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Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer) (Review)

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Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer).
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD011809.
DOI: 10.1002/14651858.CD011809.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer)

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2018.

Citation: Ata B, Abou-Setta AM, Seyhan A, Buckett W. Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer). *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD011809. DOI: 10.1002/14651858.CD011809.pub2.

ABSTRACT

Background

The female genital tract is not exposed to seminal plasma during standard assisted reproductive technology (ART) cycles. However, it is thought that the inflammatory reaction triggered by seminal plasma may be beneficial by inducing maternal tolerance to paternal antigens expressed by the products of conception, and may increase the chance of successful implantation and live birth.

Objectives

To assess the effectiveness and safety of application of seminal plasma to the female genital tract prior to embryo transfer in ART cycles.

Search methods

We searched the following databases from inception to October 2017: Cochrane Gynaecology and Fertility Group Specialised Register of Controlled Trials, Cochrane Central Register of Studies Online (CRSO), MEDLINE, Embase, CINAHL and PsycINFO. We also searched trial registers for ongoing trials, including International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov. Other sources searched were; Web of Knowledge, OpenGrey, LILACS, PubMed, Google Scholar, and the reference lists of relevant articles.

Selection criteria

We included randomised controlled trials (RCTs) conducted among women undergoing ART, comparing any procedure that would expose the female genital tract to seminal plasma during the period starting five days before embryo transfer and ending two days after it versus no seminal plasma application.

Data collection and analysis

Two review authors independently selected trials, assessed risk of bias, and extracted data. We pooled data to calculate relative risks (RRs) and 95% confidence intervals (CIs). We assessed statistical heterogeneity using the I^2 statistic. We assessed the overall quality of the evidence for the main outcomes using GRADE methods. Our primary outcomes were live birth rate and miscarriage rate. Secondary outcomes were live birth/ongoing pregnancy rate, clinical pregnancy rate, multiple pregnancy rate, ectopic pregnancy rate, and the incidence of other adverse events.

Main results

We included 11 RCTs (3215 women). The quality of the evidence ranged from very low to low. The main limitations were risk of bias (associated with poor reporting of allocation concealment and other methods) and imprecision for the primary outcome of live birth rate.

Live birth rates: Seminal plasma application made little or no difference in live birth rates (RR 1.10, 95% CI 0.86 to 1.43; 948 participants; 3 studies; I^2 = 0%). Low-quality evidence suggested that if the live birth rate following standard ART was 19%, it would be between 16% and 27% with seminal plasma application.

Miscarriage rate: Seminal plasma application made little or no difference in miscarriage rates (RR 1.01, 95% CI 0.57 to 1.79; 1209 participants; 4 studies; I^2 = 0%). Low-quality evidence suggested that if the miscarriage rate following standard ART was 3.7%, the miscarriage rate following seminal plasma application would be between 2.1% and 6.6%.

Live birth or ongoing pregnancy rates: Seminal plasma application made little or no difference in live birth or ongoing pregnancy rates (RR 1.19, 95% CI 0.95 to 1.49; 1178 participants; 4 studies; I^2 = 4%, low-quality evidence). The evidence suggested that if the live birth or ongoing pregnancy rate following standard ART was 19.5%, it would be between 18.5% and 29% with seminal plasma application.

Clinical pregnancy rates: We are uncertain whether seminal plasma application increases clinical pregnancy rates (RR 1.15, 95% CI 1.01 to 1.31; 2768 participants; 10 studies; I^2 = 0%). Very low-quality evidence suggested that if the clinical pregnancy rate following standard ART was 22.0%, it would be between 22.2% and 28.8% with seminal plasma application. This finding should be regarded with caution, as a post hoc sensitivity analysis restricted to studies at overall low risk of bias did not find a significant difference between the groups (RR 1.06, 95% CI 0.81 to 1.39; 547 participants; 3 studies; I^2 = 0%).

Multiple pregnancy rate: Seminal plasma application may make little or no difference to multiple pregnancy rates (RR 1.11, 95% CI 0.76 to 1.64; 1642 participants; 5 studies; I^2 = 9%). Low-quality evidence suggested that if the multiple pregnancy rate following standard ART was 7%, the multiple pregnancy rate following seminal plasma application would be between 5% and 11.4%.

Ectopic pregnancy: There was insufficient evidence to determine whether seminal plasma application influenced the risk of ectopic pregnancy (RR 1.59, 95% CI 0.20 to 12.78, 1521 participants; 5 studies; I^2 = 0%) .

Infectious complications or other adverse events: No data were available on these outcomes

Authors' conclusions

In women undergoing ART, there was insufficient evidence to determine whether there was a difference between the seminal plasma and the standard ART group in rates of live birth (low-quality evidence) or miscarriage (low-quality evidence). There was low-quality evidence suggesting little or no difference between the groups in rates of live birth or ongoing pregnancy (composite outcome). We found low-quality evidence that seminal plasma application may be associated with more clinical pregnancies than standard ART. There was low-quality evidence suggesting little or no difference between the groups in rates of multiple pregnancy. There was insufficient evidence to reach any conclusions about the risk of ectopic pregnancy, and no data were available on infectious complications or other adverse events.

We conclude that seminal plasma application is worth further investigation, focusing on live birth and miscarriage rates.

PLAIN LANGUAGE SUMMARY

Seminal fluid application to improve assisted reproduction outcomes

Review question

The main aim of this review was to assess whether application of seminal plasma to the female genital tract around the time of embryo transfer improves live birth rates in assisted reproductive technology (ART) cycles. Seminal plasma is the fluid part of the ejaculate, and the female genital tract consists of the vagina, the neck of the womb and the womb.

Background

In ART cycles, the egg and sperm are mixed outside the body to develop embryos. One or two of the embryos are replaced into the womb in a very small amount of artificial fluid. During this process, the woman's body does not come into contact with seminal plasma at all, unlike during normal intercourse where the male partner ejaculates in the vagina, exposing the latter to seminal fluid. It has been suggested that seminal plasma contains several molecules which can help the embryos to attach to the womb. The logical question is whether application of some seminal plasma to the vagina/neck of the womb or womb increases the chances of a live birth after ART.

Study characteristics

This Cochrane review included 11 randomised controlled trials, in which women were randomly allocated to receive seminal plasma or not. These trials included a total of 3215 women undergoing ART. The evidence is current to October 2017.

Key results

We found no clear evidence to suggest whether seminal plasma application influences rates of live birth or miscarriage in women undergoing ART. However, we found low-quality evidence suggesting that seminal plasma application may possibly lead to more clinical pregnancies than standard ART. There was low-quality evidence suggesting little or no difference between the groups in rates of multiple pregnancy. There was insufficient evidence to reach any conclusions about the risk of ectopic pregnancy (pregnancy in which the embryo attaches outside the womb), and no data were available on infectious complications or other adverse events.

We conclude that seminal plasma application is worth further investigation focusing on live birth and miscarriage rates.

Quality of evidence

The quality of evidence ranged from very low to low.The main limitations were risk of bias (associated with poor reporting of study methods) and lack of data for the primary outcome of live birth rate.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. ART with seminal plasma compared to standard ART (IVF, ICSI, and frozen embryo transfer)

ART with seminal plasma compared to standard ART (IVF, ICSI, and frozen embryo transfer)

Population: Women undergoing ART (IVF, ICSI, or frozen embryo transfer)
Setting: Assisted reproduction clinic
Intervention: Seminal plasma
Comparison: Standard IVF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk with standard IVF	Corresponding risk with seminal plasma				
Live birth	191 per 1,000	210 per 1,000 (164 to 273)	RR 1.10 (0.86 to 1.43)	948 (3 RCTs)	⊕⊕⊖⊖[1,2] **low**	
Miscarriage	38 per 1,000	38 per 1,000 (21 to 67)	RR 1.01 (0.57 to 1.79)	1209 (4 RCTs)	⊕⊕⊖⊖[3,4] **low**	
Live birth or ongoing pregnancy	195 per 1,000	232 per 1,000 (185 to 291)	RR 1.19 (0.95 to 1.49)	1178 (4 RCTs)	⊕⊕⊖⊖[2,5] **low**	
Clinical pregnancy	220 per 1,000	252 per 1,000 (222 to 288)	RR 1.15 (1.01 to 1.31)	2768 (10 RCTs)	⊕⊕⊖⊖[3,6,7] **very low**	A post hoc sensitivity analysis excluding studies at overall high risk of bias negated the statistical significance of the finding (RR 1.06, 95% CI 0.81 to 1.39; participants = 547; studies = 3; I^2 = 0%)
Multiple pregnancy	70 per 1,000	77 per 1,000 (53 to 114)	RR 1.11 (0.76 to 1.64)	1642 (5 RCTs)	⊕⊕⊖⊖[4,8] **low**	
Ectopic pregnancy	1 per 1,000	2 per 1,000 (0 to 17)	RR 1.59 (0.20 to 12.78)	1521 (5 RCTs)	⊕⊕⊖⊖[9,10] **very low**	

Adverse events, including infectious complications	No data available

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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 risk of bias: method of allocation concealment was unclear in all of the included trials. The outcomes are/may have been incompletely reported in two of the three trials.
[2] Downgraded one level for serious imprecision: total number of events was small and the confidence interval was not narrow enough to exclude potential significant benefit.
[3] Downgraded one level for serious risk of bias: method of allocation concealment was unclear in 2/4 trials. Selective reporting is a concern for one trial, incomplete data for another trial.
[4] Downgraded one level for serious imprecision: total number of events was small and the confidence interval was not narrow enough to exclude potential significant harm or benefit.
[5] Downgraded one level for serious risk of bias: method of allocation concealment is unclear. There could be incomplete reporting for some participants.
[6] Downgraded one level for serious risk of bias: method of allocation concealment was unclear in most trials and allocation was not concealed in one. Blinding was not possible in the trials of vaginal application and was not done in some others. Incomplete reporting and other biases are also concerning for two trials. Downgraded a further level for serious risk of bias, as a post hoc sensitivity analysis excluding studies at overall high risk of bias negated the statistical significance of the finding (RR 1.06, 95% CI 0.81 to 1.39; participants = 547; studies = 3; I^2 = 0%).
[7] Downgraded one level for imprecision - confidence interval was compatible with benefit in the intervention arm or with no clinically meaningful effect.
[8] Downgraded one level for serious risk of bias: method of allocation concealment was unclear in 2/4 trials and allocation was not concealed in 1/4 trials. Incomplete data can be a concern for all trials.
[9] Downgraded one level for serious risk of bias: method of allocation concealment was unclear.
[10] Downgraded two levels for very serious imprecision: only 3 events and very wide confidence intervals.

BACKGROUND

Description of the condition

Despite advances in both clinical and laboratory aspects of assisted reproductive technologies, live birth rates have plateaued for the last decade. Embryo implantation, a delicate process requiring harmony between the implantation competent embryo and receptive endometrium (inner lining of the uterus), may be the rate-limiting step. Currently, 20% to 35% of chromosomally normal embryos fail to implant (Lee 2015). This suggests that other factors than just aneuploidy (having abnormal number of chromosomes) are possibly preventing implantation. These could include inadequate maternal immune tolerance for the products of conception, which also express paternal genes. The products of the paternal genes, i.e. paternal antigens (molecules that can stimulate the immune system), can be recognised as 'foreign' by the maternal immune system and they can trigger an immune response (Tafuri 1995).

The progression of pregnancy therefore partially depends on protection of the products of conception from a destructive maternal immune response. A particular component of the maternal immune system, named regulatory T cells, can suppress such an immune reaction against the products of conception despite its expression of paternal 'foreign' antigens (Robertson 2013). However, proper activation of regulatory T cells requires their exposure to paternal antigens in advance (Samy 2006). The presence of immune-modulatory molecules such as transforming growth factor-beta (TGF-β), interleukin (IL)-10, granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-4 are also required during the initial contact of paternal antigens and T cells (Sato 2003). In summary, maternal regulatory T cells need to be primed before implantation by paternal antigens which are common with the products of conception, in order to generate immune tolerance.

The ejaculate is comprised of spermatozoa and seminal plasma. Seminal plasma is a combination of the secretions of seminal vesicles, and prostate and bulbourethral glands (secretory glands of the male reproductive system). It is a rich source of paternal antigens, cytokines (small proteins that enable communication between different cells), prostaglandins (short lived molecules that effect close by cells) and growth factors, which regulate endometrial receptivity and could play a role in inducing maternal immune tolerance (Achache 2006; Robertson 2002; Robertson 2005; Simon 2000).

However, spermatozoa are isolated from seminal plasma before being used for oocyte (egg) fertilisation in assisted reproductive technology cycles. Embryos generated in vitro (in the laboratory) are transferred to the uterus in artificial transfer media. Hence, the female genital tract is not exposed to seminal plasma during an assisted reproductive technology cycle. Already established live births with assisted reproductive technology attest to the fact that such exposure is not an absolute requirement for successful implantation. However, the lack of it could be a contributing factor to limited embryo implantation rates. It is thought that the inflammatory reaction triggered by seminal plasma in the female genital tract can induce maternal tolerance to the paternal antigens expressed by the products of conception and increase its chances to successfully implant and lead to a live birth.

Description of the intervention

In assisted reproductive technology cycles the female genital tract can be brought into contact with seminal plasma in several ways including unprotected vaginal intercourse around the time of the embryo transfer, and seminal plasma application to the vagina, cervical canal or into the endometrial cavity prior to embryo transfer. The effect on endometrial receptivity and implantation process may vary depending on the route of application. Application of seminal plasma to female genital tract is a quite straight forward procedure which is usually painless. Although very rare, upper genital tract infection is a potential complication.

How the intervention might work

Previous studies suggest that paternal antigens and the cytokines present in seminal plasma can induce regulatory T cell generation and interact with endometrial cells to suppress the maternal immune response against the products of conception that expresses similar paternal antigens (Bromfield 2014; Robertson 2013). Moreover, seminal plasma is also shown to up-regulate expression of angiogenic factors (substances that promote new blood vessel formation) by endometrial cells, which could also help vascularisation (formation of new small blood vessels) of the feto-maternal unit (Chen 2014). Eventually, seminal plasma exposure prior to embryo transfer could be expected to increase embryo implantation and live birth rates.

Why it is important to do this review

Trials investigating the effect of seminal plasma exposure on clinical outcome of assisted reproductive technology cycles have been published with conflicting results. Assessment of available evidence in its totality and conducting relevant subgroup analysis can provide either a definitive conclusion or inform future research on the subject. .

OBJECTIVES

To assess the effectiveness and safety of application of seminal plasma to the female genital tract prior to embryo transfer in assisted reproductive technology cycles.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised controlled trials (RCTs). We excluded non-randomised and quasi-randomised studies (e.g. studies with evidence of inadequate sequence generation, such as alternate days, patient numbers).

Types of participants

Women undergoing fresh or frozen thawed embryo transfer.

Types of interventions

Any procedure that would expose the female genital tract to seminal plasma during the period starting five days before embryo transfer and ending two days after it, including the following:

- unprotected vaginal intercourse;

- application of seminal plasma to the vagina;
- application of seminal plasma into the cervical canal;
- application of seminal plasma into the cervical canal and to the vagina;
- instillation of seminal plasma into the endometrial cavity;
- intrauterine insemination with unprocessed semen.

Our comparator was assisted reproductive technology cycles without any seminal plasma application. There were no studies comparing different locations of seminal plasma application.

Types of outcome measures

Primary outcomes

1. Live birth rate per randomised woman, defined as delivery of a live fetus after 20 completed weeks of gestation.

2. Miscarriage rate per randomised woman, defined as pregnancy loss before 20 weeks of gestation.

Secondary outcomes

3. Live birth or ongoing pregnancy rate per randomised woman. An ongoing pregnancy was defined as one that progresses beyond the 12th gestational week.

4. Clinical pregnancy rate per randomised woman, defined as evidence of a gestational sac, confirmed by ultrasound.

Adverse events

5. Multiple pregnancy rate per randomised woman, defined as the presence of more than one gestational sac, confirmed by ultrasound.

6. Ectopic pregnancy rate per randomised woman, defined as the presence of a gestational sac outside the endometrial cavity, confirmed by ultrasound.

7. Incidence of infections per randomised woman, as evidenced by the presence of fever > 37°C or clinical findings e.g. tenderness, mucopurulent discharge, or as reported by trialists.

8. Any other reported adverse events.

Search methods for identification of studies

We searched for all published and unpublished RCTs of seminal plasma application during assisted reproductive technology cycles, without language restriction, and in consultation with the Gynaecology and Fertility Group Information Specialist.

Electronic searches

We searched the following electronic databases, trial registers, and websites from the date of inception until 16 October 2017:

- Cochrane Gynaecology and Fertility Group Specialised Register of Controlled Trials (Procite platform) (Appendix 1);
- Cochrane Central Register of Studies Online (CRSO) (Web Platform) (Appendix 2);
- MEDLINE (Ovid platform) (Appendix 3);
- Embase (Ovid platform) (Appendix 4);
- PsycINFO (Ovid platform) (Appendix 5);
- CINAHL (EBSCO platform) (Appendix 6).

We combined our MEDLINE search with the 'Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format' (Higgins 2011). We combined our Embase, PsycINFO and CINAHL search strategies with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/methodology/filters.html).

We also searched the following electronic sources (Appendix 7):

- Trial registers for ongoing and registered trials (e.g. clinicaltrials.gov (https://clinicaltrials.gov/)), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/));
- Database of Abstracts of Reviews of Effects (DARE) (the Cochrane Library);
- Web of Knowledge;
- OpenGrey;
- LILACS;
- PubMed;
- Google Scholar.

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also searched relevant journals and conference abstracts that were not covered in the Gynaecology and Fertility Group Specialised Register, in liaison with the Group's Information Specialist.

Data collection and analysis

Selection of studies

After an initial screen of titles and abstracts retrieved by the search, conducted by two review authors (AS and AMAS), we retrieved the full texts of all potentially eligible studies. Two authors independently examined these full-text articles for compliance with the inclusion criteria and selected trials eligible for inclusion (BA and AS). We contacted study investigators, as required, to clarify study eligibility. We resolved disagreement as to study eligibility by discussion or by consulting a third review author (AMAS). We documented the selection process with a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart.

Data extraction and management

Two review authors independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. We resolved disagreements by discussion or by consulting a third review author. Extracted data included trial characteristics and outcome data. Where trials had multiple publications, we collated the multiple reports of the same study so that each trial, rather than each report, was the unit of interest in the review, and we used a single study identification number for such studies with multiple references. We contacted study investigators for further data on methods and/or results, as required.

Assessment of risk of bias in included studies

Two review authors (BA and AS) independently assessed the risk of bias in included studies using the Cochrane's tool for assessing risk of bias (Higgins 2011b). We considered the following domains:

- 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);
- other bias, including probable unprotected intercourse during the time interval of the suggested intervention.

We resolved disagreements by discussion or by consulting a third review author (AMAS). We described all judgments fully and presented the conclusions in a 'Risk of bias' table, which we incorporated into the interpretation of review findings by means of sensitivity analyses.

We searched for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We sought published protocols and compared the outcomes between the protocol and the final published trial report.

Other biases of concern included allowing unprotected intercourse during the time interval of the intervention, potentially contaminating the results.

Where identified trials failed to report the primary outcome of live birth, but did report interim outcomes such as ongoing pregnancy, we pooled these data with live birth data from other studies. In this case, we performed a sensitivity analysis to test the robustness of the results. This was presented as the livebirth or ongoing pregnancy rate outcome.

Measures of treatment effect

As all outcomes in this review were dichotomous, we used the numbers of women with events in the control and intervention groups of each study to calculate Mantel-Haenszel risk ratios (RRs); with 95% confidence intervals (CIs) for all outcomes. We compared the magnitude and direction of effect reported by trials with how they were presented in the review, taking account of legitimate differences.

Unit of analysis issues

Our primary analysis was per woman randomised. We also performed per-pregnancy analysis for multiple pregnancy, miscarriage, and ectopic pregnancy rates.

We counted multiple live births (e.g. twins or triplets) as one live birth event.

Dealing with missing data

We analysed data on an intention-to-treat basis as far as possible and we attempted to obtain missing data from the original trialists. Where these were unobtainable, we undertook imputation of individual values for the primary outcome only. We assumed that live births had not occurred in participants without a reported outcome. For other outcomes, we analysed only the available data and no imputations were undertaken.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included trials were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the measure of the I^2. We considered an I^2 value greater than 50% as substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible trials and by being alert for duplication of data. Publication bias testing was done by visual assessment of funnel plots for analyses which included 10 or more trials.

Data synthesis

We pooled data from the primary trials using the Mantel-Haenzel random-effects model for the following comparisons.

- seminal plasma application versus no seminal plasma application;
- one location of seminal plasma application versus another location of seminal plasma application.

We stratified comparisons by seminal plasma application method:

- studies in which seminal plasma was applied vaginally either by vaginal unprotected vaginal intercourse or application of processed seminal plasma into the vagina;
- studies in which seminal plasma was inseminated into the uterine cervix;
- studies in which seminal plasma was applied to both vagina and cervix;
- studies in which seminal plasma was applied by intrauterine instillation.

In our forest plots, an increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), were displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses to assess whether the effects of the intervention differed according to the following:

- seminal plasma application method (as described above)
- type of ART cycle (fresh or frozen)

We took statistical heterogeneity into account when interpreting the results.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary

decisions made regarding the eligibility and analysis. These analyses included:

- only studies without overall high risk of bias. We defined overall high risk of bias as studies at unclear or high risk of bias in multiple domains.
- using a fixed effects model.
- alternative imputation strategies for missing information.

