.38, 1.46]
6 Miscarriage rate per woman per couple	5	1497	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.68, 1.77]
7 Complications during pregnancy per woman per couple - ectopic pregnancy	3	1135	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.75, 4.63]
8 Complications during pregnancy per woman/per couple/vaginal bleeding during pregnancy	1	487	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.14, 7.13]
9 Clinical pregnancy rate - subgroup analysis - timing of treatment	10	2142	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.17]
9.1 Treatment started before down-regulation	2	362	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.80, 1.38]
9.2 Treatment started at down-regulation	4	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.92, 1.31]
9.3 Treatment started after down-regulation	4	774	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.17]
10 Clinical pregnancy rate - sensitivity analysis	3	849	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.23]

Analysis 1.1. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 1 Live birth rate per woman or couple.

Analysis 1.2. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 2 Clinical pregnancy rate per woman or couple.

Analysis 1.3. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 3 Ongoing pregnancy rate (beyond 12 weeks).

Analysis 1.4. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 4 Multiple pregnancy rate per woman per couple (on ultrasound).

Analysis 1.5. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 5 Multiple pregnancy rate per woman per couple at birth.

Analysis 1.6. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 6 Miscarriage rate per woman per couple.

Analysis 1.7. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 7 Complications during pregnancy per woman per couple - ectopic pregnancy.

Analysis 1.8. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 8 Complications during pregnancy per woman/per couple/vaginal bleeding during pregnancy.

Analysis 1.9. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 9 Clinical pregnancy rate - subgroup analysis - timing of treatment.

Analysis 1.10. Comparison 1 Low-dose aspirin versus placebo or no treatment, Outcome 10 Clinical pregnancy rate - sensitivity analysis.

APPENDICES

Appendix 1. Gynaecology and Fertility specialised register search strategy

From inception to 9 May 2016

PROCITE platform

Keywords CONTAINS "IVF" or "ICSI" or "ET" or "intracytoplasmic sperm injection techniques" or "intracytoplasmic sperm injection" or "in-vitro fertilisation " or "in vitro fertilization" or "Embryo Transfer" or "subfertility" or Title CONTAINS "IVF" or "ICSI" or "ET" or "intracytoplasmic sperm injection techniques" or "intracytoplasmic sperm injection" or "in-vitro fertilisation " or "in vitro fertilization" or "Embryo Transfer" or "subfertility"

AND

Keywords CONTAINS "aspirin" or "acetylsalicylic acid" or "acetylsalicylic" or "low-dose aspirin" or Title CONTAINS "aspirin" or "acetylsalicylic acid" or "acetylsalicylic" or "low-dose aspirin"

Appendix 2. CENTRAL CRSO search strategy

From inception until 09.05.16

WEB platform

```
# 1MESH DESCRIPTOR Aspirin EXPLODE ALL TREES (4323)
# 2(acetylsalicylic acid):TI,AB,KY (4437)
# 3Aspirin:TI,AB,KY (8247)
#4 #1 OR #2 OR #3 (10421)
#5 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES (886)
#6 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES (1737)
#7 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES (437)
#8 MESH DESCRIPTOR Oocyte Donation EXPLODE ALL TREES (61)
#9 (embryo transfer*):TI,AB,KY (1801)
#10 (in vitro fertili?ation):TI,AB,KY (1812)
#11 (intracytoplasmic sperm injection*):TI,AB,KY (952)
#12 ((ivf or icsi)):TI,AB,KY (3252)
#13 (subfertil* or infertil*):TI,AB,KY (3976)
#14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 (6779)
#15 #4 AND #14 (65)
```

Appendix 3. MEDLINE search strategy

From inception to 9 May 2016

OVID platform

- 1 exp Aspirin/ (40294)
- 2 Aspirin.tw. (40227)
- 3 acetylsalicylic acid.tw. (7840)
- 4 acetyl salicylic acid.tw. (714)
- 5 or/1-4 (60387)
- 6 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (35036)
- 7 (ivf or icsi).tw. (21528)
- 8 embryo implantation/ or "embryo implant\$.tw. (11297)
- 9 (in vitro adj5 fertili\$).tw. (21401)
- 10 (intracytoplas\$ adj5 sperm\$).tw. (5895)
- 11 (embryo\$ adj2 transfer\$).tw. (12743)
- 12 (subfertil\$ or infertil\$).tw. (50192)
- 13 or/6-12 (95822)
- 14 13 and 5 (182)
- 15 randomized controlled trial.pt. (416068)
- 16 controlled clinical trial.pt. (90685)
- 17 randomized.ab. (345922)
- 18 placebo.tw. (174380)
- 19 clinical trials as topic.sh. (176608)
- 20 randomly.ab. (248609)
- 21 trial.ti. (150461)
- 22 (crossover or cross-over or cross over).tw. (67373)
- 23 or/15-22 (1039400)
- 24 (animals not (humans and animals)).sh. (4207675)
- 25 23 not 24 (955768)
- 26 25 and 14 (56)