We also conducted a post hoc sensitivity analysis for the secondary outcome of clinical pregnancy.

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

Two review authors (BA and AMAS) working independently prepared a 'Summary of findings' table using the GRADEpro (GRADEpro GDT 2015) software (http://www.guidelinedevelopment.org). We evaluated the overall quality of the body of evidence for the main review outcomes (live birth, miscarriage, live birth or ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy, and adverse events), for the main review comparison; i.e. assisted reproductive technology cycles with seminal plasma application compared to standard assisted reproductive technology cycles without seminal plasma application (IVF, ICSI, and frozen embryo transfer), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). We justified and documented our judgments about evidence quality (high, moderate, low or very low) in the full review and incorporated these findings into the reporting of results for each outcome.

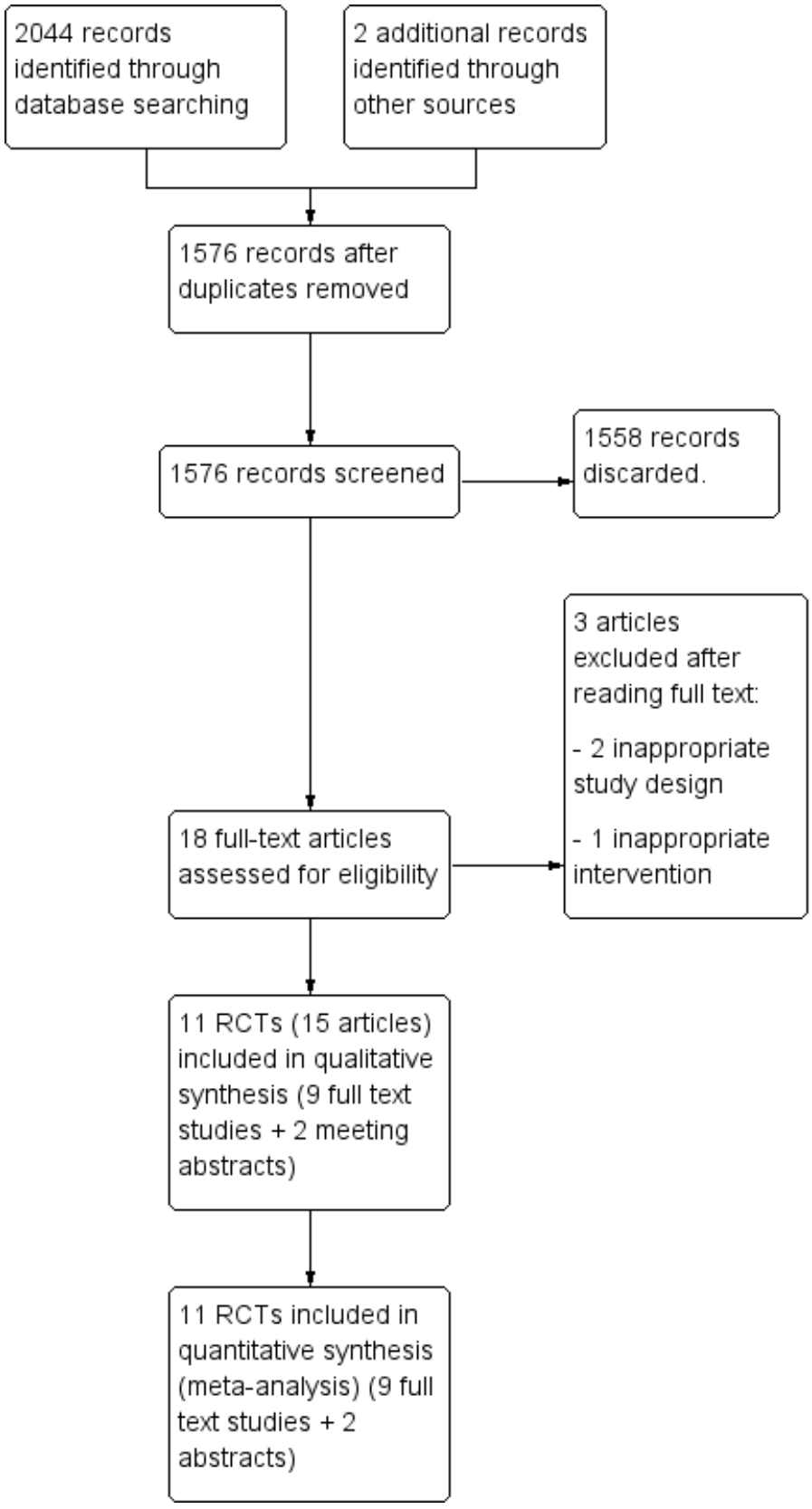
RESULTS

Description of studies

Results of the search

The electronic searches resulted in 2044 potential citations, with an additional two citations added from handsearching. After duplicate removal and screening, we identified 11 trials that met the inclusion criteria (Figure 1).

Figure 1. Study flow diagram.



Included studies

All 11 of the included studies identified from the electronic searches were conducted in 2015, 2016, and 2017. A summary of the methods, participants, interventions and outcomes are presented below. Further details are presented separately for each study in the Characteristics of included studies table.

Design

We included 11 studies with 3215 women randomised to treatment (Aflatoonian 2009; Bellinge 1986; Chicea 2013; Crawford 2015; Friedler 2013; Jafarabadi 2016; Karimian 2010; Mayer 2015; Tremellen 2000; Von Wolff 2009; Von Wolff 2013). Ten of the included studies were single centre, two-arm parallel RCTs (Aflatoonian 2009; Bellinge 1986; Chicea 2013; Crawford 2015; Friedler 2013; Jafarabadi 2016; Karimian 2010; Mayer 2015; Von Wolff 2009; Von Wolff 2013). The remaining trial was a two centre RCT, in which couples undergoing fresh embryo transfers were recruited in one centre and frozen embryo transfers were recruited in the other centre (Tremellen 2000). Each group was randomised by itself and a similar number of participants were available in seminal plasma and control groups. None of the trials used a cross-over design.

All trials included 100 or more women. The largest trials were Karimian 2010 (569 women) and Tremellen 2000 (478 women). Four trials included fewer than 200 women: Bellinge 1986 (113 women); Crawford 2015 (186 women); Mayer 2015 (100 women); and Von Wolff 2009 (133 women). The remaining five trials (Aflatoonian 2009; Chicea 2013; Friedler 2013; Jafarabadi 2016; Von Wolff 2013) included between 224 and 385 women.

The trials took place (or authors came from): Australia (Bellinge 1986); Australia and Spain (Tremellen 2000); Austria (Mayer 2015); England and Australia (Crawford 2015); Germany (Von Wolff 2009; Von Wolff 2013); Iran (Aflatoonian 2009; Jafarabadi 2016; Karimian 2010); Israel (Friedler 2013); and Romania (Chicea 2013).

Of the 11 studies, only three performed and adhered to an a priori sample size calculation (Friedler 2013; Mayer 2015; Tremellen 2000). However, Tremellen 2000 based the sample size calculation on the number of embryos transferred rather than the number of women. One study had an a priori sample size calculation but was terminated early for futility after a preplanned interim analysis (Von Wolff 2013). It was unclear whether the two studies that were published as abstracts were conducted according to a sample size calculation (Crawford 2015; Karimian 2010). The remaining five studies did not adhere to a sample size calculation (Aflatoonian 2009; Bellinge 1986; Chicea 2013; Jafarabadi 2016; Von Wolff 2009).

Participants

Inclusion Criteria

All 11 studies included women undergoing ART with a regular indication and with fresh ejaculate sperm.

One study required the couple to have at least five years of subfertility (Aflatoonian 2009).

Six studies imposed an age limit for the female partner; Chicea 2013 (< 38 years); Crawford 2015 (23 to 39 years); Friedler 2013 (< 40 years); Jafarabadi 2016 (< 40 years); Tremellen 2000 (18 to 40 years); Von Wolff 2009 (< 43 years).

Five studies mentioned a limit for number of prior ART cycles as an inclusion criterion; Chicea 2013 (< 4 prior ART cycles); Crawford 2015 (< 2 prior ART cycles); Friedler 2013 (at least one failed prior ART cycle); Jafarabadi 2016 (< 3 prior ART cycles); Mayer 2015 (< 2 prior ART cycles).

Only Tremellen 2000 included women undergoing frozen embryo transfers. This was a two centre study; one centre only recruited women undergoing fresh embryo transfers, and the other recruited only women undergoing frozen embryo transfers (Tremellen 2000). While the overall data from this trial were included in the main analyses, data from each centre were separately included in the 'fresh embryo transfer only' and 'frozen embryo transfer only' analyses.

Exclusion Criteria

Seven studies excluded couples in which the male partner had Hepatitis B, or C, HIV infection or leukocytospermia (Chicea 2013; Friedler 2013; Jafarabadi 2016; Mayer 2015; Tremellen 2000; Von Wolff 2009; Von Wolff 2013).

Only three studies excluded couples who did not have a minimum volume of seminal plasma; Mayer 2015 (0.5 ml); Von Wolff 2009 (0.5 ml); Von Wolff 2013 (0.3 ml).

Only two studies mentioned excluding women with uterine anomalies (Chicea 2013; Mayer 2015).

Four studies excluded couples based on embryology laboratory parameters. Friedler 2013 and Jafarabadi 2016 excluded couples who had no oocytes in a prior cycle. Mayer 2015 and Von Wolff 2009 excluded couples from their analyses if a couple had no embryos for transfer due to total fertilisation failure or pending ovarian hyperstimulation syndrome.

Interventions

Three studies required the couples to have unprotected vaginal intercourse around the time of embryo transfer; Aflatoonian 2009 (at least once during the 12 hours following embryo transfer); Karimian 2010 (only mentioned intercourse around the time of ART); Tremellen 2000 (for fresh embryo transfers, at least twice between 12 hours before oocyte pick up and 12 hours after embryo transfer; for frozen embryo transfers, at least once between four days before and two days after embryo transfer).

In only one study, untreated ejaculate was applied vaginally on the day of oocyte collection (Bellinge 1986). All other studies used seminal plasma (Chicea 2013; Crawford 2015; Friedler 2013; Jafarabadi 2016; Mayer 2015; Von Wolff 2009; Von Wolff 2013). Seminal plasma was applied to both cervix and vagina (Chicea 2013; Friedler 2013; Jafarabadi 2016; Mayer 2015; Von Wolff 2009; Von Wolff 2013) or only to the uterus (Crawford 2015; Von Wolff 2013).

Outcomes

Primary outcome

Only three studies reported live birth rate (Karimian 2010; Mayer 2015; Von Wolff 2013). Four studies reported miscarriage rates (Friedler 2013; Mayer 2015; Tremellen 2000; Von Wolff 2013). Definitions of these outcome measures were not clearly mentioned in the original publications.

Secondary outcomes

In addition to the three studies (Crawford 2015; Karimian 2010; Mayer 2015) reporting live birth rate, one study (Friedler 2013) reported ongoing pregnancy rate.

Clinical pregnancy was reported in 10 studies (Aflatoonian 2009; Bellinge 1986; Chicea 2013; Crawford 2015; Friedler 2013; Jafarabadi 2016; Mayer 2015; Tremellen 2000; Von Wolff 2009; Von Wolff 2013). All but one study defined clinical pregnancy with ultrasound visualisation of gestational sac and or fetal pole (Aflatoonian 2009; Bellinge 1986; Chicea 2013; Crawford 2015; Friedler 2013; Jafarabadi 2016; Tremellen 2000; Von Wolff 2009) and or fetal heart beat (Von Wolff 2013) between five and eight gestational weeks.

Five studies reported multiple pregnancy rates (Aflatoonian 2009; Bellinge 1986; Chicea 2013; Mayer 2015; Tremellen 2000). Likewise, five studies reported ectopic pregnancy rates (Aflatoonian 2009; Bellinge 1986; Mayer 2015; Tremellen 2000; Von Wolff 2013). The definitions of these outcome measures were not explicitly mentioned in the papers.

Excluded studies

Two studies (Fishel 1989; Lou 2014) were excluded since allocation was not by randomisation. Coulam 1995 was excluded because couples did not undergo ART but attempted spontaneous conception. Further details are presented in the Characteristics of excluded studies table.

Risk of bias in included studies

Of the 11 included trials, eight were at unclear or high risk of bias in multiple domains (Figure 2; Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

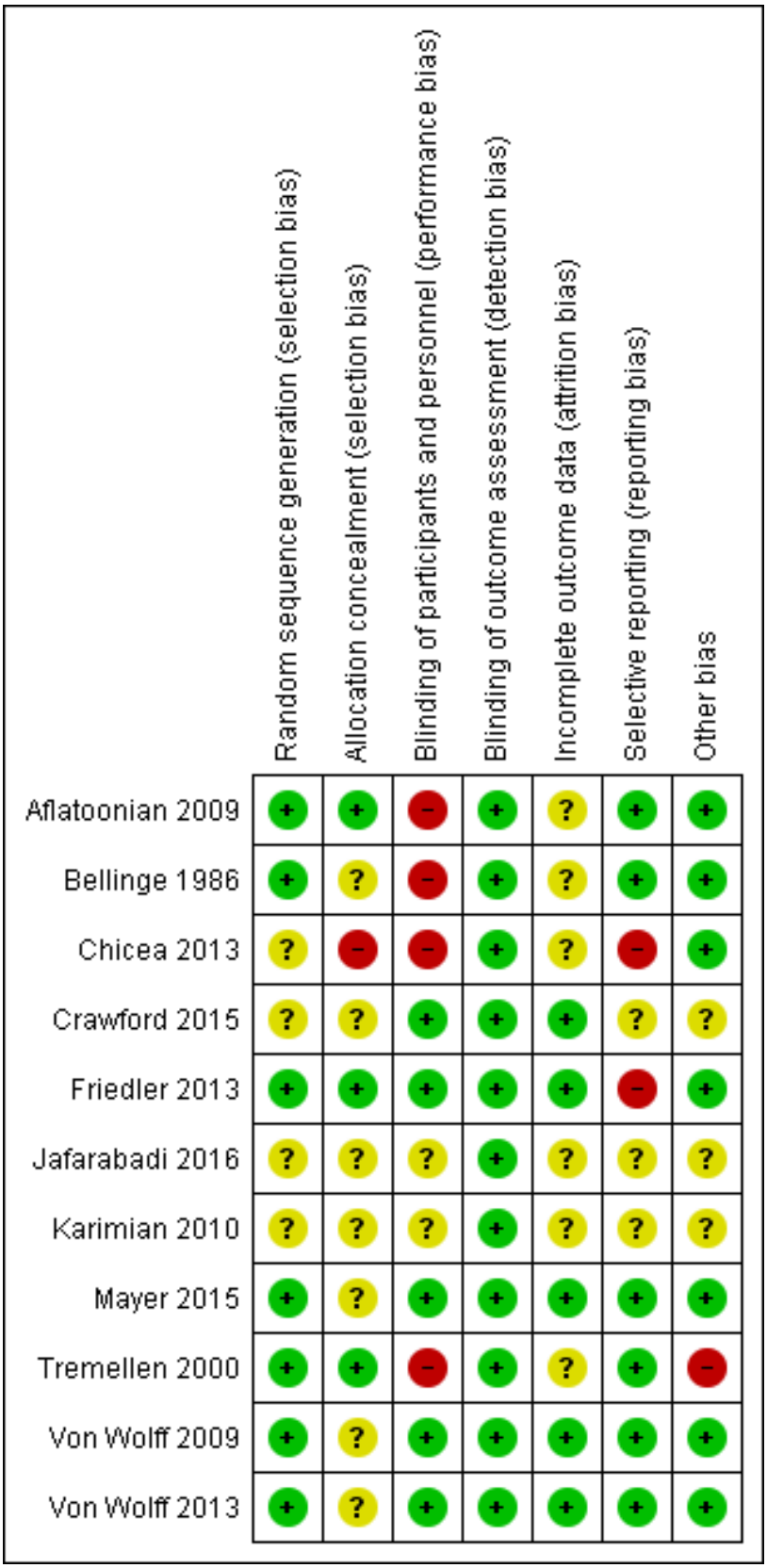
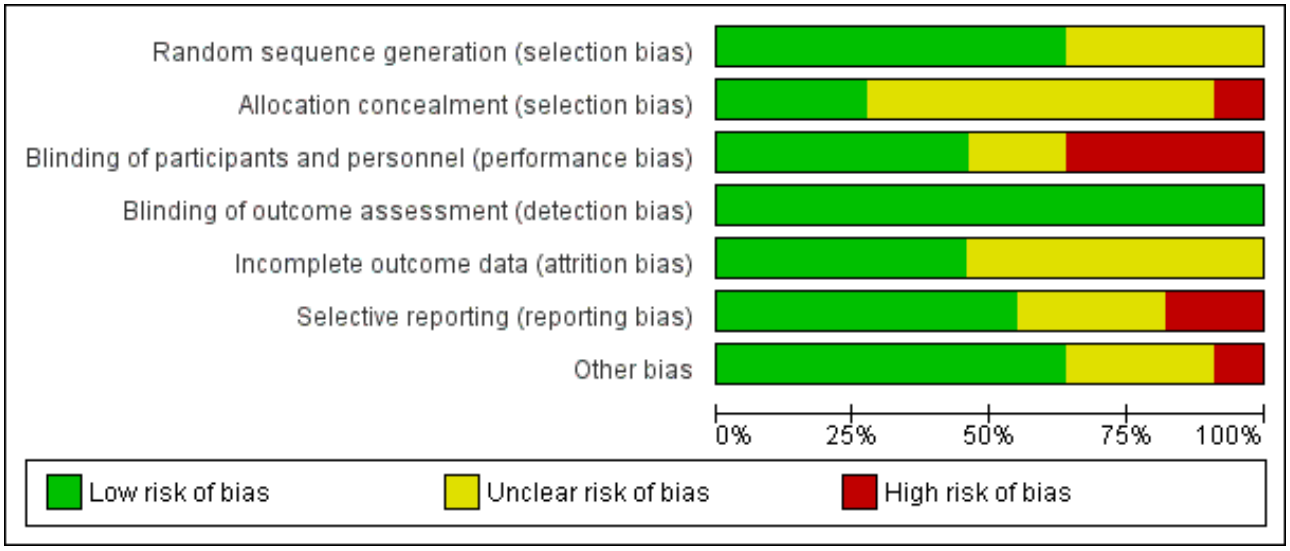


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Three studies did not mention how the randomisation sequence was generated (Chicea 2013; Crawford 2015; Karimian 2010). Two of these studies were published as an abstract (Crawford 2015; Karimian 2010). Jafarabadi 2016 mentioned use of permuted balanced block randomisation method but did not specify how this was done. Of the seven studies that were considered to be at low risk for sequence generation, one reported drawing from an equal number of paper slips from a bag (Aflatoonian 2009), three used random number tables or lists (Bellinge 1986; Von Wolff 2009; Von Wolff 2013) and three used computer-generated randomisation sequences (Friedler 2013; Mayer 2015; Tremellen 2000).

Method of allocation concealment was clearly mentioned by three studies; Aflatoonian 2009 (drawing paper slips from a bag), Friedler 2013 (by an embryologist blinded to treating physician on the day of oocyte collection), and Tremellen 2000 (sealed envelopes). These three trials were judged to be at low risk of bias due to lack of allocation concealment. Seven studies did not mention the method used for allocation concealment and were thus judged to be at unclear risk (Bellinge 1986; Crawford 2015; Jafarabadi 2016; Karimian 2010; Mayer 2015; Von Wolff 2009; Von Wolff 2013). Chicea 2013 was considered to be at high risk of bias (randomisation sequence was not concealed from the investigators).

Blinding

Several trials (Crawford 2015; Friedler 2013; Mayer 2015; Von Wolff 2009; Von Wolff 2013) reported blinding the participants, personnel and outcome assessors, while the remaining trials were judged to be at unclear or high risk of bias (mainly due to issues surrounding performance bias).

Incomplete outcome data

Several trials (Aflatoonian 2009; Chicea 2013; Karimian 2010; Mayer 2015; Tremellen 2000) were at unclear risk of attrition bias. The remaining trials were at low risk.

Selective reporting

Several trials (Aflatoonian 2009; Chicea 2013; Mayer 2015; Tremellen 2000; Von Wolff 2009; Von Wolff 2013) were at low risk of selective outcome reporting bias. The remaining trials were at unclear or high risk.

Other potential sources of bias

Approximately half of the trials (Aflatoonian 2009; Chicea 2013; Crawford 2015; Friedler 2013; Karimian 2010; Tremellen 2000) were at unclear to high risk of bias due to other sources of bias. The remaining trials were at low risk.

Effects of interventions

See: **Summary of findings for the main comparison** ART with seminal plasma compared to standard ART (IVF, ICSI, and frozen embryo transfer)

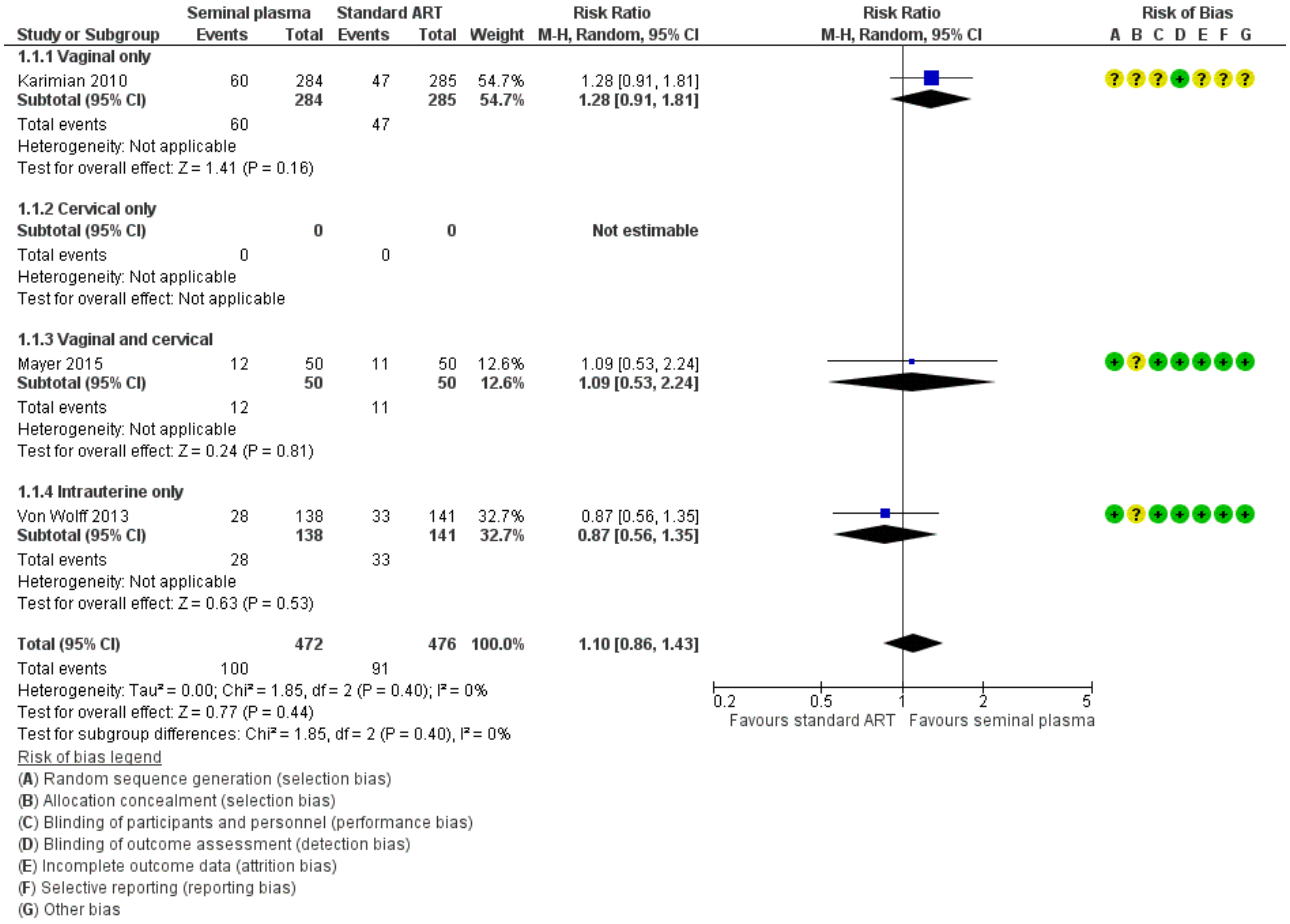
1. Seminal plasma versus no seminal plasma

Primary outcomes

1.1 Live birth

Seminal plasma application had little or no effect on live birth rates (RR 1.10, 95% CI 0.86 to 1.43; I^2 = 0%; 3 trials; 948 participants, low-quality evidence). Analysis 1.1, Figure 4

Figure 4. Forest plot of comparison: 1 Seminal plasma vs control, outcome: 1.1 Live birth.



Subgroup analyses

Seminal plasma application method

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi^2 = 1.85, df = 2 (P = 0.40), I^2 = 0%). Analysis 1.1

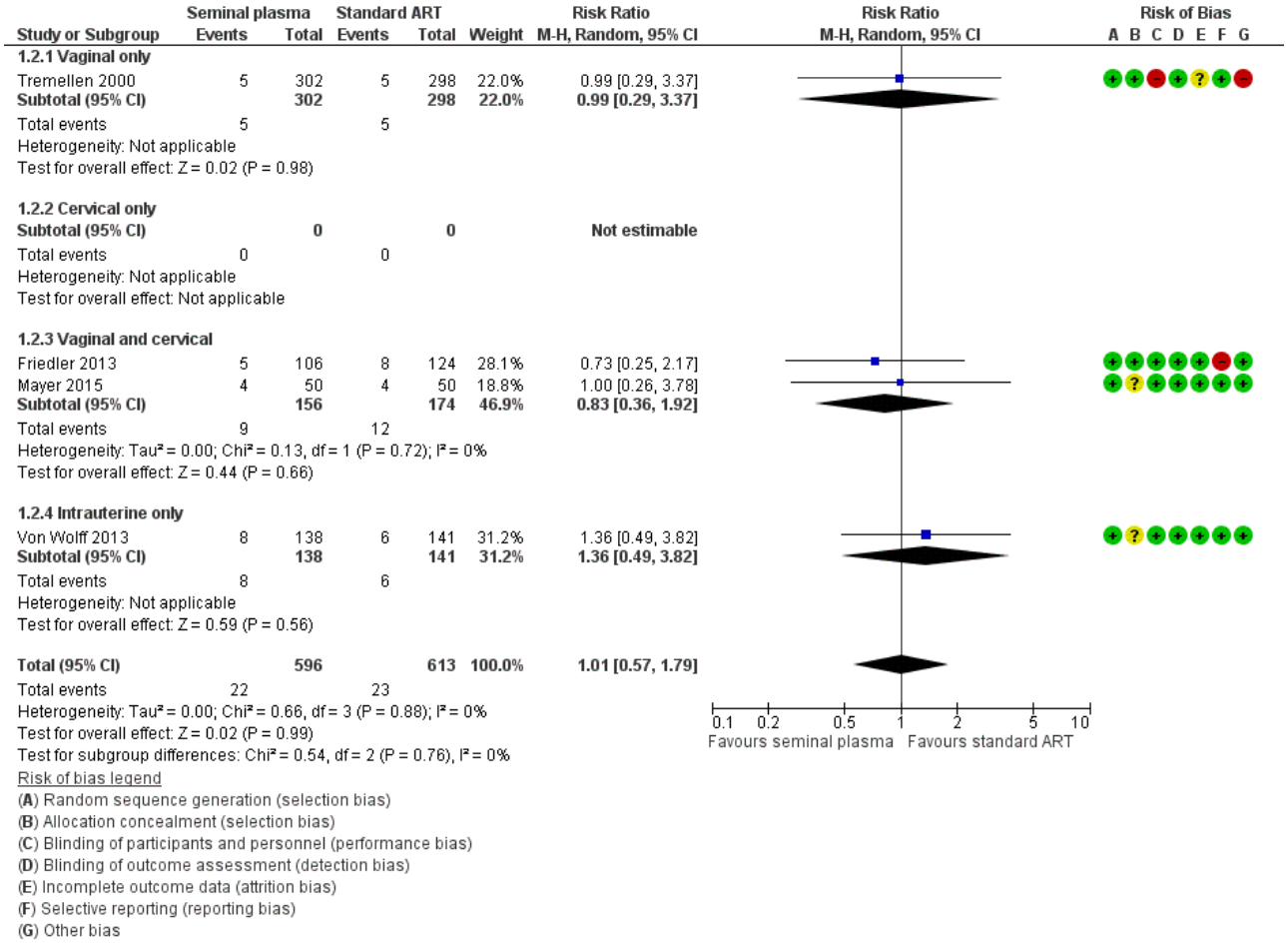
Fresh versus frozen transfer

This subgroup comparison could not be conducted as none of the studies reporting this outcome used frozen embryos.

1.2 Miscarriage

Seminal plasma application had little or no effect on miscarriage rates (RR 1.01, 95% CI 0.57 to 1.79; I^2 = 0%; 4 trials; 1209 participants, low-quality evidence). Analysis 1.2, Figure 5

Figure 5. Forest plot of comparison: 1 Seminal plasma vs control, outcome: 1.2 Miscarriage.



Subgroup and sensitivity analyses

Seminal plasma application method

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 0.54, df = 2 (P = 0.76), I² = 0%). Analysis 1.2

Fresh versus frozen transfer

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%). Analysis 3.2

Per-pregnancy analysis

There was insufficient evidence to determine whether there was a difference between the groups in rates of miscarriage per pregnancy (RR 0.92, 95% CI 0.54 to 1.57; 4 trials; 277 participants; I² = 0%). Analysis 2.1

Secondary outcomes

1.3 Live birth or ongoing pregnancy (composite outcome)

Seminal plasma application had little or no effect on rates of live birth or ongoing pregnancy (RR 1.19, 95% CI 0.95 to 1.49; I² = 4%; 4 trials; 1178 participants, low-quality evidence). Analysis 1.3

Subgroup analyses

Seminal plasma application method

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 2.62, df = 2 (P = 0.27), I² = 23.6%). Analysis 1.3

Fresh versus frozen transfer

This subgroup comparison could not be conducted as none of the studies reporting this outcome used frozen embryos.

1.4 Clinical pregnancy

We are uncertain whether seminal plasma application improves clinical pregnancy rates (RR 1.15, 95% CI 1.01 to 1.31; 10 trials; 2768 participants; I² = 0%, very low-quality evidence). Analysis 1.4

Subgroup analyses

Seminal plasma application method

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 2.43, df = 2 (P = 0.30), I² = 17.7%). Analysis 1.4

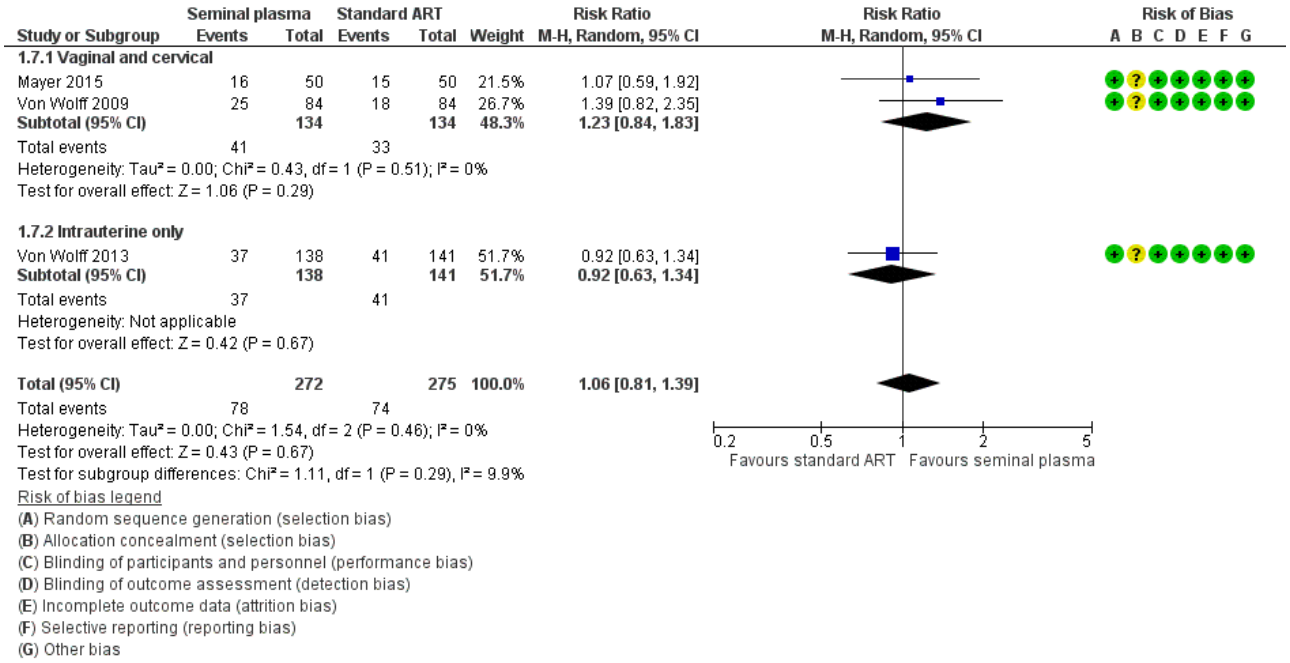
Fresh versus frozen transfer

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%). Analysis 3.4

Post hoc sensitivity analysis

A post hoc sensitivity analysis restricted to studies at overall low risk of bias (Mayer 2015; Von Wolff 2009; Von Wolff 2013) did not find a significant difference between the groups (RR 1.06, 95% CI 0.81 to 1.39; 3 trials; 547 participants; I² = 0%). Analysis 1.7 Figure 6

Figure 6. Forest plot of comparison: 1 Seminal plasma vs control, outcome: 1.7 Clinical pregnancy: Sensitivity analysis by RoB.



Safety outcomes

1.5 Multiple pregnancy

There was little or no effect of seminal plasma application on multiple pregnancy rates (RR 1.11, 95% CI 0.76 to 1.64; I² = 9%; 5 trials; 1642 participants, low-quality evidence). Analysis 1.5

Subgroup and sensitivity analyses

Seminal plasma application method

There was no clear evidence of a difference between the subgroups (test for subgroup differences: Chi² = 2.66, df = 1 (P = 0.10), I² = 62.4%). Analysis 1.5

Fresh versus frozen transfer

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.2%). Analysis 3.5

Per-pregnancy analysis

There was no clear evidence of a difference between the groups in rates of multiple pregnancy per pregnancy (RR 0.93, 95% CI 0.69 to 1.24; 5 trials; 370 participants; I² = 0%). Analysis 2.2

1.6 Ectopic pregnancy

We are uncertain whether there was a difference between the groups (RR 1.59, 95% CI 0.20 to 12.78; I² = 0%; 5 trials; 1521 participants; very low-quality evidence). Analysis 1.6

Subgroup and sensitivity analyses

Seminal plasma application method

There was no evidence of a difference between the subgroups (test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%). Analysis 1.6

Fresh versus frozen transfer

There was insufficient evidence to determine whether there was a difference between the groups in rates of ectopic pregnancy per pregnancy (RR 1.16, 95% CI 0.15 to 8.98; 277 participants; 5 trials; I² = 0%). Analysis 3.6

Per pregnancy analysis

There was insufficient evidence to determine whether there was a difference between the groups in rates of ectopic pregnancy per pregnancy ((RR 1.16, 95% CI 0.15 to 8.98; 277 participants; 5 trials;; I² = 0%). Analysis 2.3

1.7 Infection

No extractable data were available.

1.8 Other adverse events

No extractable data were available.

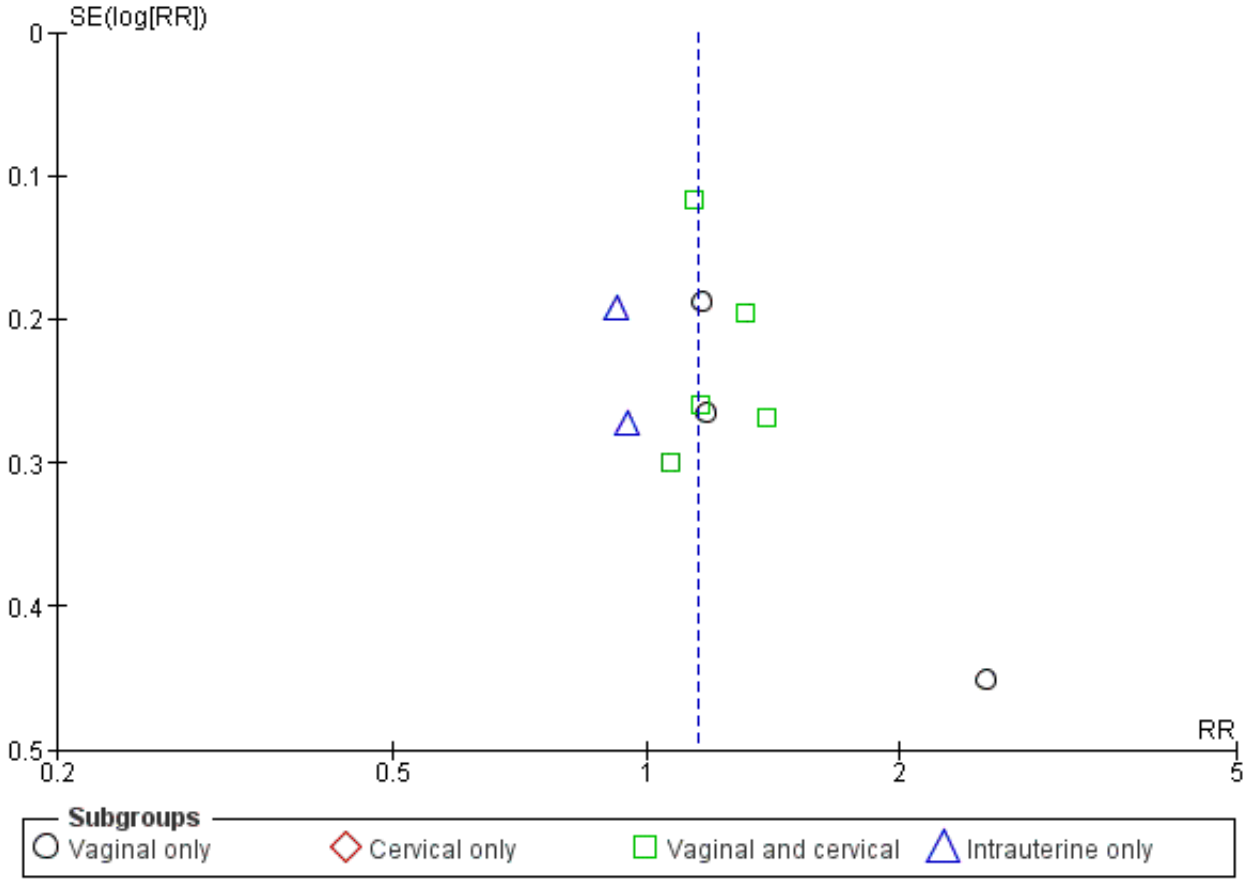
Other sensitivity analyses

- There was no or little heterogeneity and sensitivity analyses were not deemed necessary in this regard.
- A sensitivity analysis restricted to studies without high risk of bias did not change the main findings for primary outcomes. However a post hoc sensitivity analysis for the outcome of clinical pregnancy negated the significant difference between the groups.
- All the results remained unchanged when a fixed-effect model was used.
- The results were unchanged when the missing participants were assumed to have experienced the primary outcome measures.

Assessment of publication bias

Only two analyses included ten or more studies, and we have presented a funnel plot to assess publication bias for the outcome clinical pregnancy in the first comparison (Analysis 1.4); Analysis 3.4 included the same ten trials. The funnel plot did not suggest publication bias. Figure 7

Figure 7. Funnel plot of comparison: 1 Seminal plasma vs Control, outcome: 1.4 Clinical pregnancy.



DISCUSSION

This is the first Cochrane Review that aimed to determine whether exposure of the female genital tract to seminal plasma around the time of embryo transfer improves ART outcomes.

Summary of main results

Overall, there was insufficient evidence to determine whether seminal plasma exposure influenced rates of live birth or miscarriage or the composite outcome of livebirth or ongoing pregnancy. However, the clinical pregnancy rate was significantly increased. There was also insufficient evidence to determine whether seminal plasma exposure influenced rates of adverse events such as multiple pregnancy and ectopic pregnancy There was no information regarding infectious and other complications.

There was no clear evidence of any difference between the groups related to method of seminal plasma application or fresh versus frozen embryo transfers.

Overall completeness and applicability of evidence

We included 11 RCTs, totalling 3215 women. The sample sizes in the studies ranged between 100 and 569. Only three of the included trials, totalling 948 women, had data on the primary outcome measure, live birth rate. Four of the included trials, totalling 1209 women, had data on the other primary outcome measure, miscarriage. To be able to show a difference of 5% compared to a

standard live birth rate of 19%, with 80% power, one would require at least 2114 couples. However, the number of RCTs reporting either live birth or ongoing pregnancy rate was 9, totalling 1178 women.

It is noteworthy that ten of the included RCTs, totalling 2768 women, reported clinical pregnancy rate. This is an adequate sample size to demonstrate as statistically significant a ≥ 5% increase over a 21.9% clinical pregnancy rate, at 5% alpha error rate with 80% power. Clinical pregnancy rate was significantly increased with seminal plasma exposure in the main analysis, with a number needed to treat value of 30 to achieve one additional clinical pregnancy with seminal plasma exposure. However, this finding was not robust to a post hoc sensitivity analysis by study risk of bias, so should be regarded very cautiously.

Unlike some other mammals (e.g. horses, pigs, or rodents), human beings do not ejaculate into the uterus. Only two of the included RCTs investigated intrauterine seminal plasma application (Crawford 2015; Von Wolff 2013) Despite the lack of statistical evidence of a subgroup difference, the point estimates observed in these two trials are on the opposite side of the unity line compared to the rest of the included trials. It is possible that intrauterine administration of a relatively large volume of seminal plasma could have affected the implantation process. A sensitivity analysis, excluding these two RCTs, showed similar live birth rates, but significantly increased the live birth/ongoing pregnancy rate (RR: 1.32, 95% CI 1.02, 1.70) and clinical pregnancy rate (RR: 1.21, 95% CI 1.04, 1.41). The absolute increase in clinical pregnancy rate in this sensitivity analysis was 4.7% with a number needed to treat value of 22 for one additional clinical pregnancy.

Per-pregnancy comparisons for multiple pregnancy, miscarriage and ectopic pregnancy rates were similar to intention to treat analysis results, further strengthening our results.