Appendix 4. EMBASE search strategy

From inception to 9 May 2016

OVID platform

- 1 Acetylsalicylic Acid/ (169121)
- 2 (acetylsalicylic acid or aspirin).tw. (103758)
- 3 acetyl salicylic acid.tw. (949)
- 4 or/1-3 (176696)
- 5 fertilization in vitro/ or intracytoplasmic sperm injection/ (50737)
- 6 (ivf or icsi).tw. (34649)
- 7 (vitro adj5 fertili\$).tw. (26377)
- 8 (invitro adj3 fertili\$).tw. (156)
- 9 (intracytoplas\$ adj5 sperm\$).tw. (7834)
- 10 "embryo implant\$.tw. (3176)
- 11 exp embryo transfer/ (23893)
- 12 (subfertil\$ or infertil\$).tw. (67128)
- 13 embryo\$ transfer\$.tw. (15111)
- 14 blastocyst\$ transfer\$.tw. (1352)
- 15 or/5-14 (123245)
- 16 4 and 15 (560)
- 17 Clinical Trial/ (857604)
- 18 Randomized Controlled Trial/ (400657)
- 19 exp randomization/ (70433)
- 20 Single Blind Procedure/ (22044)
- 21 Double Blind Procedure/ (128143)
- 22 Crossover Procedure/ (46975)
- 23 Placebo/ (274354)
- 24 Randomized controlled trial\$.tw. (134803)

25 Rct.tw. (20138)
 26 random allocation.tw. (1517)
 27 randomly allocated.tw. (24542)
 28 allocated randomly.tw. (2103)
 29 (allocated adj2 random).tw. (753)
 30 Single blind\$.tw. (17275)
 31 Double blind\$.tw. (161303)
 32 ((treble or triple) adj blind\$).tw. (546)
 33 placebo\$.tw. (231765)
 34 prospective study/ (332279)
 35 or/17-34 (1567040)
 36 case study/ (37719)
 37 case report.tw. (304762)
 38 abstract report/ or letter/ (958196)
 39 or/36-38 (1293701)
 40 35 not 39 (1526102)
 41 16 and 40 (191)

Appendix 5. PsycINFO search strategy

From inception to 9 May 2016

OVID platform

1 exp Aspirin/ (428)
 2 (acetylsalicylic acid or aspirin).tw. (1157)
 3 1 or 2 (1183)
 4 exp Reproductive Technology/ (1555)
 5 (ivf or icsi).tw. (483)
 6 (in vitro adj5 fertili\$).tw. (630)
 7 (intracytoplas\$ adj5 sperm\$).tw. (45)
 8 (embryo transfer or ET).tw. (109022)
 9 or/4-8 (110730)
 10 3 and 9 (67)
 11 random.tw. (46576)
 12 control.tw. (361175)
 13 double-blind.tw. (19789)
 14 clinical trials/ (9544)
 15 placebo/ (4523)
 16 exp Treatment/ (649821)
 17 or/11-16 (1000321)
 18 10 and 17 (44)

Appendix 6. 'ClinicalTrials.gov' and World Health Organization International Trials Registry Platform search portal

From inception to 9 May 2016

Web platforms

"(aspirin OR acetylsalicylic acid) AND (in-vitro fertilisation OR intracytoplasmic sperm injection OR assisted reproduction)".

WHAT'S NEW

Date	Event	Description
14 December 2016	Review declared as stable	Further evidence is unlikely to change the conclusions of this review.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2007

Date	Event	Description
10 September 2016	New search has been performed	Update of the review. Change of two authors. Text was thoroughly modified according to current Cochrane guidelines. Seventeen new studies were excluded and justified, no new studies were included.
10 September 2016	New citation required but conclusions have not changed	With this update the conclusions of the review did not change.
19 April 2011	New citation required and conclusions have changed	Change of title Revision of list of outcomes - reduction to 7 (removal of admission to NICU, fetal abnormalities, birth weight and participant evaluation of aspirin). Addition under complications during pregnancy of preterm birth.
29 January 2011	Amended	Update of the review four new studies were included
5 August 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

V Poustie devised the idea for the original review, which was further refined following discussions with A Drakeley and S Dodd. A Drakeley wrote the background, S Dodd wrote the statistical content of the methods of the review and V Poustie completed the remaining sections. All authors commented on the draft of the review prior to completion.

in 2011, C Siristatidis with A Drakeley updated the review. V Poustie was not involved in that update.

During the current update (2016), S Siristatidis with P Vogiatzi updated the review, G Basios commented on and edited the final text, while V Pergialiotis followed all steps for this update, this being his first participation in a Cochrane review.

DECLARATIONS OF INTEREST

Previous author V Poustie has undergone IVF treatment in the past and has previously taken low-dose aspirin during this treatment.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- MDSG, Trials Search Coordinator, New Zealand.
- Susanna Dodd, UK.

We would like to help Susanna Dodd for her valuable help in her major contribution during the initial version and the first update of this review

- George Basios, Greece.

We would like to thank George Basios for his valuable help in selecting the studies in the initial phase of the 2014 update.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Fertilization in Vitro; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Aspirin [*administration & dosage]; Cyclooxygenase Inhibitors [*administration & dosage]; Live Birth; Platelet Aggregation Inhibitors [*administration & dosage]; Pregnancy Outcome; Pregnancy Rate; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Pregnancy