The evidence is generally applicable to women undergoing fresh ART cycles with ejaculated sperm. There was only one trial reporting ART outcomes with seminal plasma exposure in frozen embryo transfers.

Quality of the evidence

The overall quality of the evidence was low for most outcomes.

The main limitations in the evidence were imprecision, and risk of bias associated with poor reporting of study methods. Seven RCTs did not report the method for allocation concealment.

None of the studies reported funding by pharmaceutical companies.

Potential biases in the review process

The review authors minimised the risk of bias by conducting a search that was systematic and thorough and by having two review authors independently perform the data extraction, 'risk of bias' assessment, and GRADE evaluation.

Agreements and disagreements with other studies or reviews

Our results are in agreement with those of a previous systematic review and meta-analysis investigating the role of seminal plasma for improving ART outcomes (Crawford 2015b). The literature search in this study was conducted in December 2013 and the authors included seven of the 11 studies that are included in our review.

AUTHORS' CONCLUSIONS

Implications for practice

In women undergoing ART, there was insufficient evidence to determine whether there was a difference between the seminal plasma and the standard ART group in rates of live birth (low-quality evidence) or miscarriage (low-quality evidence). There was low-quality evidence suggesting little or no difference between the groups in rates of live birth or ongoing pregnancy (composite outcome). We found very low-quality evidence that seminal plasma application may possibly be associated with more clinical pregnancies than standard ART. There was low-quality evidence suggesting little or no difference between the groups in rates of multiple pregnancy. There was insufficient evidence to reach any conclusions about the risk of ectopic pregnancy, and no data were available on infectious complications or other adverse events.

We conclude that seminal plasma application is worth further investigation, focusing on live birth and miscarriage rates.

Implications for research

We suggest more and adequately powered RCTs reporting live birth rates after seminal plasma application. The leading cause of implantation failure is embryo aneuploidy, therefore, ART cycles with only euploid embryo transfers would be the ideal setting to assess the effectiveness of seminal plasma application, particularly in women with recurrent implantation failure.

ACKNOWLEDGEMENTS

We thank the editorial office of the Cochrane Gynaecology and Fertility Group for their assistance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aflatoonian 2009

Methods	Parallel group study Number of women randomised: 390 (195 in the intervention group; 195 in the control group) Number of women analysed: 385
Participants	Country of authors: Iran Inclusion criteria: couples undergoing assisted reproduction with at least 5 years of subfertility

Aflatoonian 2009 *(Continued)*

	Exclusion criteria: none reported Mean age ± SD: intervention group: 29.4 ± 4.4 years; control group: 29.6 ± 4.9 years Mean duration of infertility ± SD: intervention group: 8.7 ± 3.8 years; control group: 9.0 ± 3.9 years Women with primary infertility: not reported Setting: assisted reproduction programme in Iran
Interventions	Intervention: vaginal intercourse at least once during the 12 hours following embryo transfer Control: abstinence during the entire ART cycle
Outcomes	Clinical pregnancy defined as the presence of a gestational sac or fetal cardiac activity three weeks after embryo transfer
Notes	Pregnancy outcome was unknown for five women in the intervention arm. The corresponding author was contacted but was not able to provide missing data either for the five women with unknown primary outcome or other unreported outcome measures.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Equal number of paper slips for each method put in a bag
Allocation concealment (selection bias)	Low risk	Drawing paper slips from the bag on the day of embryo transfer
Blinding of participants and personnel (performance bias) All outcomes	High risk	Couples in the control group could have had intercourse without informing the investigators and contaminated the results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively assessed outcome measure
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Pregnancy outcome missing for 5 women in the intervention group
Selective reporting (reporting bias)	Low risk	Clinical pregnancy rate was reported
Other bias	Low risk	No other cause of potential bias identified

Bellinge 1986

Methods	Parallel group study Number of women randomised: 152 (78 in the intervention group; 74 in the control group) Number of women analysed: 113
Participants	Country of authors: Australia

Bellinge 1986 *(Continued)*

	Inclusion criteria: couples undergoing assisted reproduction with fresh ejaculate sperm Exclusion criteria: none reported Mean age (SD not stated): intervention group: 32.2 years; control group: 31.9 years Mean duration of infertility: not stated Women with primary infertility: not reported Setting: assisted reproduction programme in Western Australia
Interventions	Intervention: untreated fresh ejaculate was inseminated in the vagina at the time of oocyte fertilisation Control: women in both groups were instructed to abstain from vaginal intercourse 4 days before oocyte pick-up
Outcomes	Clinical pregnancy defined as the presence of a gestational sac
Notes	We were unable to contact the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table was used
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 to 30% of participants excluded after commencement, but similar proportions in both control and intervention groups. ITT analysis was presented
Selective reporting (reporting bias)	Low risk	Clinical pregnancy rate reported
Other bias	Low risk	No other cause of potential bias identified

Chicea 2013

Methods	Parallel group study Number of women randomised: 400 (200 in the intervention group; 200 in the control group) Number of cancellations: 54 (36 in the intervention group due to severe leukocytospermia, severe ovarian hyperstimulation syndrome, lack of oocytes after follicular aspiration, fertilisation failure, lack of

Chicea 2013 *(Continued)*

	top quality embryos; 18 in control group due to severe ovarian hyperstimulation syndrome, lack of oocytes after follicular aspiration, lack of top quality embryos) Number of women analysed: 346
Participants	Country of authors: Romania Inclusion criteria: women aged < 38 years, < 4 previous IVF attempts Exclusion criteria: Infection in the male partner or leukocytospermia, Hepatitis B, or C or HIV positivity in any partner, syphilis in any partner, uterine anomalies Transfer of top quality embryos was required for inclusion in the analysis Mean age (SD not reported): intervention group: 33.1 years; control group: 33.9 years Mean duration of infertility ± SD: intervention group: 8.7 ± 3.8 years; control group: 9.0 ± 3.9 years Women with primary infertility: not reported Setting: assisted reproduction programme in Romania
Interventions	Intervention: 0.5 ml of seminal plasma was injected 1 to 2 cm into the uterine cervix immediately after the oocyte pick-up procedure. The rest of the available seminal plasma (0 to 1 ml) was deposited at the posterior vaginal fornix. Control: women in both groups were instructed to abstain from vaginal intercourse 3 days before oocyte pick-up until the pregnancy test.
Outcomes	Clinical pregnancy defined as the presence of a gestational sac or fetal pole four weeks after oocyte pick-up
Notes	We tried to contact the corresponding author by email, twice, one month apart, but did not receive a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	High risk	The randomisation sequence was not concealed from the investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomised on the day of ovulation trigger, halfway through treatment. Although unlikely, it is not impossible that the rest of the treatment procedures could be affected by the knowledge of allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Even though the participants were randomised on the day of ovulation trigger, only those who had good quality embryos were included in the analyses. Embryo quality is a subjectively assessed parameter and selective inclusion is possible, especially in the absence of allocation concealment.

Chicea 2013 *(Continued)*

Selective reporting (reporting bias)	High risk	Only women undergoing embryo transfer, and in addition with good quality embryos were included
Other bias	Low risk	No other cause of potential bias identified

Crawford 2015

Methods	Parallel group study Number of women randomised: 186 (91 in the intervention group; 95 in the control group) Number of cancellations: none reported Number of women analysed: 186
Participants	Country of authors: United Kingdom and Australia Inclusion criteria: women aged 23 to 39 years, < 2 previous IVF attempts Exclusion criteria: not reported. Mean age: not reported Mean duration of infertility: not reported Women with primary infertility: not reported Setting: assisted reproduction programme in Homerton University Hospital
Interventions	Intervention: intrauterine injection of 0.5 ml seminal plasma immediately after the oocyte pick-up procedure Control: intrauterine injection of 0.5 ml culture medium immediately after the oocyte pick-up procedure
Outcomes	Clinical pregnancy rate
Notes	Abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both clinicians and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome

Crawford 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Accounted for all randomised women
Selective reporting (reporting bias)	Unclear risk	Unable to assess
Other bias	Unclear risk	Unable to assess

Friedler 2013

Methods	Parallel group study Number of women randomised: 230 (106 in the intervention group; 124 in the control group) Number of cancellations: 10 (3 women in intervention group did not undergo an embryo transfer; 7 women in control group did not undergo an embryo transfer) Number of women analysed: 230
Participants	Country of authors: Israel Inclusion criteria: women aged < 40 years, having at least 1 previous failed IVF attempt Exclusion criteria: prior cycle cancellation due to lack of oocytes, use of donor sperm, endometriosis, Hepatitis B, or C or HIV positivity or other infection in the male partner, leukocytospermia Mean age ± SD: intervention group: 31.2 ± 5.3 years; control group: 32 ± 5.7 years. Mean duration of infertility ± SD: intervention group: 2.5 ± 1.8 years; control group: 2.7 ± 1.7 years. Women with primary infertility: not reported Setting: assisted reproduction programme in Israel
Interventions	Intervention: intracervical injection of 0.5 ml seminal plasma was after the oocyte pick-up procedure. The rest of the available seminal plasma was deposited at the posterior vaginal fornix. Control: intracervical injection of 0.5 ml culture medium was after the oocyte pick-up procedure. The rest was deposited at the posterior vaginal fornix. Women in both groups were instructed to abstain from vaginal intercourse 2 days before oocyte pick-up until 7 days after oocyte pick-up.
Outcomes	Ongoing pregnancy defined as one that progressed beyond 22nd gestational week. Clinical pregnancy defined as the presence of gestational sac at 3 weeks gestational age.
Notes	Live birth defined in the text but not reported. The corresponding author was contacted but live birth rates were not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random number sequence

Friedler 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation by an embryologist blinded to treating physician on the day of oocyte collection
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both physicians and patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% attrition rate, which is similar between the study groups. Reasons for attrition given and intention to treat analysis was presented.
Selective reporting (reporting bias)	High risk	Live birth rate defined in the materials and methods, but not reported in the text. Multiple pregnancy rate was not reported.
Other bias	Low risk	No other cause of potential bias identified

Jafarabadi 2016

Methods	Parallel group study Number of women randomised: 266 (133 in the intervention group; 133 in the control group) Number of cancellations: 3 women in the intervention group did not receive the intervention Number of women analysed: 263
Participants	Country of authors: Iran Inclusion criteria: couples undergoing assisted reproduction with a female partner < 40 years of age Exclusion criteria: history of no oocytes in a former ART cycle, > 2 prior ART cycles, providing semen by any other means than ejaculation, active hepatitis B, or C or HIV in one partner, leukocytospermia Mean age ± SD: intervention group: 32.2 ± 6.0 years; control group: 31.1 ± 6.0 years. Mean duration of infertility ± SD: not reported. Women with primary infertility: not reported. Setting: assisted reproduction programme in Iran
Interventions	Intervention: intracervical injection of 0.5 ml seminal plasma was after the oocyte pick-up procedure. The rest of the available seminal plasma was deposited at the posterior vaginal fornix. Control: no intervention
Outcomes	Clinical pregnancy defined as visualisation of embryo by ultrasound at sixth gestational week
Notes	We tried to contact the authors by email, twice one month apart, however did not receive a response

Risk of bias

Bias	Authors' judgement	Support for judgement

Jafarabadi 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Permuted block randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Embryologist not blinded for allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three women in the intervention group were unaccounted for in the analyses
Selective reporting (reporting bias)	Unclear risk	Several outcome measures that should be available to the authors were not reported, e.g. multiple pregnancy rate, miscarriage rate
Other bias	Unclear risk	Poor reporting quality

Karimian 2010

Methods	Parallel group study Number of women randomised: 569 (284 in intervention group; 285 in control group) Number of cancellations: not reported Number of women analysed: not reported
Participants	Country of authors: Iran Inclusion criteria: women undergoing ART Exclusion criteria: not reported Mean age: not reported Mean duration of infertility: not reported Women with primary infertility: not reported Setting: assisted reproduction programme in Tehran
Interventions	Intervention: intercourse around the time of ART Control: abstinence during ART cycle
Outcomes	Biocehmical pregnancy and live birth without gestational age at delivery
Notes	Abstract. We were unable to contact the authors.
Risk of bias	

Karimian 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Unable to assess

Mayer 2015

Methods	Parallel group study Number of women randomised: 100 (50 in the intervention group; 50 in the control group) Number of cancellations: 15 (6 women in the intervention group did not undergo an embryo transfer; 9 women in the control group did not undergo an embryo transfer) Number of women analysed: 87. Pregnancy data were available for all 100 and ITT analyses were possible for outcomes relevant to our review.
Participants	Country of authors: Austria Inclusion criteria: nulliparous women aged 18 to 41 years, nonsmoker, body mass index < 35 kg/m^2, undergoing 1st or 2nd ART cycle Exclusion criteria: cancellation of embryo transfer due to total fertilisation failure or pending OHSS, Hepatitis B, or C or HIV infection or leukocytospermia in the male partner, seminal plasma volume < 0.5 ml, uterine or endometrial anomaly, indication for seminal plasma application Mean age ± SD: intervention group: 32.2 ± 4.48 years; control group: 31.1 ± 4.63 years Mean duration of infertility: not reported Women with primary infertility: not reported Setting: Landes Frauen und Kinderklinik Linz, Austria
Interventions	Intervention: 0.5 to 1.5 ml seminal plasma application into the cervical canal by an intrauterine insemination catheter right after oocyte pick-up. The rest of SP was applied at the posterior fornix.

Mayer 2015 *(Continued)*

	Comparator: saline application in the same way.
Outcomes	Clinical pregnancy, live birth, multiple pregnancy, ectopic pregnancy, miscarriage. Definitions were not reported.
Notes	The authors provided unpublished data on baseline characteristics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation list prepared by an independent party
Allocation concealment (selection bias)	Unclear risk	The embryologist had the sequence, but whether the next allocation was concealed somehow is not mentioned at all. However, the patients were recruited by the clinician in advance.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinician and participant blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% of women did not undergo an embryo transfer. Reasons for losses were reported and similar between the groups. ITT analysis done
Selective reporting (reporting bias)	Low risk	Live birth rate reported
Other bias	Low risk	None detected

Tremellen 2000

Methods	Multicentre, parallel group study Randomisation stratified for centre, hence for fresh or frozen embryo transfer Number of women randomised: 600 (302 in the intervention group; 298 in the control group) Number of cancellations: 122 cycles (60 in the intervention group, 62 in the control group) which did not reach embryo transfer Number of cycles analysed: 478
Participants	Country of authors: Spain and Australia Inclusion criteria: women aged 18 to 40 years, in a stable relationship, undergoing ART with fresh (in the Spanish centre) or frozen (in the Australian centre) embryo transfer Exclusion criteria: hepatitis B, or C or HIV positivity in the male partner Mean age ± SD: Spanish centre: intervention group: 33.3 ± 3.3 years, control group: 33.2 ± 3.3 years; Australian centre: intervention group: 33.8 ± 4.4 years, control group: 33.1 ± 4.4 years

Tremellen 2000 *(Continued)*

	Mean duration of infertility ± SD: Spanish centre: intervention group: 4.7 ± 2.6 years, control group: 4.1 ± 2.8 years; Australian centre: intervention group: 5 ± 2.5 years, control group: 5.1 ± 2.8 years Women with primary infertility: not reported Setting: assisted reproduction programmes in Spain (Valencia and Murcia Clinics of the Instituto Valenciano de Infertilidad) and Australia (University of Adelaide Reproductive Medicine Unit)
Interventions	Interventions: fresh ART cycles in Spain: vaginal intercourse at least twice, 12 hours before oocyte pick up and 12 hours after embryo transfer Frozen embryo transfer cycles in Australia: vaginal intercourse at least once, during the period between four days before and two days after embryo transfer Comparator: abstinence during the same period.
Outcomes	Biochemical pregnancy, clinical pregnancy at 6 to 8 weeks of gestation, multiple pregnancy
Notes	We contacted the corresponding author, who understandably did not have the missing data for this trial, which was published 18 years ago.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation list stratified for centre
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes managed by 3rd party
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded, though they were asked about adherence to the protocol
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objectively measured outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	25% of cycles cancelled after randomisation. However, the proportion of cancelled cycles were similar between the groups and ITT analysis was done.
Selective reporting (reporting bias)	Low risk	Clinical pregnancy reported
Other bias	High risk	Significantly more embryos transferred in the control group

Von Wolff 2009

Methods	Parallel group study Number of women randomised: 168 (84 in the intervention group; 84 in the control group) Number of cancellations: 31 cycles (14 in the intervention group, 17 in the control group) which did not reach embryo transfer

Von Wolff 2009 *(Continued)*

	Number of cycles analysed: 133
Participants	Country of authors: Germany Inclusion criteria: women aged 18 to 42 years, in a stable relationship Exclusion criteria: cancellation of embryo transfer due to total fertilisation failure or pending OHSS, Hepatitis B, or C or HIV infection or leukocytospermia in the male partner, seminal plasma volume < 0.5 ml Mean age (SD not reported): intervention group: 34.4 years; control group: 34.1 years Mean duration of infertility: not reported Women with primary infertility: not reported Setting: ART Center of the Women's University Hospital, Heidelberg, Germany
Interventions	Intervention: 0.5 ml seminal plasma application into the cervical canal by an intrauterine insemination catheter right after oocyte pick-up. The rest of SP was applied at the posterior fornix. Comparator: saline application in the same way.
Outcomes	Clinical pregnancy
Notes	We tried to contact the authors by email, twice one month apart, however did not receive a response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified, block randomisation using lists
Allocation concealment (selection bias)	Unclear risk	Authors did not report that allocation concealment was used during the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical looking placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcome measure
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 to 30% attrition with reasons. Similar rate between the two groups
Selective reporting (reporting bias)	Low risk	Clinical pregnancy rate reported
Other bias	Low risk	No other cause of potential bias identified

Von Wolff 2013

Methods	Parallel group study

Von Wolff 2013 *(Continued)*

	Number of women randomised: 279 (138 in the intervention group; 141 in the control group) Number of cancellations: 40 cycles (16 in the intervention group, 14 in the control group) which did not reach embryo transfer Number of cycles analysed: 279
Participants	Country of authors: Germany Inclusion criteria: women undergoing IVF or ICSI Exclusion criteria: hepatitis B, or C or HIV infection or leukocytospermia in the male partner, seminal plasma volume < 0.3 ml Mean age (SD not reported): intervention group: 34.6 years; control group: 34.9 years Mean duration of infertility: not reported Women with primary infertility: not reported Setting: ART Center of the Women's University Hospital, Heidelberg, Germany
Interventions	Intervention: seminal plasma was collected 1 to 2 weeks before follicle aspiration and stored in sterile flasks. Following two rounds of centrifugation, 0.4 ml of supernatant was mixed with 1.6 ml sterile saline and stored at -20C. The solution was thawed 30 to 60 minutes before follicle aspiration and 1.5 ml was injected into the uterine cavity after follicle aspiration. Comparator: 1.5 ml sterile saline application after follicle aspiration
Outcomes	Clinical pregnancy, defined as an embryo with heart beat 4 to 5 weeks after follicle aspiration, live birth rate, ectopic pregnancy, miscarriage, and infection rates
Notes	We tried to contact the authors by email, twice one month apart, however did not receive a response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified, block randomisation using lists
Allocation concealment (selection bias)	Unclear risk	Authors did not report that allocation concealment was used during the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical looking placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcome measure
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women were accounted for in the final analysis
Selective reporting (reporting bias)	Low risk	Live birth rate reported

Von Wolff 2013 *(Continued)*

Other bias	Low risk	None detected

ART: assisted reproductive technology
HIV: human immunodeficiency virus
ICSI: intracytoplasmic sperm injection
ITT: intention to treat
IVF: in vitro fertilisation
OHSS: ovarian hyperstimulation syndrome
SD: standard deviation
SP: seminal plasma

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

Study	Reason for exclusion
Coulam 1995	Couples who were trying spontaneous conception were recruited
Fishel 1989	Quasi-randomised design
Lou 2014	Quasi-randomised design

DATA AND ANALYSES

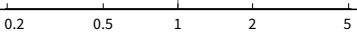
Comparison 1. Seminal plasma vs standard ART

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	948	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.86, 1.43]
1.1 Vaginal only	1	569	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.91, 1.81]
1.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Vaginal and cervical	1	100	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.53, 2.24]
1.4 Intrauterine only	1	279	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.35]
2 Miscarriage	4	1209	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.57, 1.79]
2.1 Vaginal only	1	600	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.29, 3.37]
2.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Vaginal and cervical	2	330	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.36, 1.92]
2.4 Intrauterine only	1	279	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.49, 3.82]
3 Live birth or ongoing pregnancy	4	1178	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.95, 1.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Vaginal only	1	569	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.91, 1.81]
3.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Vaginal and cervical	2	330	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.93, 1.99]
3.4 Intrauterine only	1	279	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.35]
4 Clinical pregnancy	10	2768	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.01, 1.31]
4.1 Vaginal only	3	1142	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.92, 1.85]
4.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Vaginal and cervical	5	1161	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.01, 1.40]
4.4 Intrauterine only	2	465	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.68, 1.27]
5 Multiple pregnancy	5	1642	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.64]
5.1 Vaginal only	3	1142	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.89, 2.69]
5.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Vaginal and cervical	2	500	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.56, 1.33]
5.4 Intrauterine only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Ectopic pregnancy	5	1521	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.20, 12.78]
6.1 Vaginal only	3	1142	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.12, 68.83]
6.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Vaginal and cervical	1	100	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 Intrauterine only	1	279	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.17]
7 Clinical pregnancy: Sensitivity analysis by RoB	3	547	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.81, 1.39]
7.1 Vaginal and cervical	2	268	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.84, 1.83]
7.2 Intrauterine only	1	279	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.63, 1.34]

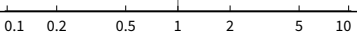
Analysis 1.1. Comparison 1 Seminal plasma vs standard ART, Outcome 1 Live birth.

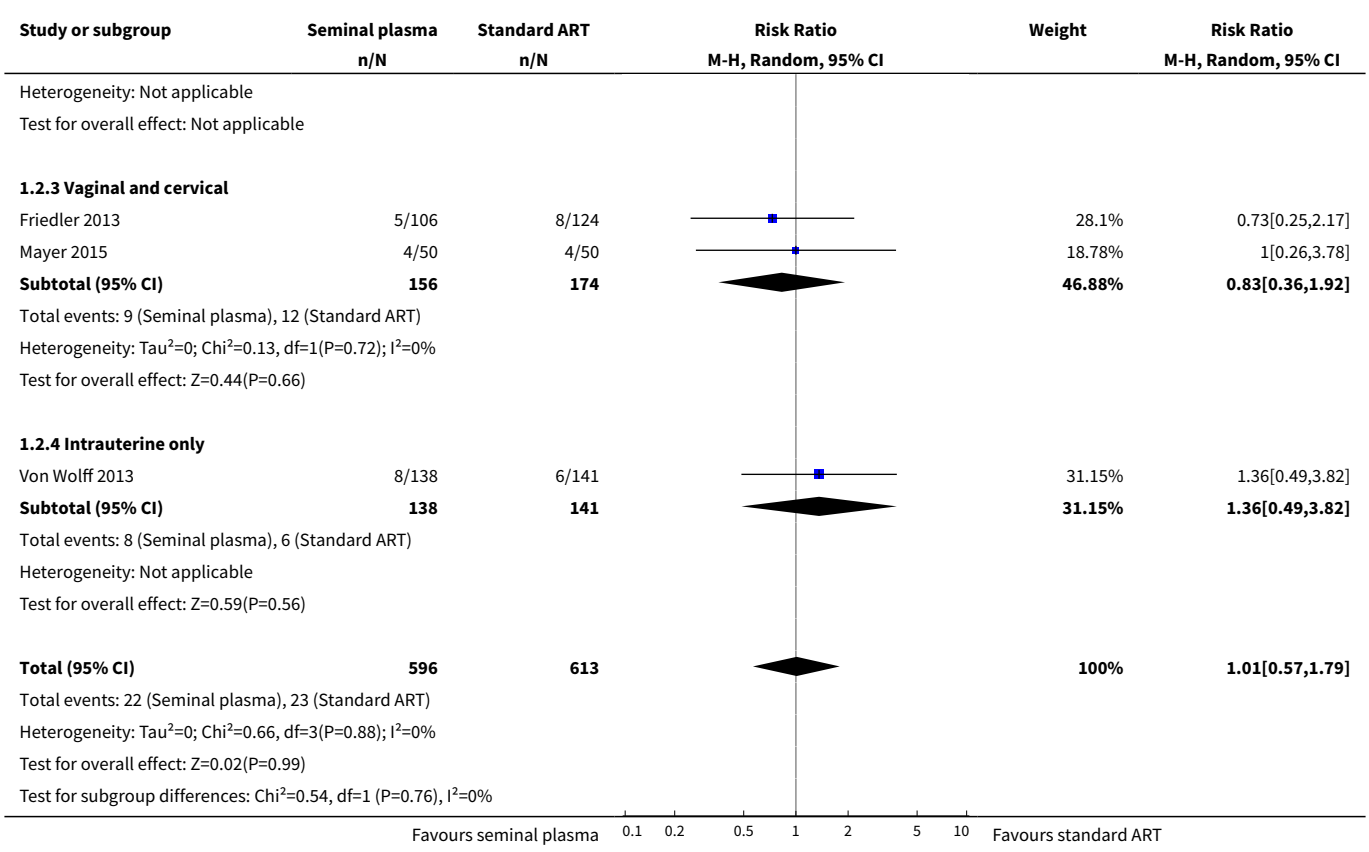
Study or subgroup	Seminal plasma n/N	Standard ART n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Vaginal only					
Karimian 2010	60/284	47/285		54.69%	1.28[0.91,1.81]
Subtotal (95% CI)	**284**	**285**		**54.69%**	**1.28[0.91,1.81]**
Total events: 60 (Seminal plasma), 47 (Standard ART)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					
1.1.2 Cervical only					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Seminal plasma), 0 (Standard ART)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.3 Vaginal and cervical					
Mayer 2015	12/50	11/50		12.59%	1.09[0.53,2.24]
Subtotal (95% CI)	**50**	**50**		**12.59%**	**1.09[0.53,2.24]**
Total events: 12 (Seminal plasma), 11 (Standard ART)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.1.4 Intrauterine only					
Von Wolff 2013	28/138	33/141		32.72%	0.87[0.56,1.35]
Subtotal (95% CI)	**138**	**141**		**32.72%**	**0.87[0.56,1.35]**
Total events: 28 (Seminal plasma), 33 (Standard ART)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Total (95% CI)	**472**	**476**		**100%**	**1.1[0.86,1.43]**
Total events: 100 (Seminal plasma), 91 (Standard ART)					
Heterogeneity: Tau^2=0; Chi^2=1.85, df=2(P=0.4); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					
Test for subgroup differences: Chi^2=1.85, df=1 (P=0.4), I^2=0%					



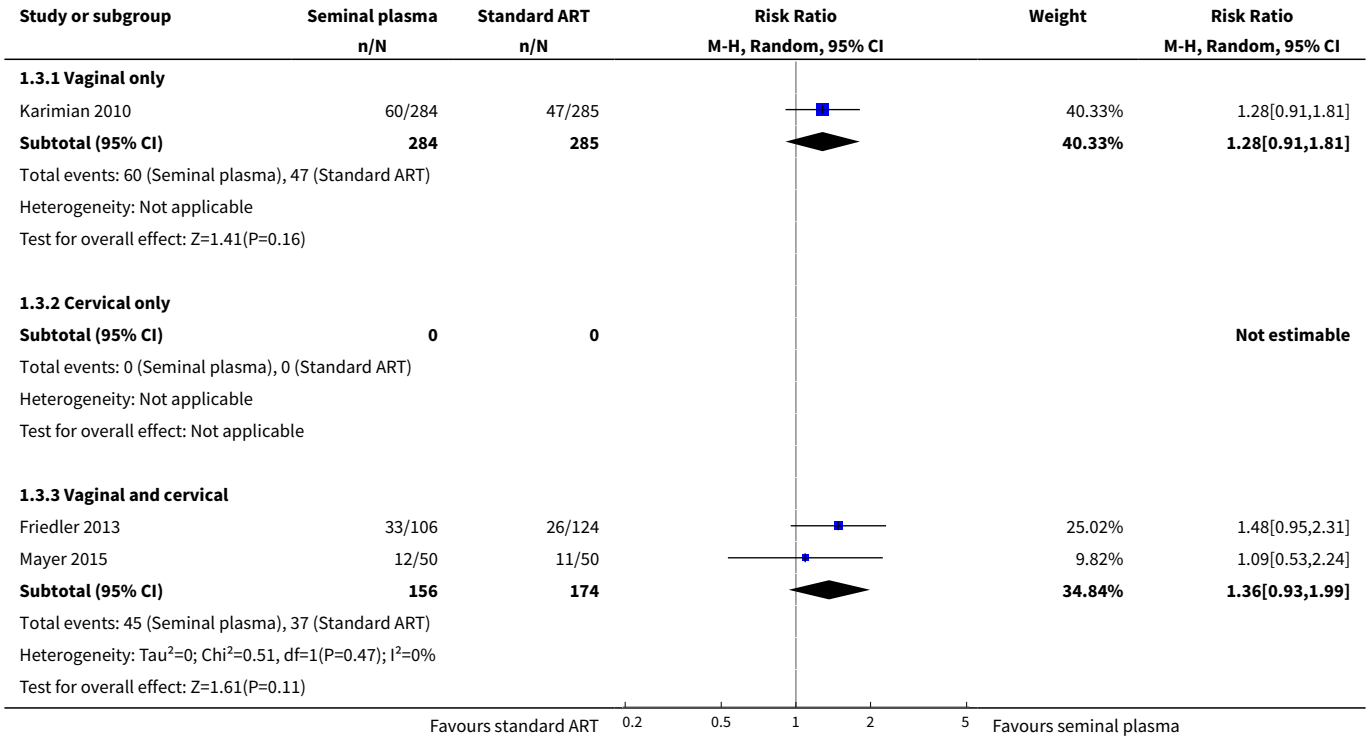
Analysis 1.2. Comparison 1 Seminal plasma vs standard ART, Outcome 2 Miscarriage.

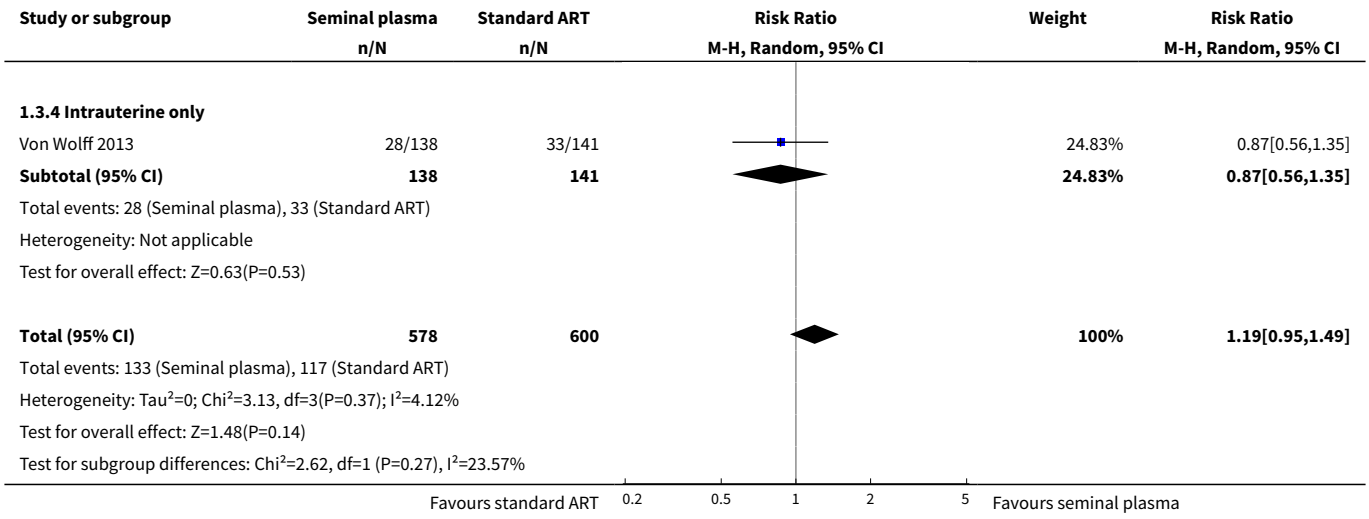
Study or subgroup	Seminal plasma n/N	Standard ART n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Vaginal only					
Tremellen 2000	5/302	5/298		21.97%	0.99[0.29,3.37]
Subtotal (95% CI)	**302**	**298**		**21.97%**	**0.99[0.29,3.37]**
Total events: 5 (Seminal plasma), 5 (Standard ART)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.98)					
1.2.2 Cervical only					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Seminal plasma), 0 (Standard ART)					



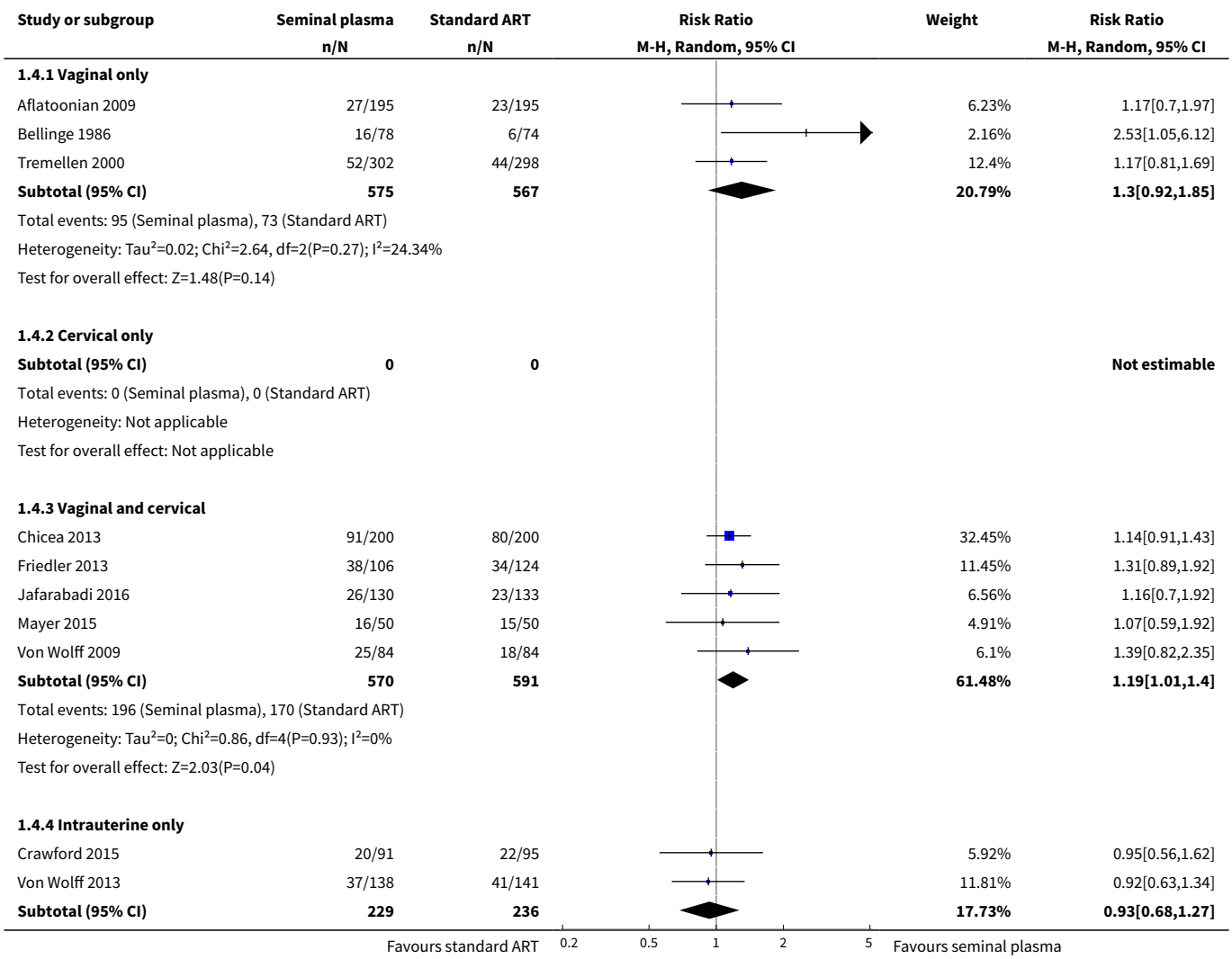


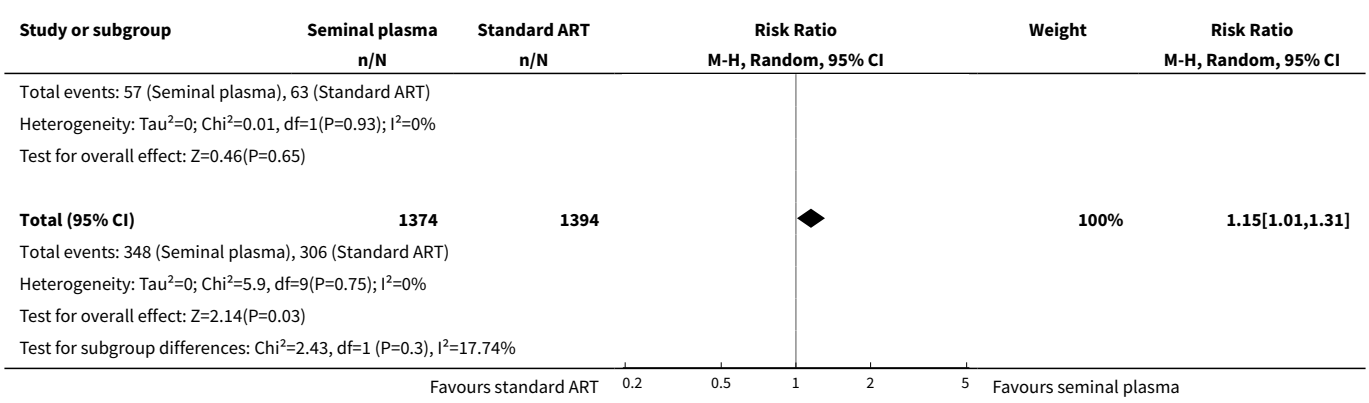
Analysis 1.3. Comparison 1 Seminal plasma vs standard ART, Outcome 3 Live birth or ongoing pregnancy.



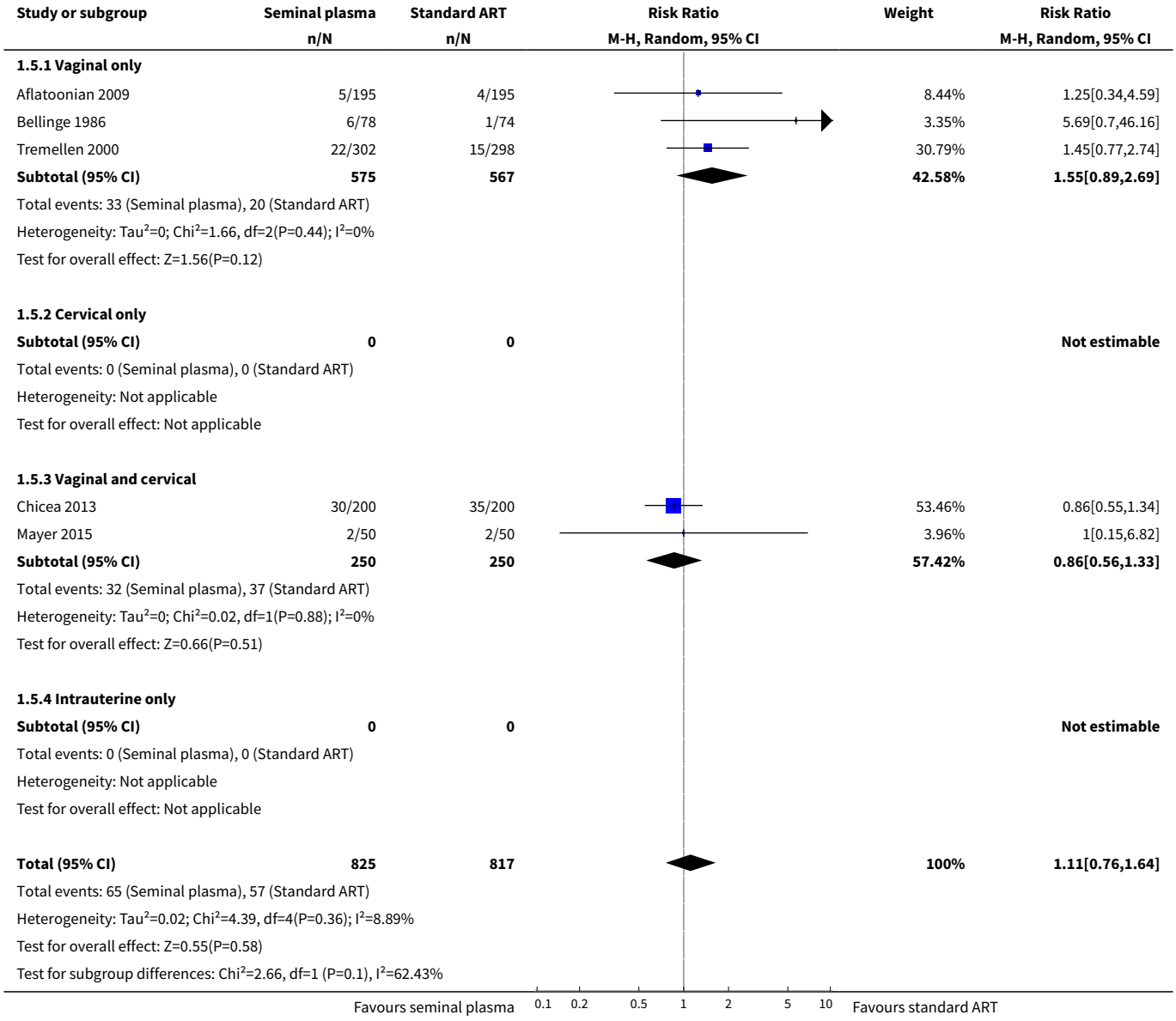


Analysis 1.4. Comparison 1 Seminal plasma vs standard ART, Outcome 4 Clinical pregnancy.

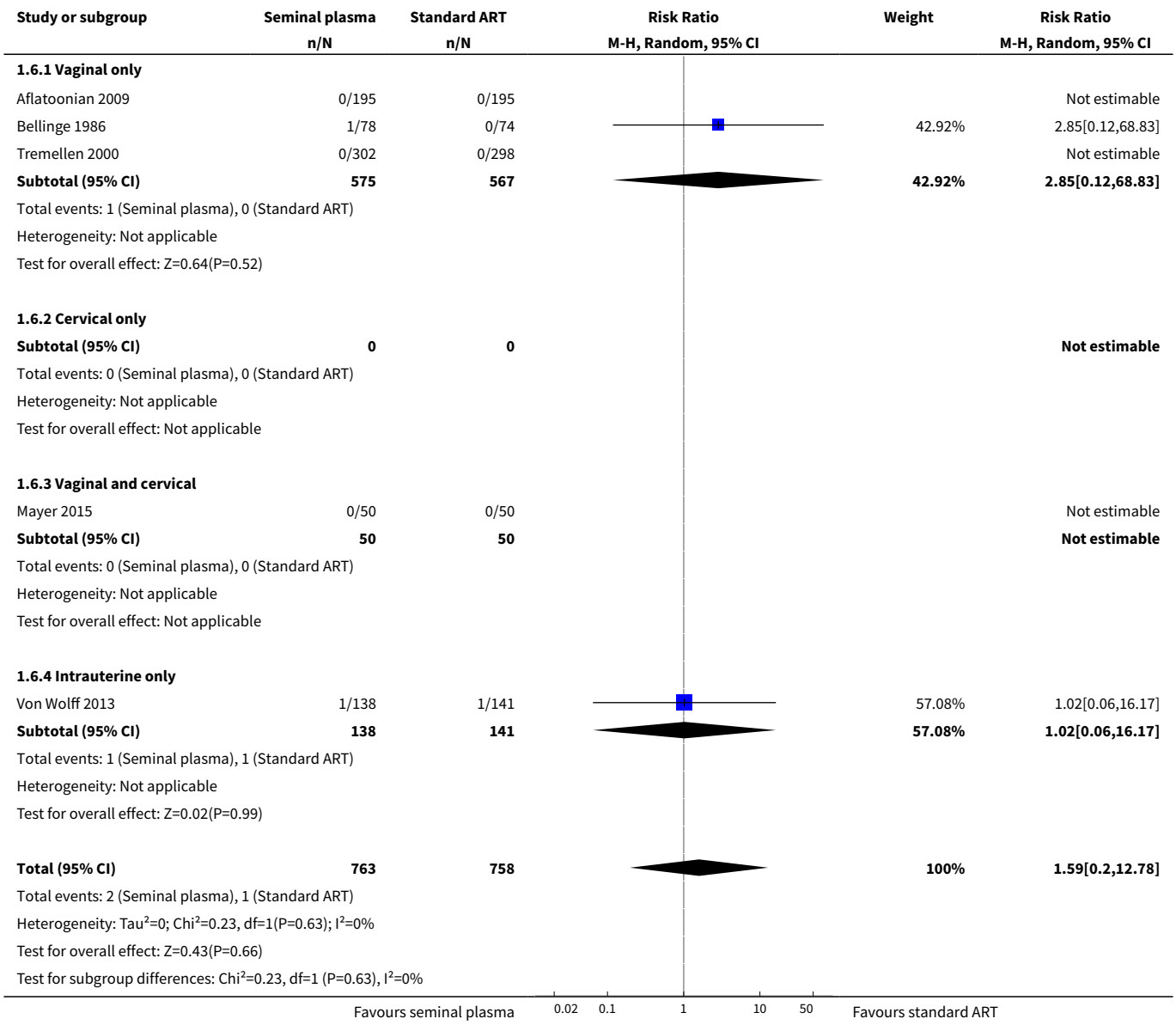




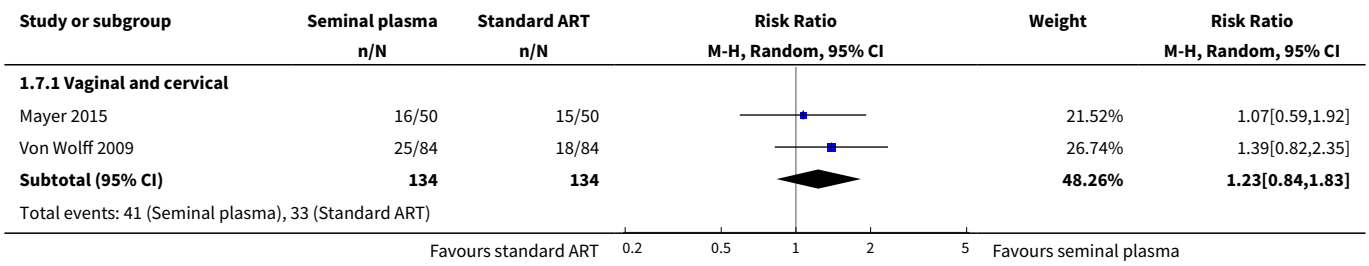
Analysis 1.5. Comparison 1 Seminal plasma vs standard ART, Outcome 5 Multiple pregnancy.

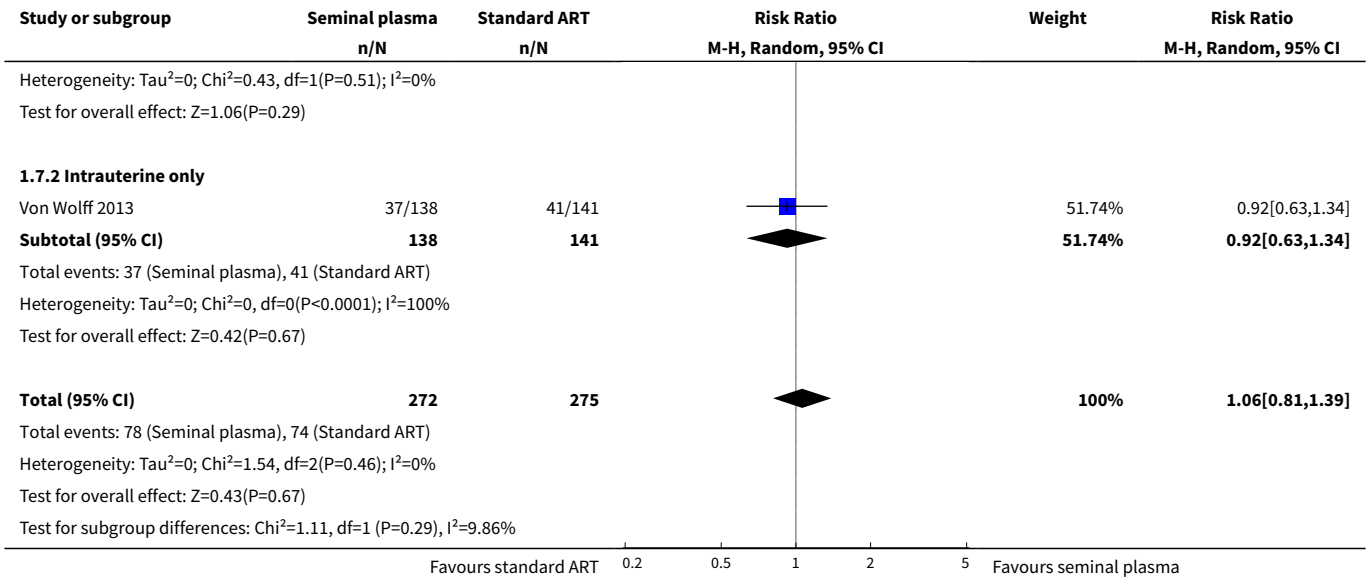


Analysis 1.6. Comparison 1 Seminal plasma vs standard ART, Outcome 6 Ectopic pregnancy.



Analysis 1.7. Comparison 1 Seminal plasma vs standard ART, Outcome 7 Clinical pregnancy: Sensitivity analysis by RoB.

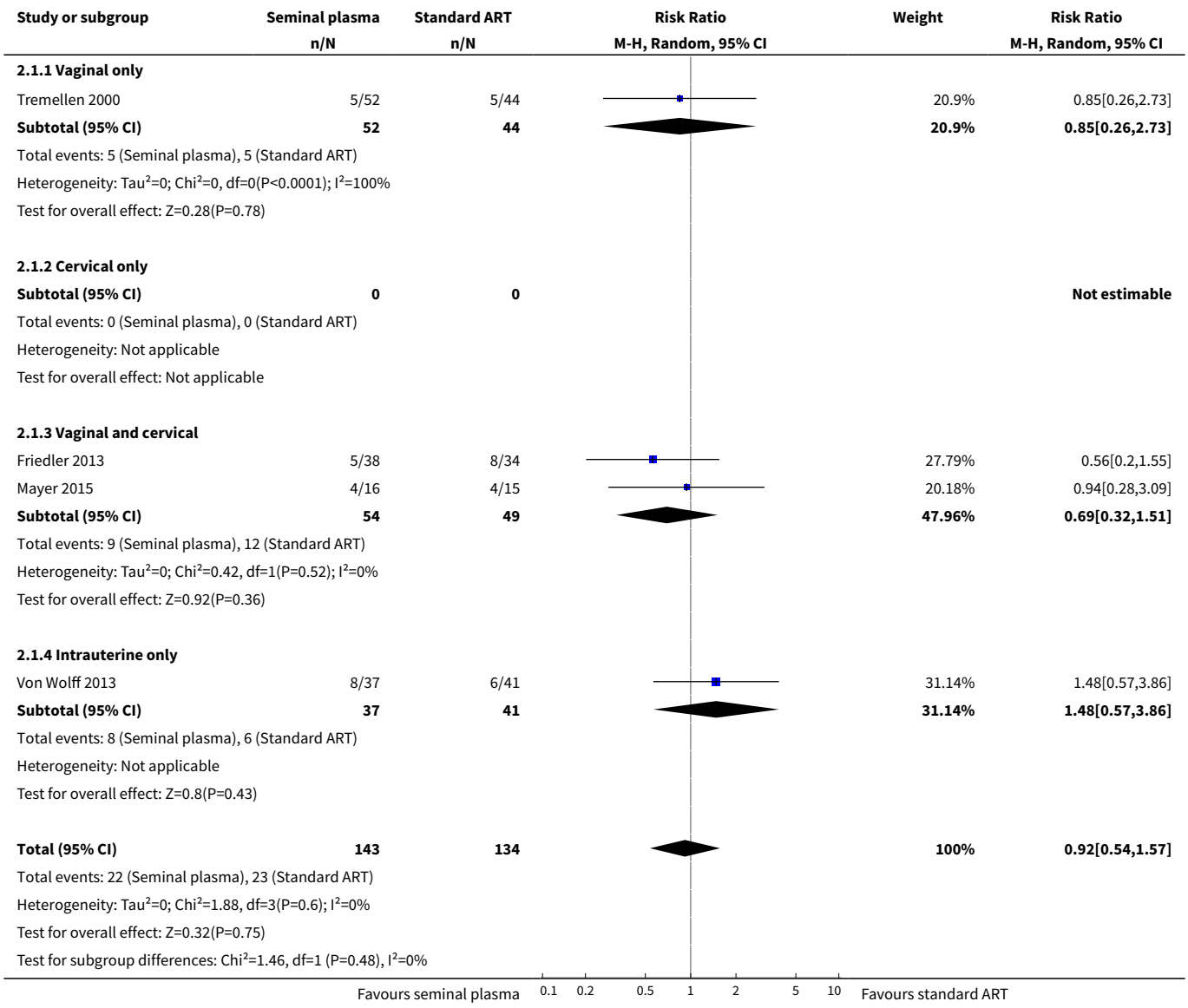




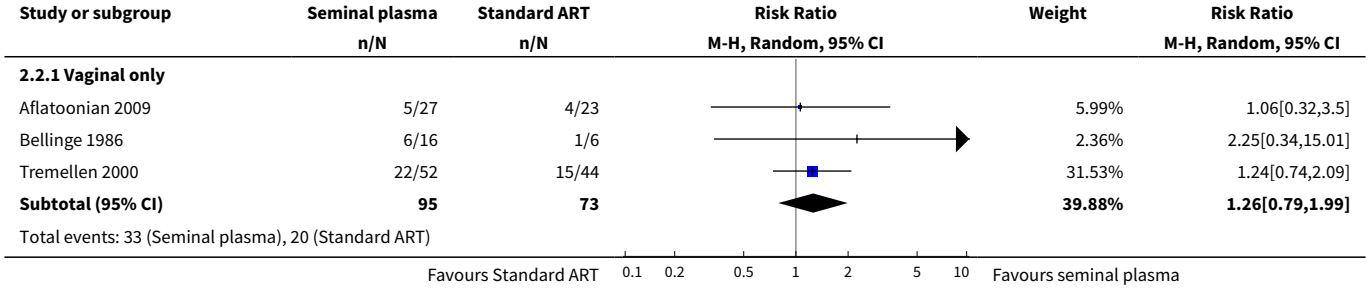
Comparison 2. Seminal plasma vs standard ART, per-pregnancy analyses

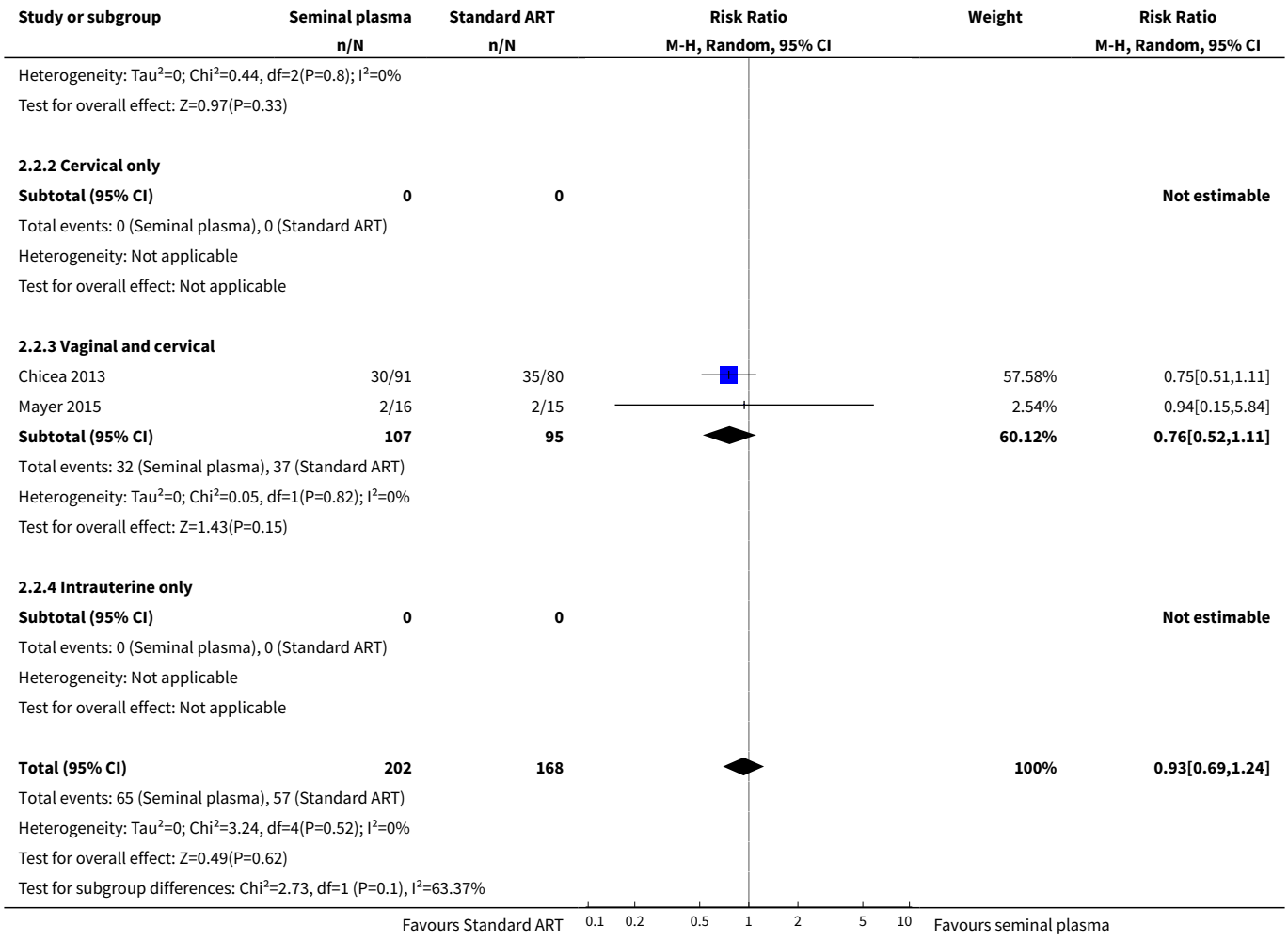
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Miscarriage	4	277	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.54, 1.57]
1.1 Vaginal only	1	96	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.26, 2.73]
1.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Vaginal and cervical	2	103	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.32, 1.51]
1.4 Intrauterine only	1	78	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.57, 3.86]
2 Multiple pregnancy	5	370	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.24]
2.1 Vaginal only	3	168	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.79, 1.99]
2.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Vaginal and cervical	2	202	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.52, 1.11]
2.4 Intrauterine only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Ectopic pregnancy	5	277	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.15, 8.98]
3.1 Vaginal only	3	168	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.06, 26.80]
3.2 Cervical only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Vaginal and cervical	1	31	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Intrauterine only	1	78	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.07, 17.09]

Analysis 2.1. Comparison 2 Seminal plasma vs standard ART, per-pregnancy analyses, Outcome 1 Miscarriage.

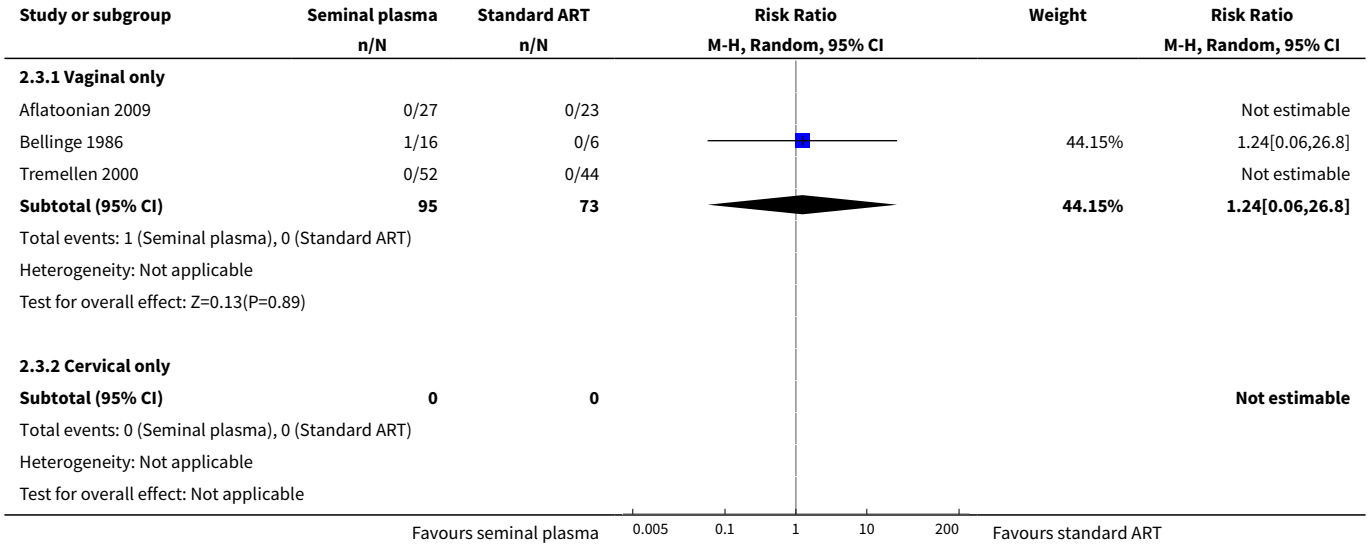


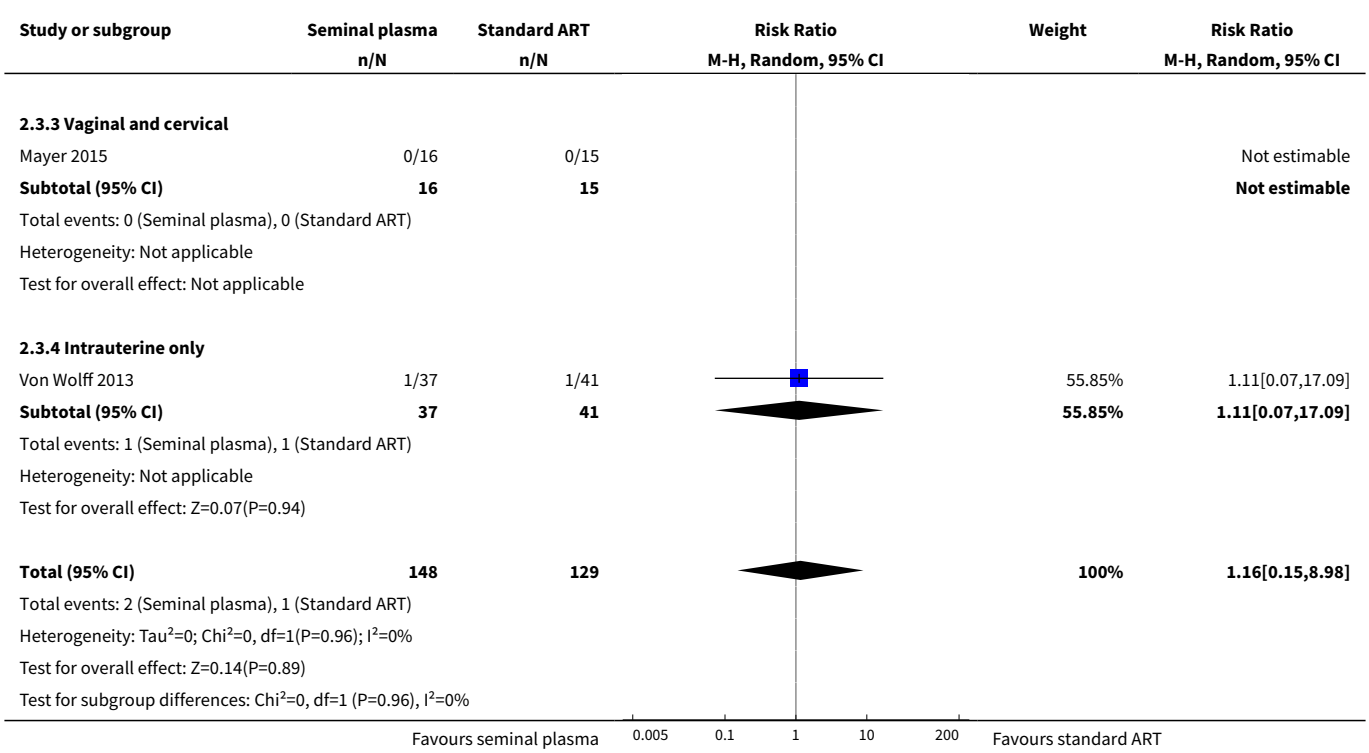
Analysis 2.2. Comparison 2 Seminal plasma vs standard ART, per-pregnancy analyses, Outcome 2 Multiple pregnancy.





Analysis 2.3. Comparison 2 Seminal plasma vs standard ART, per-pregnancy analyses, Outcome 3 Ectopic pregnancy.



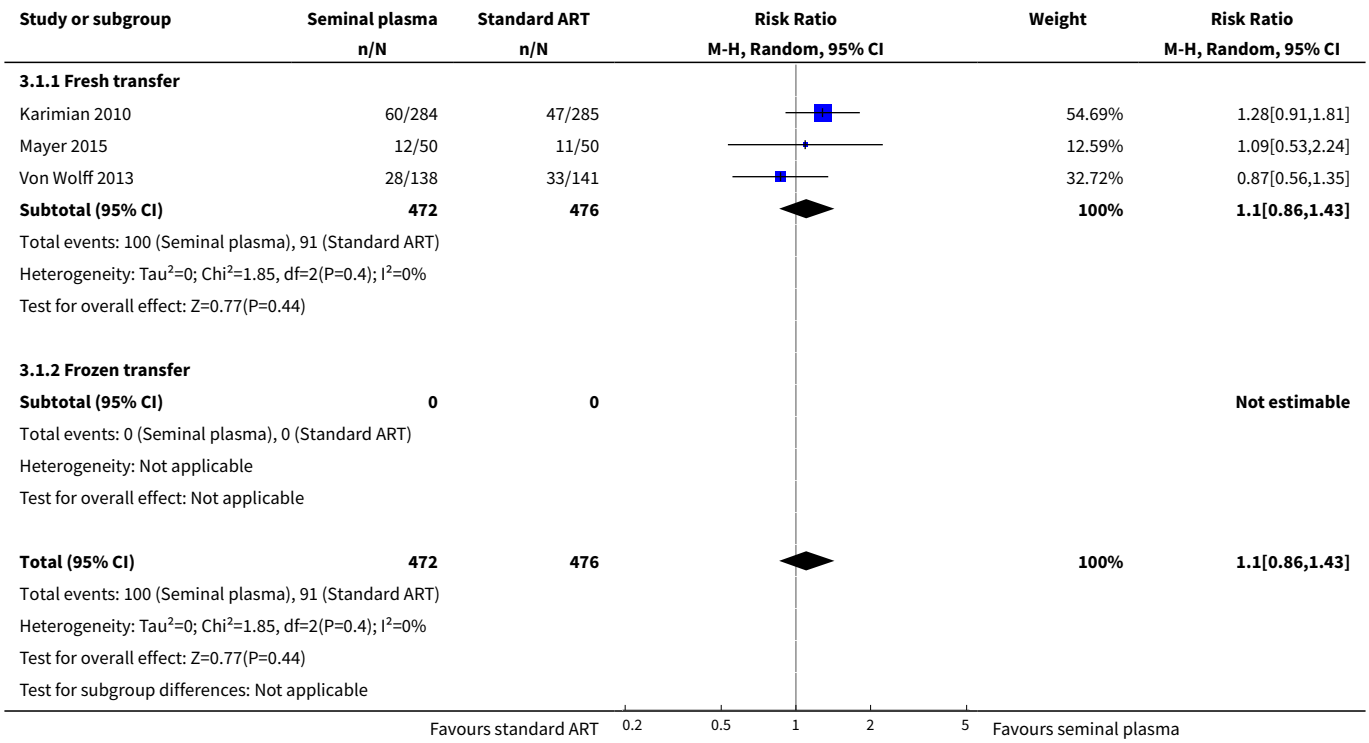


Comparison 3. Grouped by fresh or frozen embryo transfer

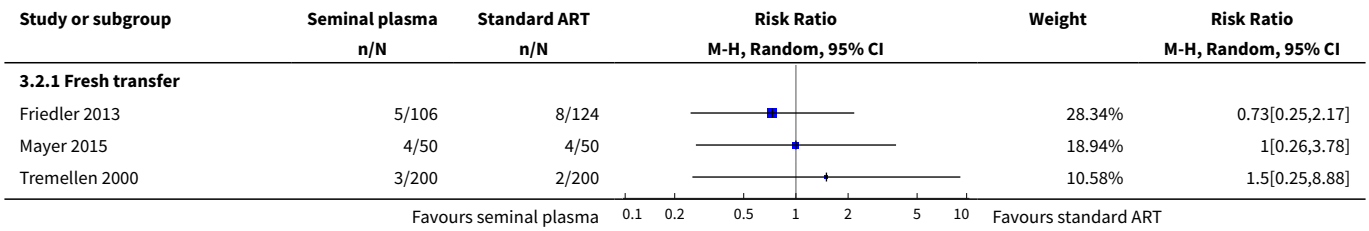
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	948	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.86, 1.43]
1.1 Fresh transfer	3	948	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.86, 1.43]
1.2 Frozen transfer	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Miscarriage	4	1209	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.56, 1.79]
2.1 Fresh transfer	4	1009	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.57, 1.95]
2.2 Frozen transfer	1	200	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.11, 3.75]
3 Live birth or ongoing pregnancy	4	1178	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.95, 1.49]
3.1 Fresh transfer	4	1178	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.95, 1.49]
3.2 Frozen transfer	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Clinical pregnancy	10	2768	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.01, 1.31]
4.1 Fresh transfer	10	2568	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.02, 1.32]
4.2 Frozen transfer	1	200	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.44, 2.11]

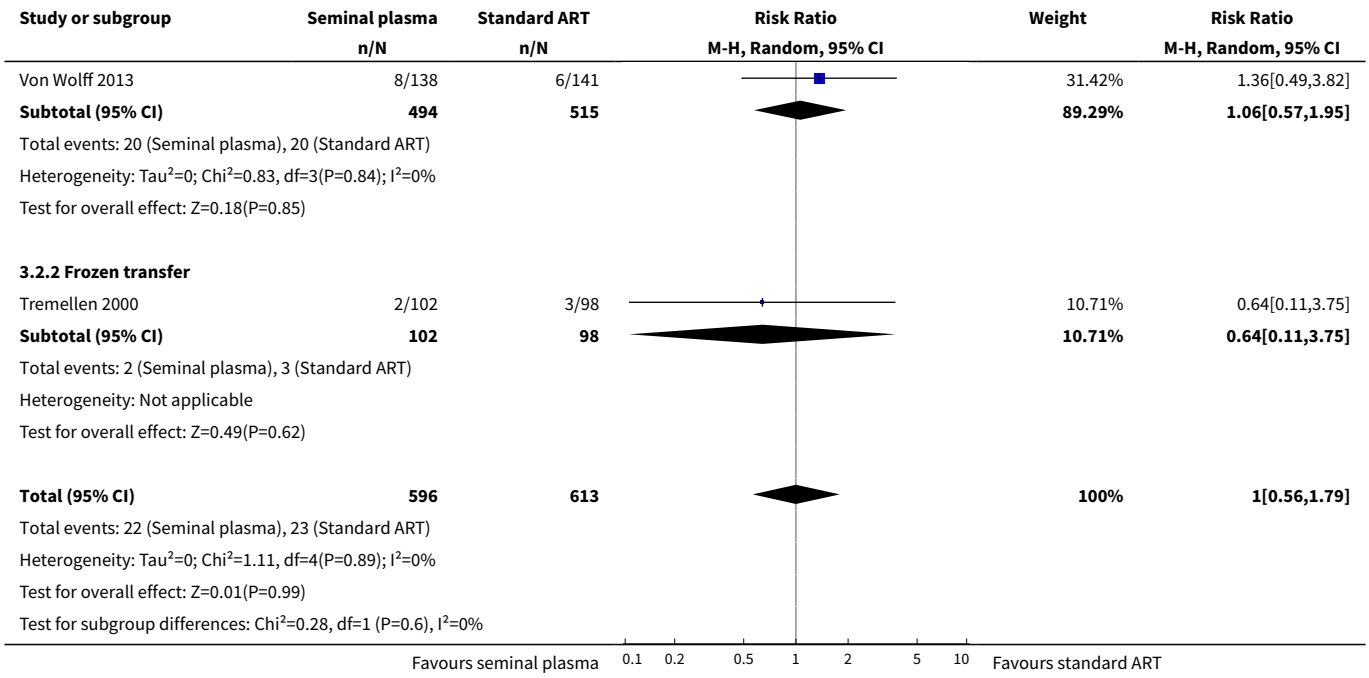
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Multiple pregnancy	5	1642	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.75, 1.60]
5.1 Fresh transfer	5	1442	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.74, 1.46]
5.2 Frozen transfer	1	200	Risk Ratio (M-H, Random, 95% CI)	6.73 [0.35, 128.59]
6 Ectopic pregnancy	5	1521	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.20, 12.78]
6.1 Fresh transfer	5	1321	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.20, 12.78]
6.2 Frozen transfer	1	200	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Grouped by fresh or frozen embryo transfer, Outcome 1 Live birth.

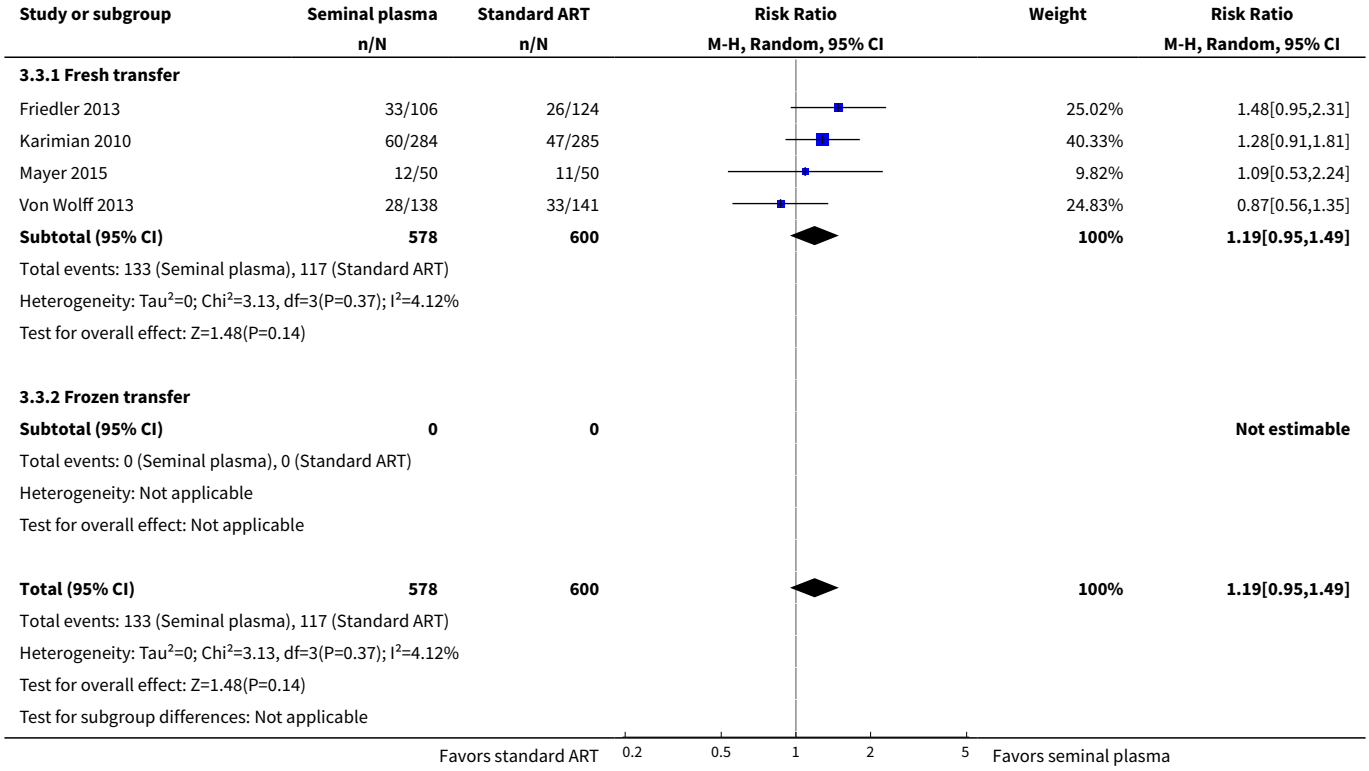


Analysis 3.2. Comparison 3 Grouped by fresh or frozen embryo transfer, Outcome 2 Miscarriage.





Analysis 3.3. Comparison 3 Grouped by fresh or frozen embryo transfer, Outcome 3 Live birth or ongoing pregnancy.



Analysis 3.4. Comparison 3 Grouped by fresh or frozen embryo transfer, Outcome 4 Clinical pregnancy.

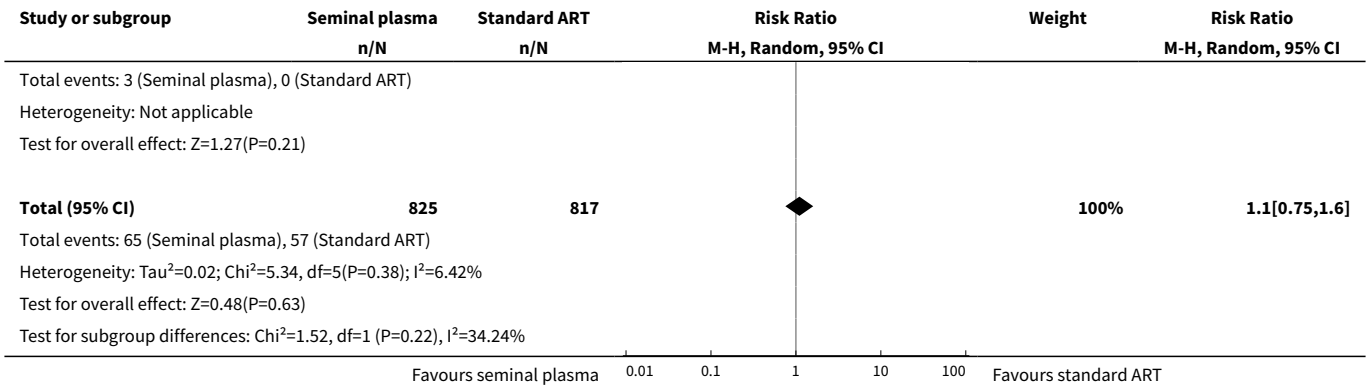
Study or subgroup	Seminal plasma n/N	Standard ART n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Fresh transfer					
Aflatoonian 2009	27/195	23/195		6.22%	1.17[0.7,1.97]
Bellinge 1986	16/78	6/74		2.16%	2.53[1.05,6.12]
Chicea 2013	91/200	80/200		32.42%	1.14[0.91,1.43]
Crawford 2015	20/91	22/95		5.92%	0.95[0.56,1.62]
Friedler 2013	38/106	34/124		11.44%	1.31[0.89,1.92]
Jafarabadi 2016	26/130	23/133		6.55%	1.16[0.7,1.92]
Mayer 2015	16/50	15/50		4.9%	1.07[0.59,1.92]
Tremellen 2000	41/200	33/200		9.79%	1.24[0.82,1.88]
Von Wolff 2009	25/84	18/84		6.1%	1.39[0.82,2.35]
Von Wolff 2013	37/138	41/141		11.8%	0.92[0.63,1.34]
Subtotal (95% CI)	**1272**	**1296**		**97.3%**	**1.16[1.02,1.32]**
Total events: 337 (Seminal plasma), 295 (Standard ART)					
Heterogeneity: Tau^2=0; Chi^2=6.02, df=9(P=0.74); I^2=0%					
Test for overall effect: Z=2.2(P=0.03)					
3.4.2 Frozen transfer					
Tremellen 2000	11/102	11/98		2.7%	0.96[0.44,2.11]
Subtotal (95% CI)	**102**	**98**		**2.7%**	**0.96[0.44,2.11]**
Total events: 11 (Seminal plasma), 11 (Standard ART)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.1(P=0.92)					
Total (95% CI)	**1374**	**1394**		**100%**	**1.15[1.01,1.31]**
Total events: 348 (Seminal plasma), 306 (Standard ART)					
Heterogeneity: Tau^2=0; Chi^2=6.23, df=10(P=0.8); I^2=0%					
Test for overall effect: Z=2.16(P=0.03)					
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.65), I^2=0%					

Favours standard ART — Favours seminal plasma

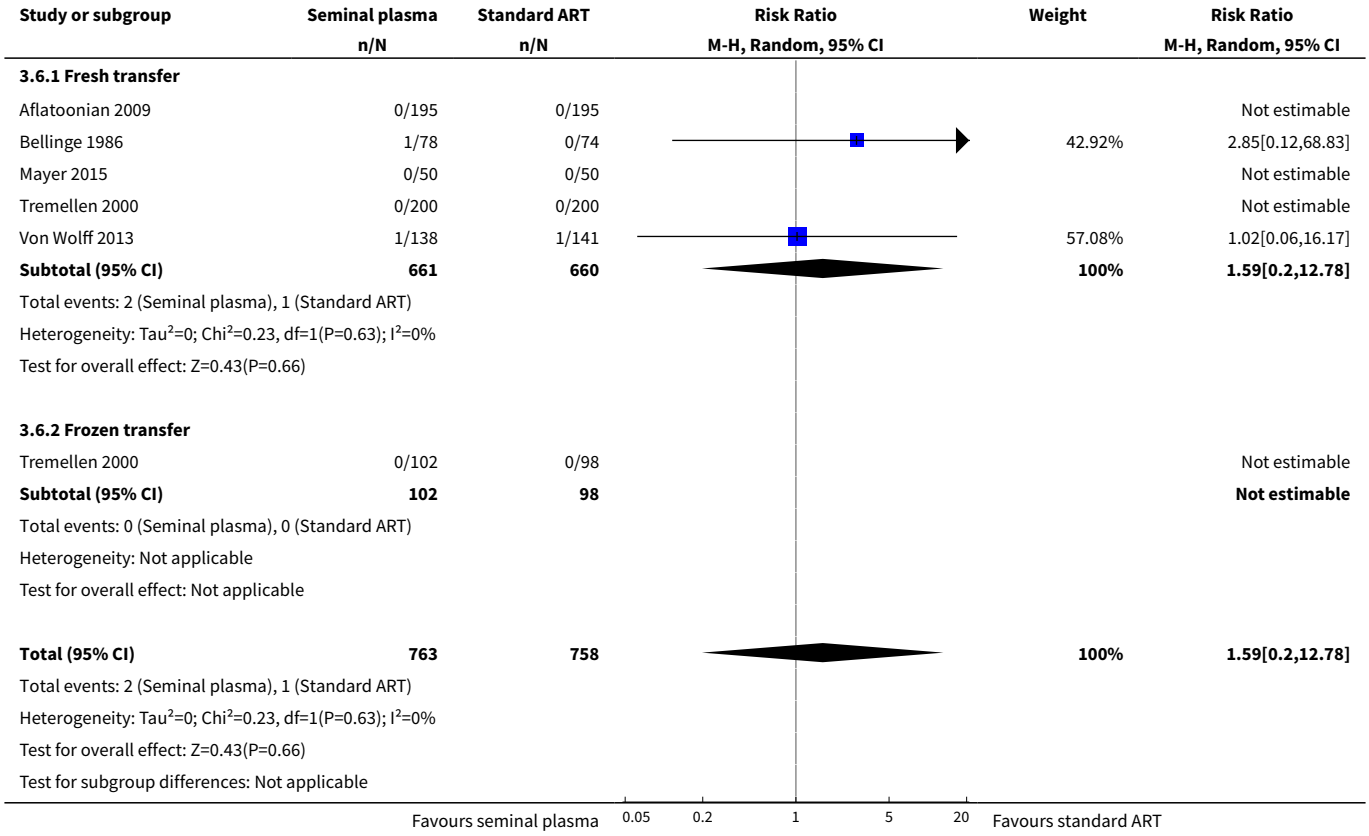
Analysis 3.5. Comparison 3 Grouped by fresh or frozen embryo transfer, Outcome 5 Multiple pregnancy.

Study or subgroup	Seminal plasma n/N	Standard ART n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Fresh transfer					
Aflatoonian 2009	5/195	4/195		8.19%	1.25[0.34,4.59]
Bellinge 1986	6/78	1/74		3.24%	5.69[0.7,46.16]
Chicea 2013	30/200	35/200		53.64%	0.86[0.55,1.34]
Mayer 2015	2/50	2/50		3.83%	1[0.15,6.82]
Tremellen 2000	19/200	15/200		29.45%	1.27[0.66,2.42]
Subtotal (95% CI)	**723**	**719**		**98.36%**	**1.04[0.74,1.46]**
Total events: 62 (Seminal plasma), 57 (Standard ART)					
Heterogeneity: Tau^2=0; Chi^2=3.75, df=4(P=0.44); I^2=0%					
Test for overall effect: Z=0.21(P=0.83)					
3.5.2 Frozen transfer					
Tremellen 2000	3/102	0/98		1.64%	6.73[0.35,128.59]
Subtotal (95% CI)	**102**	**98**		**1.64%**	**6.73[0.35,128.59]**

Favours seminal plasma — Favours standard ART



Analysis 3.6. Comparison 3 Grouped by fresh or frozen embryo transfer, Outcome 6 Ectopic pregnancy.



APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group Specialised Register search strategy

Searched 16 October 2017

Procite platform

Keywords CONTAINS "ART" or "assisted reproduction" or "assisted reproduction techniques" or "IVF" or "ICSI" or "in vitro fertilisation" or "in-vitro fertilisation techniques" or "in vitro fertilization" or "in vitro maturation" or "intracytoplasmic sperm injection" or "subfertility" or "Infertility" or "IUI" or "Intrauterine Insemination" or "*Embryo Transfer" or "ET" or Title CONTAINS "ART" or "assisted reproduction" or "assisted reproduction techniques" or "IVF" or "ICSI" or "in vitro fertilisation" or "in-vitro fertilisation techniques" or "in vitro fertilization" or "in vitro maturation" or "intracytoplasmic sperm injection" or "subfertility" or "Infertility" or "IUI" or "Intrauterine Insemination" or "*Embryo Transfer" or "ET"

AND

Keywords CONTAINS "seminal fluid" or"*Semen" or "seminal plasma" or "sperm" or "ejaculated sperm" or "ejaculation" or "intercourse" or "coitus" or Title CONTAINS "seminal fluid" or"*Semen" or "seminal plasma" or "sperm" or "ejaculated sperm" or "ejaculation" or "intercourse" or "coitus"

AND

Keywords CONTAINS "Vaginal" or "vaginal application" or "vaginal preparation" or "intracervical" or "intracervical insemination" or "intrauterine" or "intrautero tuboperitoneal insemination" or "Intravaginal" or "cervical" or "cervix"or"insemination-pericervical"or"insemination-intrauterine"or"insemination, intracervical" or "insemination-cervical cap" or "Endometrium" or Title CONTAINS "Vaginal" or "vaginal application" or "vaginal preparation" or "intracervical" or "intracervical insemination" or "intrauterine" or "intrautero tuboperitoneal insemination" or "Intravaginal" or "cervical" or "cervix"or"insemination-pericervical"or"insemination-intrauterine"or"insemination, intracervical" or "insemination-cervical cap" or "Endometrium" (404 hits)

Appendix 2. CENTRAL Register of Studies Online (CRSO) search strategy

Searched 16 October 2017

Web platform

#1 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 967

#2 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 1861

#3 MESH DESCRIPTOR sperm injections, intracytoplasmic EXPLODE ALL TREES 481

#4 (embryo* transfer*):TI,AB,KY 2365

#5 (vitro fertili?ation):TI,AB,KY 2149

#6 (ivf or icsi):TI,AB,KY 4042

#7 (intracytoplasmic sperm injection*):TI,AB,KY 1315

#8 (blastocyst* adj2 transfer*):TI,AB,KY 253

#9 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 2848

#10 MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES 345

#11 MESH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES 1203

#12 (assisted reproduct*):TI,AB,KY 829

#13 (artificial insemination):TI,AB,KY 182

#14 iui:TI,AB,KY 550

#15 (intrauterine insemination):TI,AB,KY 707

#16 (ovulation induc*):TI,AB,KY 1915

#17 (ovary* adj2 stimulat*):TI,AB,KY 18

#18 superovulat*:TI,AB,KY 176

#19 (ovarian hyperstimulation):TI,AB,KY 950

#20 infertil*:TI,AB,KY 4472

#21 subfertil*:TI,AB,KY 598

#22 (ovary* adj2 induction):TI,AB,KY 137

#23 MESH DESCRIPTOR Oocyte Retrieval EXPLODE ALL TREES 147

#24 (Oocyte* adj2 Retrieval*):TI,AB,KY 818

#25 (Oocyte* adj2 pick up*):TI,AB,KY 51

#26 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 9185

#27 (seminal adj5 intravagina*):TI,AB,KY 1

#28 (seminal adj5 plasma*):TI,AB,KY 213

#29 (seminal adj5 vagina*):TI,AB,KY 4

#30 (seminal adj5 intracervi*):TI,AB,KY 0

#31 (seminal adj5 cervi*):TI,AB,KY 4

#32 (seminal adj5 instillation*):TI,AB,KY 0

#33 (seminal adj5 intrauter*):TI,AB,KY 0

#34 (seminal adj5 uter*):TI,AB,KY 2

#35 (seminal adj5 inseminat*):TI,AB,KY 5

#36 (seminal adj5 injection*):TI,AB,KY 1

#37 (seminal adj5 endometr*):TI,AB,KY 3

#38 (semen adj5 intravagina*):TI,AB,KY 0

#39 (semen adj5 vagina*):TI,AB,KY 15

#40 (semen adj5 intracervi*):TI,AB,KY 2

#41 (semen adj5 cervi*):TI,AB,KY 11

#42 (semen adj5 instillation*):TI,AB,KY 0

#43 (semen adj5 intrauter*):TI,AB,KY 12

#44 (semen adj5 uter*):TI,AB,KY 15

#45 (semen adj5 injection*):TI,AB,KY 40

#46 (semen adj5 endometr*):TI,AB,KY 1

#47 (semen adj5 intracervi*):TI,AB,KY 2

#48 (ejaculate* adj5 intracerv*):TI,AB,KY 1

#49 (ejaculate* adj5 vagina*):TI,AB,KY 1

#50 (ejaculate* adj5 intravagina*):TI,AB,KY 1

#51 (ejaculate* adj5 cervi*):TI,AB,KY 0

#52 (ejaculate* adj5 instillation*):TI,AB,KY 0

#53 (ejaculate* adj5 intrauter*):TI,AB,KY 1

#54 (ejaculate* adj5 uter*):TI,AB,KY 1

#55 (ejaculate* adj5 injection*):TI,AB,KY 1

#56 (ejaculate* adj5 endometr*):TI,AB,KY 0

#57 (intercourse adj7 embryo*):TI,AB,KY 5

#58 (coitus adj7 embryo*):TI,AB,KY 3

#59 (ejaculate* adj7 embryo*):TI,AB,KY 1

#60 MESH DESCRIPTOR coitus EXPLODE ALL TREES 311

#61 MESH DESCRIPTOR Ejaculation EXPLODE ALL TREES 198

#62 MESH DESCRIPTOR Spermatozoa EXPLODE ALL TREES 407

#63 #60 OR #61 OR #62 874

#64 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 304

#65 #63 AND #64 57

#66 #64 OR #65 304

#67 #26 AND #66 192

Appendix 3. MEDLINE search strategy

Searched from 1946 to 16 October 2017

Ovid platform

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (40320)
2 embryo transfer$.tw. (10937)
3 vitro fertili?ation.tw. (22192)
4 ivf-et.tw. (2465)
5 ivf.tw. (22151)
6 icsi.tw. (7338)
7 intracytoplasmic sperm injection$.tw. (6437)
8 (blastocyst adj2 transfer$).tw. (821)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (66566)
10 assisted reproduct$.tw. (12890)
11 artificial insemination.tw. (6205)
12 iui.tw. (1654)
13 intrauterine insemination$.tw. (2382)
14 ovulation induc$.tw. (4243)
15 (ovari$ adj2 stimulat$).tw. (6482)
16 superovulat$.tw. (3381)
17 ovarian hyperstimulation.tw. (4994)
18 COH.tw. (1559)
19 infertil$.tw. (57008)
20 subfertil$.tw. (4797)
21 (ovari$ adj2 induction).tw. (280)
22 exp Oocyte Retrieval/ (1384)
23 Oocyte Retrieval$.tw. (2666)
24 oocyte$ pick up$.tw. (204)
25 or/1-24 (130075)
26 exp Semen/ (19619)
27 (seminal adj5 intravagina$).tw. (15)
28 (seminal adj5 plasma$).tw. (6706)
29 (seminal adj5 vagina$).tw. (173)
30 (seminal adj5 intracervi$).tw. (2)
31 (seminal adj5 cervi$).tw. (142)
32 (seminal adj5 instillation$).tw. (3)

33 (seminal adj5 intrauter$).tw. (19)
34 (seminal adj5 uter$).tw. (190)
35 (seminal adj5 inseminat$).tw. (63)
36 (seminal adj5 injection$).tw. (49)
37 (seminal adj5 endometr$).tw. (43)
38 (semen adj5 intravagina$).tw. (26)
39 (semen adj5 vagina$).tw. (503)
40 (semen adj5 intracervi$).tw. (14)
41 (semen adj5 cervi$).tw. (278)
42 (semen adj5 instillation$).tw. (2)
43 (semen adj5 intrauter$).tw. (167)
44 (semen adj5 uter$).tw. (147)
45 (semen adj5 injection$).tw. (118)
46 (semen adj5 endometr$).tw. (38)
47 (ejaculat$ adj5 intracervi$).tw. (3)
48 (ejaculat$ adj5 vagina$).tw. (182)
49 (ejaculat$ adj5 intravagina$).tw. (341)
50 (ejaculat$ adj5 cervi$).tw. (36)
51 (ejaculat$ adj5 instillation$).tw. (3)
52 (ejaculat$ adj5 intrauter$).tw. (17)
53 (ejaculat$ adj5 uter$).tw. (45)
54 (ejaculat$ adj5 injection$).tw. (133)
55 (ejaculat$ adj5 endometr$).tw. (1)
56 (ejaculat$ adj5 intravagina$).tw. (341)
57 (intercourse adj7 embryo$).tw. (7)
58 (coitus adj7 blastocyst$).tw. (9)
59 (coitus adj7 embryo$).tw. (63)
60 (ejaculat$ adj7 embryo$).tw. (76)
61 (ejaculat$ adj7 blastocyst$).tw. (18)
62 (seminal adj3 priming).tw. (7)
63 coitus/ or ejaculation/ (13611)
64 or/26-63 (35255)
65 25 and 64 (8158)
66 randomized controlled trial.pt. (496904)
67 controlled clinical trial.pt. (99253)
68 randomized.ab. (433409)
69 randomised.ab. (87389)
70 placebo.tw. (208017)
71 clinical trials as topic.sh. (195527)
72 randomly.ab. (298737)
73 trial.ti. (195716)
74 (crossover or cross-over or cross over).tw. (80801)
75 or/66-74 (1269996)
76 exp animals/ not humans.sh. (4677556)
77 75 not 76 (1171818)
78 65 and 77 (416)

Appendix 4. Embase search strategy

Searched from 1980 to 16 October 2017

Ovid platform

1 (seminal adj5 intravagina$).tw. (23)
2 (seminal adj5 vagina$).tw. (173)
3 (seminal adj5 intracervi$).tw. (6)
4 (seminal adj5 cervi$).tw. (131)
5 (seminal adj5 instillation$).tw. (7)
6 (seminal adj5 intrauter$).tw. (22)
7 (seminal adj5 uter$).tw. (201)
8 (seminal adj5 inseminat$).tw. (59)
9 (seminal adj5 injection$).tw. (56)
10 (seminal adj5 endometr$).tw. (63)

11 (semen adj5 intravagina$).tw. (26)
12 (semen adj5 vagina$).tw. (502)
13 (semen adj5 intracervi$).tw. (14)
14 (semen adj5 cervi$).tw. (244)
15 (semen adj5 instillation$).tw. (0)
16 (semen adj5 intrauter$).tw. (176)
17 (semen adj5 uter$).tw. (146)
18 (semen adj5 injection$).tw. (136)
19 (semen adj5 endometr$).tw. (48)
20 seminal fluid.tw. (2481)
21 (seminal adj3 plasma$).tw. (6635)
22 exp seminal plasma/ (6375)
23 (ejaculat$ adj5 intracervi$).tw. (2)
24 (ejaculat$ adj5 vagina$).tw. (238)
25 (ejaculat$ adj5 intravagina$).tw. (496)
26 (ejaculat$ adj5 cervi$).tw. (35)
27 (ejaculat$ adj5 intrauter$).tw. (25)
28 (ejaculat$ adj5 uter$).tw. (48)
29 (ejaculat$ adj5 injection$).tw. (179)
30 (ejaculat$ adj5 endometr$).tw. (2)
31 (ejaculat$ adj5 intravagina$).tw. (496)
32 (intercourse adj7 embryo$).tw. (19)
33 (coitus adj7 blastocyst$).tw. (9)
34 (coitus adj7 embryo$).tw. (62)
35 (ejaculat$ adj7 embryo$).tw. (122)
36 (ejaculat$ adj7 blastocyst$).tw. (25)
37 (seminal adj3 priming).tw. (18)
38 coitus/ (5867)
39 ejaculation/ (8334)
40 or/1-37 (13222)
41 38 or 39 (13953)
42 40 and 41 (1105)
43 40 or 42 (13222)
44 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (58626)
45 embryo$ transfer$.tw. (18006)
46 in vitro fertili?ation.tw. (26529)
47 icsi.tw. (13887)
48 intracytoplasmic sperm injection$.tw. (8367)
49 (blastocyst adj2 transfer$).tw. (1929)
50 ivf.tw. (34746)
51 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (86147)
52 assisted reproduct$.tw. (18955)
53 artificial insemination.tw. (5540)
54 iui.tw. (2796)
55 intrauterine insemination$.tw. (3297)
56 ovulation induc$.tw. (5203)
57 (ovari$ adj2 stimulat$).tw. (9655)
58 superovulat$.tw. (3517)
59 ovarian hyperstimulation.tw. (6740)
60 COH.tw. (2119)
61 infertil$.tw. (72808)
62 subfertil$.tw. (6020)
63 (ovari$ adj2 induction).tw. (333)
64 exp oocyte retrieval/ (5521)
65 Oocyte Retrieval$.tw. (4130)
66 oocyte$ pick up$.tw. (388)
67 or/44-66 (167021)
68 43 and 67 (4341)
69 Clinical Trial/ (949969)
70 Randomized Controlled Trial/ (471914)
71 exp randomization/ (75860)
72 Single Blind Procedure/ (29732)

73 Double Blind Procedure/ (140776)
74 Crossover Procedure/ (53437)
75 Placebo/ (300796)
76 Randomi?ed controlled trial$.tw. (168408)
77 Rct.tw. (25850)
78 random allocation.tw. (1695)
79 randomly allocated.tw. (28434)
80 allocated randomly.tw. (2269)
81 (allocated adj2 random).tw. (785)
82 Single blind$.tw. (19880)
83 Double blind$.tw. (175965)
84 ((treble or triple) adj blind$).tw. (717)
85 placebo$.tw. (256628)
86 prospective study/ (405705)
87 or/69-86 (1812459)
88 case study/ (50227)
89 case report.tw. (340144)
90 abstract report/ or letter/ (1013008)
91 or/88-90 (1395186)
92 87 not 91 (1766305)
93 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5884177)
94 92 not 93 (1701104)
95 68 and 94 (418)

Appendix 5. PsycINFO search strategy

Searched from 1806 to 16 October 2017

Ovid platform

1 exp reproductive technology/ (1654)
2 in vitro fertili?ation.tw. (672)
3 ivf-et.tw. (17)
4 (ivf or et).tw. (123147)
5 icsi.tw. (67)
6 intracytoplasmic sperm injection$.tw. (50)
7 (blastocyst adj2 transfer$).tw. (4)
8 assisted reproduct$.tw. (819)
9 artificial insemination.tw. (243)
10 iui.tw. (31)
11 intrauterine insemination$.tw. (23)
12 ovulation induc$.tw. (27)
13 (ovari$ adj2 stimulat$).tw. (55)
14 ovarian hyperstimulation.tw. (11)
15 COH.tw. (97)
16 superovulat$.tw. (6)
17 infertil$.tw. (3145)
18 subfertil$.tw. (82)
19 (ovari$ adj2 induction).tw. (7)
20 or/1-19 (127435)
21 exp Sperm/ (826)
22 semen.tw. (438)
23 seminal.tw. (4782)
24 or/21-23 (5878)
25 20 and 24 (477)
26 random.tw. (51148)
27 control.tw. (395551)
28 double-blind.tw. (21024)
29 clinical trials/ (10608)
30 placebo/ (4990)
31 exp Treatment/ (696683)
32 or/26-31 (1080895)
33 25 and 32 (118)

Appendix 6. CINAHL search strategy

Searched 1961 to 16 October 2017

Ebsco platform

#	Query	Results
S58	S45 AND S57	53
S57	S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56	1,168,494
S56	TX allocat* random*	7,286
S55	(MH "Quantitative Studies")	16,546
S54	(MH "Placebos")	10,402
S53	TX placebo*	47,633
S52	TX random* allocat*	7,286
S51	(MH "Random Assignment")	44,289
S50	TX randomi* control* trial*	132,848
S49	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	912,372
S48	TX clinic* n1 trial*	212,242
S47	PT Clinical trial	80,036
S46	(MH "Clinical Trials+")	222,921
S45	S26 AND S44	242
S44	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	1,023
S43	TX(seminal N3 priming)	2
S42	TX(ejaculat* N7 embryo*)	3
S41	TX (intercourse N7 embryo*)	1
S40	TX semen N5 injection*	3
S39	TX seminal plasma	91
S38	TX(semen N5 inseminat*)	20
S37	TX(semen N5 uter*)	3

(Continued)

S36	TX (semen N5 intrauter*)	9
S35	TX (semen N5 cervi*)	15
S34	TX (semen N5 intravagina*)	1
S33	TX (seminal N5 uter*)	4
S32	TX (seminal N5 intrauter*)	2
S31	TX (seminal N5 cervi*)	6
S30	TX (seminal N5 vagina*)	5
S29	TX (seminal N5 intravagina*)	2
S28	(MM "Spermatozoa")	656
S27	(MM "Semen")	310
S26	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	10,930
S25	TX intra-uterine insemination	15
S24	TX coitus	2,005
S23	(MM "Coitus")	880
S22	TX natural cycle*	173
S21	TX expectant management	638
S20	TX timed intercourse	29
S19	TX oocyte* N2 pick up*	11
S18	TX embryo transfer or TX oocyte* retrieval$	1,146
S17	TX ovarian hyperstimulation	443
S16	TX superovulat*	27
S15	TX ovulation induc*	721
S14	TX intrauterine insemination	214
S13	TX IUI	143
S12	TX artificial insemination	525
S11	TX assisted reproduct*	1,940
S10	(MM "Insemination, Artificial")	267

(Continued)

S9	(MM "Reproduction Techniques+")	4,822
S8	TX intracytoplasmic sperm injection*	376
S7	TX embryo* N3 transfer*	1,115
S6	TX ovar* N3 hyperstimulat*	447
S5	TX ovari* N3 stimulat*	407
S4	TX IVF or TX ICSI	2,112
S3	(MM "Fertilization in Vitro")	1,763
S2	TX vitro fertilization	3,806
S1	TX vitro fertilisation	3,806

Appendix 7. Search strategy for ClinicalTrials.gov, WHO ICTRP Search Portal, DARE, Web of Knowledge, OpenGrey, LILACS, PubMed, Google Scholar

Web platforms

searched 16 October 2017

Combinations of words: "seminal plasma", "intercourse", ejaculate", "insemination", "IVF", "assisted reproduction", "embryo transfer"

WHAT'S NEW

Date	Event	Description
9 March 2018	Amended	Clarifications and corrections made to review text in order to meet Cochrane standards

CONTRIBUTIONS OF AUTHORS

- Baris Ata conceived and wrote the protocol. He also drafted the text of review, extracted data from eligible trials, and conducted the analyses.
- William Buckett provided a clinical perspective and reviewed the final text.
- Ayse Seyhan provided a clinical perspective, screened literature search results, extracted data, and reviewed the final text.
- Ahmed Abou-Setta provided general advice on the protocol, screened the literature search results, adjudicated conflicting data extraction results, and reviewed the final text.

DECLARATIONS OF INTEREST

WB, AS and AMAS have no interests to declare.

BA's institution has received fees for a consultancy, two lectures and a conference registration, all relating to contraception.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The major change from the protocol was the formation of a new composite outcome measure of 'live birth/ongoing pregnancy rate'. We anticipated that few studies might report live birth and that this composite outcome might give us an extra and useful estimate of effectiveness.

We added a subgroup analysis comparing fresh versus frozen embryo transfer, as we considered this would be clinically useful.

We defined studies at (overall) high risk of bias for the purpose of the sensitivity analysis, as studies at unclear or high risk of bias in multiple domains.

INDEX TERMS

Medical Subject Headings (MeSH)

*Embryo Transfer; *Genitalia, Female; *Semen [physiology]; Abortion, Spontaneous [*epidemiology]; Fertilization in Vitro; Live Birth [*epidemiology]; Pregnancy Rate; Pregnancy, Ectopic [epidemiology]; Pregnancy, Multiple; Publication Bias; Randomized Controlled Trials as Topic; Reproductive Techniques, Assisted; Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy