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Antibiotics prior to embryo transfer in ART.

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Antibiotics prior to embryo transfer in ART (Review)

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[Intervention Review]

# Antibiotics prior to embryo transfer in ART

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## ABSTRACT

### Background

Embryo transfer (ET) involves the placement of one or more embryos into the uterine cavity, usually by passing a catheter through the cervical os. ET is the final step in an assisted reproductive technology (ART) cycle, where a woman has undergone controlled ovarian stimulation, egg retrieval and in vitro fertilisation of her eggs. Despite the transfer of high quality embryos, many ETs do not result in a pregnancy. There are many factors which may affect the success of ET, including the presence of upper genital tract microbial colonisation. The administration of antibiotics prior to ET has been suggested as an intervention to reduce levels of microbial colonisation and hence improve pregnancy rates.

### Objectives

To evaluate the effectiveness and safety of antibiotic administration prior to ET during ART cycles.

### Search methods

We searched the Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library*, MEDLINE, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® (from inception to February 2011), Ovid EMBASE (January 2010 to February 2011), Ovid PsycINFO, CINAHL, LILACS, trial registers for ongoing and registered trials, citation indexes, ClinicalStudyResults, PubMed, OpenSIGLE database and for for herbal and complimentary therapy protocols and reviews.

### Selection criteria

Only randomised controlled trials were included.

### Data collection and analysis

The titles and abstracts of articles identified by the search were screened by one review author for eligibility. Two review authors then independently examined the full text articles for suitability for inclusion in the review. Data were extracted independently by two review authors.

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**Antibiotics prior to embryo transfer in ART (Review)**

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## **Main results**

We identified four potential studies, of which three were excluded.

The included trial reported clinical pregnancy rates but not live births. There was no evidence of a difference in clinical pregnancy rate between those receiving an amoxicillin and clavulanic acid antibiotic combination (64/178: 36%) and those not (61/172: 35.5%) (OR1.02, 95% CI 0.66 to 1.58). Genital tract colonisation was significantly reduced in women receiving this antibiotic regimen (OR 0.59, 95% CI 0.37 to 0.95).

## **Authors' conclusions**

This review suggests that the administration of amoxicillin and clavulanic acid prior to embryo transfer reduced upper genital tract microbial contamination but did not alter clinical pregnancy rates. The effect of this intervention on live birth is unknown. There are no data from randomised controlled trials to support or refute other antibiotic regimens in this setting.

Future research is warranted to assess the efficacy of alternative antibiotic regimens. Researchers should assess live birth as the primary outcome and address quantitative microbial colonization as a secondary outcome.

## **PLAIN LANGUAGE SUMMARY**

### **Antibiotics prior to embryo transfer in ART**

In vitro fertilisation (IVF) describes an assisted reproductive technology (ART) during which a woman undergoes ovarian stimulation, surgical retrieval of eggs, fertilisation of eggs outside of the body, and finally the transfer of resulting embryo(s) into the uterus by an embryo transfer (ET) procedure. During an ET, the embryo(s) is passed through the cervix by means of a catheter. Many variables affect the chance of pregnancy after ET, including embryo quality, uterine factors and the embryo transfer technique. High levels of bacteria and other organisms in the upper genital tract have a detrimental effect on pregnancy rate after ET. Administration of antibiotics prior to ET may reduce the growth of these organisms and improve the outcomes of IVF. This review considered the question of whether antibiotics given at any time prior to ET affect pregnancy rates and other important outcomes of IVF.

In the only study which addressed this question, the use of an amoxicillin and clavulanic acid antibiotic regimen had no effect on clinical pregnancy rate despite demonstrating a reduction in upper genital tract colonisation. The effect on live birth rate is unknown.

The findings of this review do not support the use of an amoxicillin and clavulanic acid antibiotic regimen prior to ET for the purposes of improving IVF success. The effect of alternative antibiotic regimens on IVF outcomes is unknown and needs further research.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antibiotics prior to embryo transfer in ART						
<b>Patient or population:</b> Patients undergoing ART cycles						
<b>Settings:</b> IVF Unit						
<b>Intervention:</b> Antibiotics prior to embryo transfer						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotics prior to embryo transfer				
Clinical Pregnancy	355 per 1000	359 per 1000 (266 to 465)	OR 1.02 (0.66 to 1.58)	350 (1 study)	⊕⊕⊕⊕ high	
Genital Tract Colonisation	623 per 1000	494 per 1000 (380 to 611)	OR 0.59 (0.37 to 0.95)	284 (1 study)	⊕⊕⊕○ moderate <sup>1</sup>	

\*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; **OR:** Odds 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.

<sup>1</sup> Bacteriological catheter analysis was performed on 284 of 350 women randomised. In the antibiotic arm 154/178 (86.5%) were analysed. In the control arm, 130/172 (75.6%) were analysed.

## BACKGROUND

### Description of the condition

In vitro fertilisation (IVF) is a form of assisted reproductive technology (ART) during which an egg is fertilised by sperm outside of the female reproductive tract and the resulting embryo placed in the uterus. The process of IVF involves controlled ovarian stimulation, egg retrieval, fertilisation by either combining eggs and sperm or intracytoplasmic sperm injection (ICSI), and embryo transfer (ET). During ET, a catheter is inserted via the cervical canal to deliver one or more embryos into the uterus.

ET is a critical step in the ART cycle. While many women will reach the stage of ET with embryos of adequate quality, few of these embryos will implant and even fewer will achieve a live birth. The success of ET may be affected by technical aspects of the ET procedure (Mains 2010) as well as by factors beyond operator control, such as embryo quality and uterine receptivity.

An additional modifier of ET success may be the genital tract microbial milieu. While clinical pelvic infection is relatively rare following embryo transfer (Sowerby 2004), there is evidence to suggest that increased endocervical microbial colonization at the time of embryo transfer results in lower pregnancy rates (Egbase 1999; Fanchin 1998; Moore 2000; Salim 2002). The effect of colonisation on pregnancy rates depends on the organism and degree of colonisation (Salim 2002). This effect may be due to inoculation of the uterine cavity by the ET catheter, but may potentially also represent the presence of a pre-existing subclinical endometrial infection (Salim 2002).

### Description of the intervention

This systematic review considered the effect of any antibiotic given by any route prior to ET, where the primary purpose of this intervention was to increase IVF success rates.

### How the intervention might work

The association between increased cervico-vaginal microbial growth and reduced pregnancy rates after ET may indicate that the passage of the ET catheter is responsible for the introduction of microbes into the endometrial cavity. This upper genital tract infection or contamination may have a negative impact on implantation and IVF success rates by both endometrial and embryonic mechanisms (Moore 2000; Paulson 1990; Spandorfer 2001). In the event of organisms stimulating an endometrial inflammatory response, pro-inflammatory cytokines may negatively alter the ability of an embryo to successfully implant (Spandorfer 2001). Additionally, with the loss of the protective zona pellucida prior to implantation, the embryo is potentially exposed to nearby

organisms (Lavilla-Apelo 1992) that may affect both embryo development and implantation.

Antibiotics have long been used in surgical procedures to reduce the risk of surgical site infections by endogenous patient flora. Pre-operative surgical site asepsis is integral to the reduction in microbial load, however concerns about the negative effect of vaginal antiseptics on oocytes and embryos limit their use in ART procedures (Moore 2000). The administration of antibiotics at the time of a surgical procedure pharmacologically augments natural host immunity, reducing bacteria that are inoculated into a wound (ACOG Practice Bulletin 2009). In the case of ET, there is no physical disruption of a skin surface, however a breach of the endocervix and cervical mucus may allow for analogous seeding of microbes into the upper genital tract. Clinical endometritis and pelvic inflammatory disease (PID) seldom result from simple instrumentation of the lower genital tract (ACOG Practice Bulletin 2009). In the case of ET, however, it is possible that abnormal colonisation of the endometrium or a subclinical infection may be enough to alter pregnancy rates.

The administration of antibiotics prior to or at the time of ET is hypothesised to alter the endocervical and vaginal flora and thereby reduce the likelihood of endometrial bacterial contamination by the ET catheter (Brook 2006; Moore 2000). As endometrial contamination in women with increased cervico-vaginal organisms is associated with a reduction in pregnancy rates, the administration of antibiotics may increase pregnancy rates after IVF.

While this review incorporates all published data on antibiotic therapy prior to ET, it does not specifically address the use of antibiotics given at the time of egg pick up (EPU) for the purposes of reducing post-surgical infectious complications.

### Why it is important to do this review

Embryo transfer (ET) has become the subject of much interest in recent years as practitioners seek to improve relatively poor implantation rates (Mains 2010). Systematic reviews addressing the effect of different ET catheters (Abou-Setta 2005), different technical aspects of ET (Derks 2009), the effect of ultrasound guided ET versus 'clinical touch' (Brown 2010), and of post-embryo transfer interventions (Abou-Setta 2010) have been published. Despite the suggestion that upper genital tract contamination reduces pregnancy rates, there is limited evidence from randomised controlled trials (RCTs) on the role of antibiotics prior to ET.

While the theory of antibiotic prophylaxis for ET may be compelling, the practice is not without potential costs and risks. Adverse antibiotic effects range from skin rash or gastrointestinal side effects to life threatening anaphylaxis and death, with the individual risk dependent on a number of patient factors (ACOG Practice Bulletin 2009). Furthermore, prolonged or repeated exposure to prophylactic antibiotics may pre-dispose to antibiotic resistance (ACOG Practice Bulletin 2009). Additionally, exposure of an em-

bryo to an antimicrobial in the setting of ART might carry the risk of teratogenicity.

Given that antibiotic administration could confer benefit, yet carries potential embryo and patient risks, a systematic review is warranted.

## OBJECTIVES

To evaluate the effectiveness and safety of antibiotic administration prior to ET during ART cycles.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

This review considered all published and unpublished randomised controlled trials (RCTs) which assessed the use of antibiotics prior to or at the time of embryo transfer in IVF cycles. The trials must have addressed at least one of the review's outcome measures to be included, however any studies identified as part of the systematic review that did not address the primary outcome criteria were assessed for pertinent summary statistics that should be included as part of the analysis. Quasi-randomised studies were not considered.

#### Types of participants

Women of any age undergoing fresh or frozen embryo transfer (ET) as part of an IVF or IVF and ICSI cycle for infertility of any cause.

#### Types of interventions

Trials comparing the use of antibiotic(s) prior to ET with any other antibiotic(s), placebo, or no intervention were eligible for inclusion.

#### Types of outcome measures

##### Primary outcomes

Live birth rate or ongoing pregnancy (beyond 20 completed weeks gestation) per woman randomised.

##### Secondary outcomes

1. Clinical pregnancy rate per woman randomised (identification of a fetal heart on ultrasound at  $\geq 7$  weeks gestation).
2. Miscarriage rate (at  $< 20$  completed weeks gestation or weighing  $< 500$  g), as confirmed by ultrasound and pregnancy test or histology) per woman randomised (including partial loss of multiple pregnancies).
3. Ectopic pregnancy rate per woman randomised.
4. Multiple pregnancy rate per clinical pregnancy, confirmed by ultrasound or delivery.
5. Fetal abnormalities (as determined by fetal anatomy scan or after delivery) per woman randomised.
6. Adverse events associated with antibiotic administration and ET per woman randomised; adverse events included pain and adverse drug reactions such as hypersensitivity reactions, anaphylaxis, and gastrointestinal side effects (nausea, vomiting, diarrhoea).
7. Genital tract colonization rate, as defined by the study authors.
8. Pelvic infection, as defined by the study authors but including presentation post-ET with lower abdominal pain and one or more of fevers; abnormal cervico-vaginal discharge; raised C-reactive protein (CRP), erythrocyte sedimentation ratio (ESR) or white cell count (WCC).

##### Search methods for identification of studies

All published and unpublished RCTs of antibiotic use prior to ET were sought using the following search strategy, without any language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

##### Electronic searches

The following electronic databases, trial registers and websites were searched (from inception to 02 February 2011).

The Menstrual Disorders and Subfertility Group Specialised Register, which includes the results of handsearching abstracts from conference proceedings (see [Appendix 1](#) for search strategy), Cochrane Central Register of Controlled Trials (CENTRAL) (see [Appendix 2](#)), MEDLINE (see [Appendix 3](#)), Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® (inception to present), Ovid EMBASE (01 January 2010 to 02 February 2011) (see [Appendix 4](#)), Ovid PsycINFO (see [Appendix 5](#)).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.0.2, Chapter 6, 6.4.11).

The EMBASE and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) ([www.sign.ac.uk/mehodology/filters.html#random](http://www.sign.ac.uk/mehodology/filters.html#random)).

The following electronic sources of trials were searched:

- CINAHL;



- *The Cochrane Library* ([www.cochrane.org/index.htm](http://www.cochrane.org/index.htm));
- trial registers for ongoing and registered trials - 'Current Controlled Trials' ([www.controlled-trials.com/](http://www.controlled-trials.com/)), 'ClinicalTrials.gov' a service of the US national Institutes of Health (<http://clinicaltrials.gov/ct2/home>), or 'The World Health Organization International Trials Registry Platform search portal' ([www.who.int/trialsearch/Default.aspx](http://www.who.int/trialsearch/Default.aspx));
- Citation indexes (<http://scientific.thomson.com/products/sci/>);
- conference abstracts on the ISI Web of Knowledge (<http://isiwebofknowledge.com/>);
- LILACS database as a source of trials from the Portuguese and Spanish speaking world (<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F>);
- ClinicalStudyResults for clinical trial results of marketed pharmaceuticals ([www.clinicalstudyresults.org/](http://www.clinicalstudyresults.org/));
- PubMed ([www.ncbi.nlm.nih.gov/pubmed/](http://www.ncbi.nlm.nih.gov/pubmed/)), the random control filters for PubMed were taken from Chapter 6 of *The Cochrane Handbook for Systematic Reviews of Interventions*;
- OpenSIGLE database (<http://opensigle.inist.fr/>) for grey Literature from Europe;
- herbal or complimentary therapy protocols and reviews (at least one Chinese database was searched).

### Searching other resources

The reference lists of articles retrieved by the search were hand-searched and personal contact was made with experts in the field to obtain any additional data, when required. Any relevant journal and conference abstracts that were not covered in the MDSDG register were handsearched in liaison with the Trials Search Coordinator. No additional relevant material was identified.

### Data collection and analysis

Data collection and analysis was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Selection of studies

The titles and abstracts of articles identified by the search were screened independently by one review author (BK); and those that were clearly irrelevant were removed. Articles were sourced if they appeared to be eligible for inclusion in the review based on the title and abstract. Two review authors (BK and AY) then independently examined the full text articles for suitability for inclusion in the review. Review authors corresponded with study authors to clarify study eligibility. Disagreements with regards to study eligibility were resolved by consensus.

### Data extraction and management

Two authors (AY and BK) independently extracted data using a custom-designed data extraction form. Where studies had multiple publications, the main trial report was used as the reference and additional details supplemented by secondary papers. Review authors corresponded with study investigators in order to resolve any data queries, as required. One author (EF) entered the data into RevMan, which was checked by all authors against the data extraction forms to ensure against data entry errors.

### Assessment of risk of bias in included studies

The included study was assessed for bias using the Cochrane risk of bias assessment tool (see Appendix 6) to assess: sequence generation, allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and any other sources of bias. Individual study authors were contacted to complete missing data. If no response was received, authors were followed up by a repeat email. Two authors (BK and AY) assessed the risk of bias, with any disagreements resolved by consensus or by discussion with a third author (RH).

### Measures of treatment effect

Statistical analysis was performed in accordance with the guidelines for statistical analysis (Higgins 2011).

### Unit of analysis issues

The primary analysis was per woman randomised. Multiple live births (for example twins or triplets) were counted as one live birth event.

In future reviews, where data are reported that does not allow valid analysis (for example 'per cycle' rather than 'per woman', where women contribute more than one cycle), the data will be summarised in an additional table and not subject to meta-analysis. Where applicable, a secondary analysis will be performed on such data where only a small proportion of multiple cycles have occurred.

### Dealing with missing data

Attempts were made to obtain missing data from the original investigators, by contacting authors at the correspondence address provided and failing that by an e-mail to their last recorded address identified by an internet search. Only the available data were analysed.

In future reviews, where data are unavailable an imputation of individual values will be undertaken for the primary outcomes only. Live births will be assumed not to have occurred in participants with unreported outcomes. Any imputation undertaken will be subject to sensitivity analysis (see below).

## Assessment of heterogeneity

As only one study met the inclusion criteria, an assessment of heterogeneity was not required.

In future updates of this review, the authors will consider whether the clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a meaningful summary. Statistical heterogeneity will be assessed by the  $I^2$  statistic, where necessary. An  $I^2$  value > 50% will be taken to indicate substantial heterogeneity (Higgins 2011). If substantial heterogeneity is detected, possible explanations will be explored in the sensitivity analysis.

## Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, the authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. Because only one study was identified, a funnel plot was not required. For updates of this review, if 10 or more studies are analysed a funnel plot will be used to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Care was taken to search for 'within study' reporting bias, such as the failure to report obvious outcomes or reporting them in insufficient detail to allow inclusion. The primary outcome of live birth was not reported by the single study included in this review. In future updates, where identified studies fail to report the primary outcome of live birth, but do report interim outcomes such as pregnancy, assessment will be undertaken to assess whether those reporting the primary outcomes have typical values of the interim outcomes.

The conclusions are presented in the 'Risk of bias' table. No reporting bias was detected.

If reporting bias is found in future updates of this review, it will be incorporated in to the interpretation of review findings by means of a sensitivity analysis.

## Data synthesis

The review protocol was to combine data from primary studies using fixed-effect models in the following comparisons:

1. a single antibiotic or an antibiotic combination versus placebo or no treatment;
2. a single antibiotic or an antibiotic combination versus another antibiotic or antibiotic combination.

For each comparison, data synthesis was to be stratified by antibiotic dosage regimen (a single dose or course of multiple doses) and mode of antibiotic administration (either oral, topical or intravenous).

An increase in the odds of an outcome measure, be that beneficial (for example live birth) or detrimental (for example miscarriage), is displayed graphically in the meta-analyses to the right of the

centre-line. If there is a decrease in the odds of an outcomes, this will appear on the graph to the left of the centre-line.

## Subgroup analysis and investigation of heterogeneity

The review protocol was to analyse the evidence for differences between the following subgroups.

1. A single antibiotic versus placebo or no treatment.
2. A single antibiotic versus another antibiotic.
3. An antibiotic combination versus placebo or no treatment.
4. An antibiotic combination versus another antibiotic(s).

Further subgroup analysis was to be performed within the following groups: age, body mass index (BMI), IVF or ICSI, fresh and frozen ETs, luteal phase support prior to ET, pre-implantation genetic diagnosis (PGD), and patients receiving antibiotics because of risk factors for pelvic infection (such as endometriomas, hydrosalpinges, multiple punctures at egg pick up). Subgroup analysis was also to be undertaken by date of study publication (prior to and after 2000) to account for changes in practice that may have occurred over time. In the setting of heterogeneity exceeding 50%, subgroup analysis was to be performed to explain the findings. No subgroup analysis was possible for the current review.

## Sensitivity analysis

Sensitivity analyses were to be conducted for the primary outcome to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility of studies and analysis. These analyses were to include consideration of whether conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias;
2. alternative imputation strategies had been adopted.

No sensitivity analysis was required.

# RESULTS

## Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#).

## Results of the search

Our search strategy identified four potentially relevant studies (Brook 2006; Karimzadeh 2000; Peikrishvili 2004; Primi 2004). Three were excluded from analysis, one because it was an abstract of an oral conference presentation and, at the time of publication, the author was unable to provide any data for inclusion (Karimzadeh 2000). The study by Peikrishvili (Peikrishvili 2004) was excluded on the basis of a pseudo-random treatment allocation and the third because of co-intervention (Primi 2004).

**Included studies**

Brook 2006 reported a randomised controlled trial of antibiotic prophylaxis in 350 patients attending an English IVF clinic who underwent a transvaginal oocyte retrieval and ET as part of IVF or ICSI with or without PGD treatment. Patients were randomly allocated to 1.5 g of co-amoxyclav tablets (750 mg the night before ET and 750 mg 2 hours prior to ET) or no treatment. Outcome measures were the bacterial contamination rate of ET catheters and clinical pregnancy rate.

**Excluded studies**

Peikrishvili 2004 reported a pseudo-randomised controlled trial of antibiotic prophylaxis in women undergoing ET as part of an ART cycle. While this paper addressed intervention and outcome

measures relevant to this review, the method of randomisation (based on year of birth) made it inadequate for inclusion.

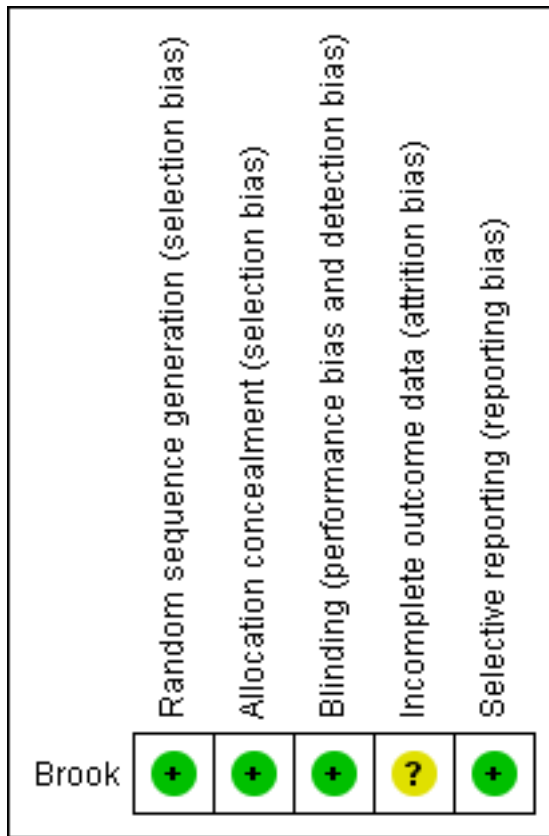
Karimzadeh 2000 appeared in the literature only as a conference abstract. The author was contacted and was unable to provide data at the time of publication of the review.

Primi 2004 assessed both the benefits of laser assisted hatching and the use of combined antibiotic and immunosuppressive therapy associated with this technology. As methylprednisolone was used as co-treatment with antibiotics, this paper was excluded from further analysis.

**Risk of bias in included studies**

For further risk of bias information refer to Figure 1.

Figure 1. Risk of bias summary



**Allocation**

Brook 2006 used computer generated randomisation with ran-

domisation codes placed in sealed opaque envelopes. A third party not involved in the trial produced the randomisation codes and

sealed the envelopes. There was no evidence of allocation bias in this study.

### Blinding

The embryologist performing the ET and the microbiologist who assessed bacterial growth were blinded to treatment [Brook 2006](#). The clinician performing the oocyte collection was aware of treatment allocation. It is unclear whether the clinician performing the ET was blinded. It is unclear whether this would have a significant impact on outcomes.

### Incomplete outcome data

In [Brook 2006](#) all randomised patients were assessed for the outcome of clinical pregnancy but bacteriological catheter analysis was only performed on 284 of the 350 women randomised. In the antibiotic arm 154/178 (86.5%) were analysed. The reasons for failure to analyse were: 12 catheters were discarded in error, 10 patients had failed fertilisation, 2 patients had failed cleavage. In the control arm 130/172 (75.6%) were analysed. The reasons for failure to analyse were: 26 catheters were discarded in error, 12 patients had failed fertilisation, 4 patients had failed cleavage. The authors reported that 215 women who presented for oocyte collection and ET during the time period of recruitment were ineligible for randomisation because they received antibiotic prophylaxis at the time of oocyte collection. The indications for this were a history of pelvic infection, endometriosis, hydrosalpinges or multiple ovarian punctures at the time of oocyte collection.

### Selective reporting

There was no evidence of selective reporting.

### Other potential sources of bias

No other potential sources of bias were identified.

### Effects of interventions

See: [Summary of findings for the main comparison](#)

#### Comparison 1: antibiotics versus no treatment prior to embryo transfer (ET)

A single trial addressed the question of whether antibiotics given prior to ET improved IVF success ([Brook 2006](#)). This trial investigated the use of 1.5 g of co-amoxycylav tablets (750 mg the night before ET and 750 mg 2 hours prior to ET).

#### Primary outcome - live birth rate

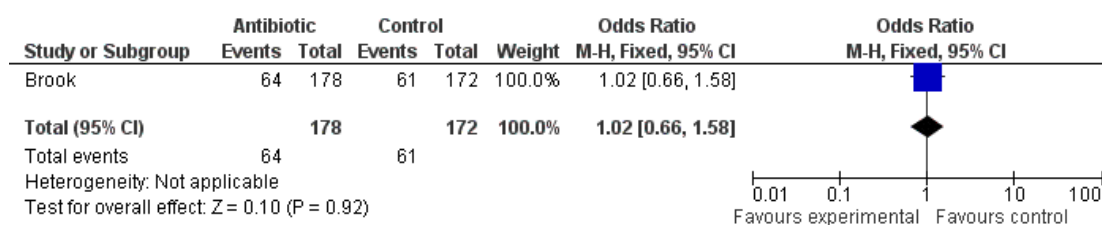
This outcome was not reported.

#### Secondary outcomes

##### 1. Clinical pregnancy rate

There was no difference in clinical pregnancy rate between those receiving an amoxycillin and clavulanic acid antibiotic combination (64/178: 36%) and those not (61/172: 35.5%) (OR 1.02, 95% CI 0.66 to 1.58) ([Analysis 1.1, Figure 2](#)).

**Figure 2. The influence of antibiotics prior to ET on clinical pregnancy rate**



##### 2. Miscarriage rate

Not reported.

##### 3. Ectopic pregnancy rate

Not reported.

#### 4. Multiple pregnancy rate

Not reported.

#### 5. Fetal abnormalities

Not reported.

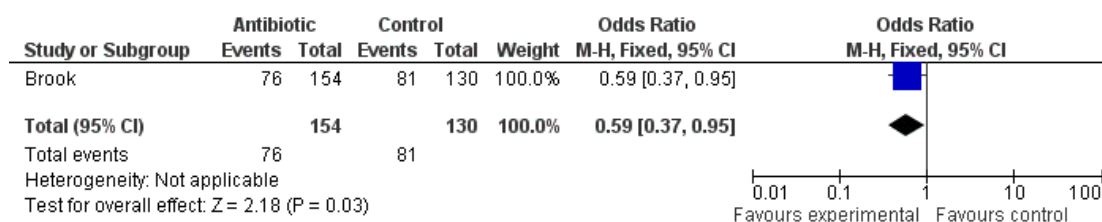
#### 6. Adverse events

Not reported.

#### 7. Genital tract colonisation

Genital tract colonisation was significantly more likely in women who did not receive antibiotics prior to ET (81/130) compared to those that did (76/154) (OR 0.59, 95% CI 0.37 to 0.95). See [Analysis 2.1, Figure 3](#).

**Figure 3. The influence of antibiotics prior to ET on genital tract colonisation rate**



#### 8. Pelvic infection

Not reported.

## DISCUSSION

### Summary of main results

There is limited evidence from a single randomised controlled trial which addressed the question of whether antibiotics prior to embryo transfer (ET) improve IVF success rates. The reported study found no evidence of an improvement in clinical pregnancy rate despite identifying a reduction in genital tract colonization in women receiving antibiotics prior to ET. The effect on live birth rate is unknown ([Summary of findings for the main comparison](#)).

### Overall completeness and applicability of evidence

The available study suggests that antibiotic administration prior to ET has no effect on IVF success. The combination of amoxicillin and clavulanate, when given in the regimen trialled, does not affect clinical pregnancy rates. The gold standard outcome measure in studies assessing fertility outcomes is live birth rates, however these data are not reported. In the absence of live birth

data it is impossible to infer the influence of this antibiotic regimen on this outcome. Outcome data on rates of clinical pelvic infection and fetal anomalies, two outcomes of particular interest when discussing administration of pre-conception antibiotics, are not available. The impact of an alternative antibiotic regimen has also not been addressed. It is unfortunate that more high quality evidence from RCTs is not available.

A study by [Peikrishvili 2004](#) is the only other publication addressing the clinical question of this review, however substandard methodological quality made it ineligible for inclusion in a meta-analysis. Participants were pseudo-randomised based on odd or even year of birth and it is unclear whether they were recruited more than once. Additionally, it is unclear whether investigators or assessors were blinded to treatment allocation, and patient flow and attrition were not reported. This study reported on 275 women attending a single unit as part of an IVF or ICSI cycle. Patients received either amoxicillin 1000 mg + 125 mg clavulanic acid per day from day of egg pick up, for six days, or no treatment. As found by [Brook 2006](#), the clinical pregnancy rate did not differ between those who received antibiotics (43/130: 31.1%) and the control group (48/145: 31.1%). Miscarriage rate was no different in those receiving antibiotics (11/43: 25.6%) compared to those who were not (16/48: 33.3%). Adverse effects only occurred in the antibiotic group and were nausea (10/130), diarrhoea (12/130) and vaginitis (15/130).

The association between microbial colonization of the genital tract at the time of ET and poorer IVF outcomes is reasonably well

established. In addition to assessing the effect of antibiotics on IVF outcomes, Brook 2006 also reported pregnancy rates relative to the degree of bacterial contamination of ET catheters (irrespective of antibiotic prophylaxis). Catheters that showed no growth were associated with a pregnancy rate of 47.2%, compared with 15.8% in the group whose catheter had a semi-confluent growth of gram positive bacteria ( $P < 0.05$ ). This finding concurs with multiple prior studies which reported poorer pregnancy rates in the setting of increased endocervical microbial colonization at the time of ET (Egbase 1999; Fanchin 1998; Moore 2000; Salim 2002). Despite this, a reduction in colonising bacteria through the use of antibiotic prophylaxis prior to ET, as demonstrated by Brook 2006, does not correlate with improved outcomes. Accepting an impact on success rates by genital tract bacterial colonization, the reason for a lack of impact of antibiotic prophylaxis is unclear. It may be that the degree of microbial eradication needs to be greater for there to be a relevant clinical effect. Alternatively, the antibiotic regimen may need to target different bacterial subgroups. It may also be the case that the antibiotic itself could be having a detrimental effect on IVF success.

### Quality of the evidence

Brook 2006 was methodologically sound overall. There was failure to blind the clinician performing oocyte collection, possibly the clinician performing ET, and the patient, however it is unclear whether this would have introduced significant bias. There was no attrition for the outcome of clinical pregnancy, but not all patients randomised were assessed for the major outcome measure of catheter bacterial contamination. In the antibiotic arm 154/178 (86.5%) were analysed, while in the control arm 130/172 (75.6%) were analysed. The reasons for failure to analyse were similar in both groups apart from the number of catheters discarded in error, which was more than double in the intervention group (26 versus 12). Finally, it is worth noting that the population in the Brook 2006 study may have introduced bias as 215/775 (27.7%) of women who underwent transvaginal oocyte retrieval during the recruitment period were deemed ineligible for trial inclusion because they were 'at risk' for pelvic infection. These women received routine antibiotic prophylaxis at the time of oocyte collection. Outcomes were not described for this group. The indications for antibiotic prophylaxis were a history of pelvic infection, endometriosis, hydrosalpinges or multiple ovarian punctures at

the time of oocyte collection. Not all IVF units would routinely administer antibiotic prophylaxis to this subgroup of women. It is plausible that including this 'at risk' subgroup could alter the study findings.

### Potential biases in the review process

There were no identified biases in the review process.

### Agreements and disagreements with other studies or reviews

There were no previous reviews identified.

## AUTHORS' CONCLUSIONS

### Implications for practice

This review suggests that, based on the limited available evidence, antibiotic prophylaxis with an amoxicillin and clavulanic acid combination reduces upper genital tract microbial contamination but there is no evidence that it improves clinical pregnancy rate. The effect of this intervention on live birth is unknown. There are no randomised controlled data to support or refute the use of other antibiotic regimens in this setting. More studies of sound methodological quality are required, particularly addressing the outcome of live birth.

### Implications for research

Future research is warranted to assess the efficacy of alternative antibiotic regimens. Researchers should aim to assess live birth as a primary outcome and specifically address quantitative microbial colonization rates.

## ACKNOWLEDGEMENTS

We wish to acknowledge the peer reviewers and the staff at the MDSG, in particular Marian Showell, for their contribution to this review.

## REFERENCES

### References to studies included in this review

#### Brook {published data only}

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### References to studies excluded from this review

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Karimzadeh M, Taheripannah R. The effect of prophylactic antibiotic therapy on the outcome of IVF cycles. *Human Fertility* 2000;**3**(4):363.

#### Peikrishvili {published data only}

\* Peikrishvili R, Evrard B, Pouly JL, Janny L. Prophylactic antibiotic therapy (amoxicillin + clavulanic acid) before embryo transfer for IVF is useless. Results of a randomized study. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 2004;**33**(8):713–9.

#### Primi {published data only}

Primi MP, Senn A, Montag M, Van der Ven H, Mandelbaum J, Veiga A, et al. European multicentre prospective randomized study to assess the use of assisted hatching with a diode laser and the benefit of an immunosuppressive/antibiotic treatment in different patient populations. *Human Reproduction* 2004;**19**(10):2325–33.

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**Primi 2004**

Primi MP, Senn A, Montag M, Van der Ven H, Mandelbaum J, Veiga A, et al. A European multicentre prospective randomized study to assess the use of assisted hatching with a diode laser and the benefit of an immunosuppressive/antibiotic treatment in different patient populations. *Human Reproduction* 2004;**19**(10):2325–33.

**Salim 2002**

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**Sowerby 2004**

Sowerby E, Parsons J. Prevention of iatrogenic pelvic infection during in vitro fertilization - Current practice in the UK. *Human Fertility* 2004;**7**(2):135–40.

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Spandorfer SD, Neuer A, Giraldo PC, Rosenwaks Z, Witkin SS. Relationship of abnormal vaginal flora, proinflammatory cytokines and idiopathic infertility in women undergoing IVE. *Journal of Reproductive Medicine for the Obstetrician and Gynecologist* 2001;**46**(9):806–10.

\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

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

#### Brook

Methods	Randomised controlled trial conducted between April 2004 and March 2005. Patients were randomised through computer generated numbers and information on treatment allocation was sealed in opaque envelopes which were opened sequentially
Participants	350 consecutive patients attending an IVF clinic in England to undergo a transvaginal oocyte retrieval and embryo transfer as part of IVF/ICSI ± PGD treatment. 750 patients attended during the recruitment period, of which 114 refused to participate, 37 had previously participated and 274 did not meet the inclusion criteria. Excluded patients were allergic to penicillin (n=55), undergoing oncology freeze (n=1), on concurrent antibiotics (n=3) and requiring antibiotic prophylaxis at the time of transvaginal oocyte collection (n=215)
Interventions	Patients were randomly allocated to antibiotics (1.5g of co-amoxycylav tablets - 750mg the night before the transfer and 750mg 2 hours prior to transfer), or no-treatment. No placebo tablets were used
Outcomes	Bacterial contamination rate of embryo transfer catheter Clinical pregnancy rate (gestational sac with cardiac activity seen on ultrasound)
Notes	Antibiotic prophylaxis was received at the time of oocyte collection in 215 women. The indications for this were; a history of pelvic infection , endometriosis, hydrosalpinges or multiple ovarian punctures at the time of oocyte collection

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	A third party not involved in the trial produced the randomisation codes and sealed envelopes. Embryologist assisting the embryo transfer and the microbiologist were blinded to treatment The clinician performing the oocyte collection was aware of treatment allocation It is unclear whether the clinician performing embryo transfer was blinded

**Brook** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All randomised patients were assessed for the outcome of clinical pregnancy. Bacteriological catheter analysis was performed on 284 of 350 women randomised. In the antibiotic arm 154/178 (86.5%) were analysed. The reasons for failure to analyse were; 12 catheters discarded in error, 10 patients had failed fertilisation, 2 patients had failed cleavage. In the control arm, 130/172 (75.6%) were analysed. The reasons for failure to analyse were; 26 catheters discarded in error, 12 patients had failed fertilisation, 4 patients had failed cleavage
Selective reporting (reporting bias)	Low risk	All identified outcomes were addressed

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

Study	Reason for exclusion
Karimzadeh	Paper identified was a conference presentation. The author has been contacted but has been unable to provide data at the time of publication
Peikrishvili	A pseudo-randomised study utilising year of birth as randomisation
Primi	Featured co-treatment with methylprednisolone and doxycycline

## DATA AND ANALYSES

### Comparison 1. The influence of antibiotics prior to ET on clinical pregnancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Pregnancy	1	350	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.66, 1.58]

### Comparison 2. The influence of antibiotics prior to ET on genital tract colonisation

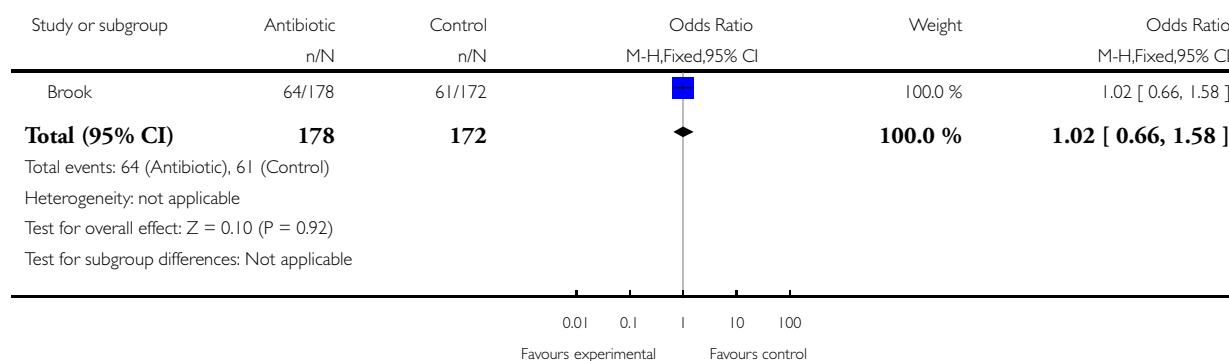
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Genital Tract Colonization	1	284	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.95]

#### Analysis 1.1. Comparison 1 The influence of antibiotics prior to ET on clinical pregnancy, Outcome 1 Clinical Pregnancy.

Review: Antibiotics prior to embryo transfer in ART

Comparison: 1 The influence of antibiotics prior to ET on clinical pregnancy

Outcome: 1 Clinical Pregnancy

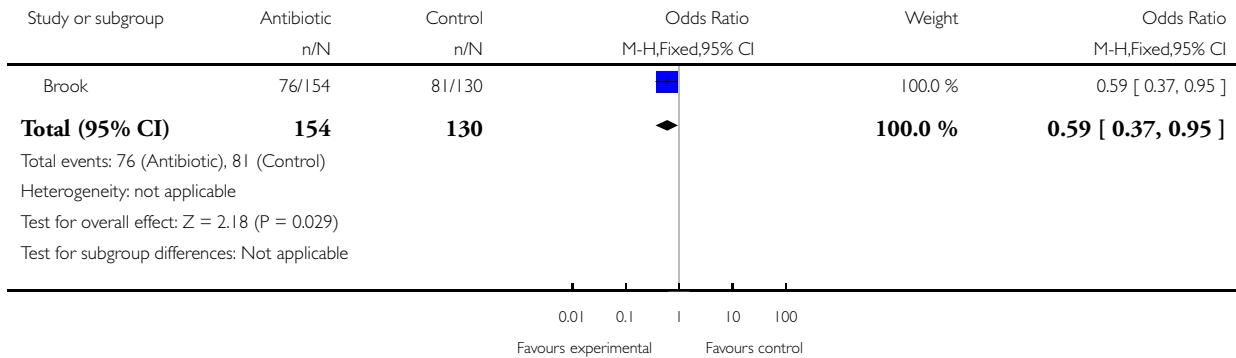


## Analysis 2.1. Comparison 2 The influence of antibiotics prior to ET on genital tract colonisation, Outcome 1 Genital Tract Colonization.

Review: Antibiotics prior to embryo transfer in ART

Comparison: 2 The influence of antibiotics prior to ET on genital tract colonisation

Outcome: 1 Genital Tract Colonization



## APPENDICES

### Appendix I. Menstrual Disorders and Subfertility Specialised Register search strategy

Menstrual Disorders and Subfertility Database search strategy for EN1382 02.02.2011

Keywords CONTAINS “IVF” or “in vitro fertilisation” or “in vitro fertilization” or “\*Embryo Transfer” or “ET” or “blastocyst transfer” or “ICSI” or “intracytoplasmic sperm injection” or Title CONTAINS “IVF” or “in vitro fertilisation” or “in vitro fertilization” or “\*Embryo Transfer” or “ET” or “blastocyst transfer” or “ICSI” or “intracytoplasmic sperm injection”

AND

Keywords CONTAINS “antibiotics” or “amoxicillin” or “Amoxicillin-Clavulanic Acid” or “ampicillin” or “ceftezole” or “\*Ceftizoxime” or “Ceftriaxone” or “Cefuroxime” or “Azithromycin” or “co-amoxiclav” or “Augmentin” or “cephalosporin” or “Cephalosporins” or “doxycycline” or “erythromycin” or “Metronidazole” or “tetracycline” or Title CONTAINS “antibiotics” or “amoxicillin” or “Amoxicillin-Clavulanic Acid” or “ampicillin” or “ceftezole” or “\*Ceftizoxime” or “Ceftriaxone” or “Cefuroxime” or “Azithromycin” or “co-amoxiclav” or “Augmentin” or “cephalosporin” or “Cephalosporins” or “doxycycline” or “erythromycin” or “Metronidazole” or “tetracycline”

## Appendix 2. Cochrane CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2010> Search Strategy: 1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ 2 (ET or IVF or ICSI).tw. 3 (embryo\$ adj2 transfer\$).tw. 4 (blastocyst\$ adj2 transfer\$).tw. 5 vitro fertili?ation.tw. 6 intracytoplasmic sperm injection\$.tw. 7 or/1-6 8 exp anti-bacterial agents/ or exp amoxicillin/ or exp amoxicillin-potassium clavulanate combination/ or exp cephalosporins/ or exp doxycycline/ or exp erythromycin/ or exp tetracycline/ 9 anti-biotic\$.tw. 10 Anti-Bacteri\$.tw. 11 amoxicillin.tw. 12 Azithromycin\$.tw. 13 co-amoxiclav\$.tw. 14 rocephin.tw. 15 amoxicillin-potassium clavulanate.tw. 16 Ceftriaxone\$.tw. 17 cephalosporin\$.tw. 18 doxycycline.tw. 19 erythromycin.tw. 20 B-lactam\$.tw. 21 metronidazole.tw. 22 macrolide\$.tw. 23 augmentin.tw. 24 tetracycline\$.tw. 25 antibiotic\$.tw. 26 or/8-25 27 7 and 26

## Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1950 to Present> Search Strategy: 1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ 2 (ET or IVF or ICSI).tw. 3 (embryo\$ adj2 transfer\$).tw. 4 (blastocyst\$ adj2 transfer\$).tw. 5 vitro fertili?ation.tw. 6 intracytoplasmic sperm injection\$.tw. 7 or/1-6 8 exp anti-bacterial agents/ or exp amoxicillin/ or exp amoxicillin-potassium clavulanate combination/ or exp cephalosporins/ or exp doxycycline/ or exp erythromycin/ or exp tetracycline/ 9 anti-biotic\$.tw. 10 Anti-Bacteri\$.tw. 11 amoxicillin.tw. 12 Azithromycin\$.tw. 13 co-amoxiclav\$.tw. 14 rocephin.tw. 15 amoxicillin-potassium clavulanate.tw. 16 Ceftriaxone\$.tw. 17 cephalosporin\$.tw. 18 doxycycline.tw. 19 erythromycin.tw. 20 B-lactam\$.tw. 21 metronidazole.tw. 22 macrolide\$.tw. 23 augmentin.tw. 24 tetracycline\$.tw. 25 antibiotic\$.tw. 26 or/8-25 27 7 and 26 28 randomised controlled trial.pt. 29 controlled clinical trial.pt. 30 randomized.ab. 31 placebo.tw. 32 clinical trials as topic.sh. 33 randomly.ab. 34 trial.ti. 35 (crossover or cross-over or cross over).tw. 36 or/28-35 37 exp animals/ not humans.sh. 38 36 not 37 39 27 and 38

## Appendix 4. EMBASE search strategy

Database: EMBASE <1980 to 2010 Week 32> Search Strategy: 1 exp embryo transfer/ 2 exp fertilization in vitro/ 3 exp intracytoplasmic sperm injection/ 4 (ET or IVF or ICSI).tw. 5 (embryo\$ adj2 transfer\$).tw. 6 (blastocyst\$ adj2 transfer\$).tw. 7 vitro fertili?ation.tw. 8 intracytoplasmic sperm injection\$.tw. 9 or/1-8 10 exp antiinfective agent/ 11 antiinfective.tw. 12 anti-biotic\$.tw. 13 Anti-Bacteri\$.tw. 14 amoxicillin.tw. 15 Azithromycin\$.tw. 16 co-amoxiclav\$.tw. 17 rocephin.tw. 18 amoxicillin-potassium clavulanate.tw. 19 Ceftriaxone\$.tw. 20 cephalosporin\$.tw. 21 doxycycline.tw. 22 erythromycin.tw. 23 B-lactam\$.tw. 24 metronidazole.tw. 25 macrolide\$.tw. 26 augmentin.tw. 27 tetracycline\$.tw. 28 antibiotic\$.tw. 29 or/10-28 30 9 and 29 31 Clinical Trial/ 32 Randomized Controlled Trial/ 33 exp randomization/ 34 Single Blind Procedure/ 35 Double Blind Procedure/ 36 Crossover Procedure/ 37 Placebo/ 38 Randomized controlled trial\$.tw. 39 Rct.tw. 40 random allocation.tw. 41 randomly allocated.tw. 42 allocated randomly.tw. 43 (allocated adj2 random).tw. 44 Single blind\$.tw. 45 Double blind\$.tw. 46 ((treble or triple) adj blind\$).tw. 47 placebo\$.tw. 48 prospective study/ 49 or/31-48 50 case study/ 51 case report.tw. 52 abstract report/ or letter/ 53 or/50-52 54 49 not 53 55 30 and 54 56 2010\$.em. 57 55 and 56

## Appendix 5. PsycINFO search strategy

Database: PsycINFO <1806 to August Week 3 2010> Search Strategy: 1 exp reproductive technology/ 2 (ET or IVF or ICSI).tw. 3 (embryo\$ adj2 transfer\$).tw. 4 (blastocyst\$ adj2 transfer\$).tw. 5 vitro fertili?ation.tw. 6 intracytoplasmic sperm injection\$.tw. 7 or/1-6 8 exp antibiotics/ 9 anti-biotic\$.tw. 10 Anti-Bacteri\$.tw. 11 amoxicillin.tw. 12 Azithromycin\$.tw. 13 co-amoxiclav\$.tw. 14 rocephin.tw. 15 amoxicillin-potassium clavulanate.tw. 16 Ceftriaxone\$.tw. 17 cephalosporin\$.tw. 18 doxycycline.tw. 19 erythromycin.tw. 20 B-lactam\$.tw. 21 metronidazole.tw. 22 macrolide\$.tw. 23 augmentin.tw. 24 tetracycline\$.tw. 25 antibiotic\$.tw. 26 or/8-25 27 7 and 26

## Appendix 6. The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
<b>Random sequence generation</b>	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
<b>Allocation concealment</b>	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
<b>Blinding of participants and personnel</b> Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
<b>Blinding of outcome assessment</b> <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
<b>Incomplete outcome data</b> <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		

(Continued)

<b>Selective reporting</b>	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting.
Other bias		
<b>Other sources of bias</b>	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table.

## HISTORY

Protocol first published: Issue 2, 2011

Review first published: Issue 3, 2012

Date	Event	Description
23 January 2012	Feedback has been incorporated	Final incorporation of feedback and agreement by authors on changes
16 November 2011	Feedback has been incorporated	Amended based on feedback from peer review.
6 June 2011	Amended	Protocol carried out and draft review completed
24 January 2011	Amended	New author added to the review
14 April 2008	Amended	converted to new review format
8 December 2006	New citation required and major changes	Substantive amendment

## **CONTRIBUTIONS OF AUTHORS**

Ben Kroon, Anusch Yazdani and Brittany Wong conducted a preliminary literature search and reviewed the available literature. Ben Kroon, Anusch Yazdani and Roger Hart authored the draft proposal. Emily Ford was involved in the collation and analysis of data. All authors were involved with the review of the final manuscript.

## **DECLARATIONS OF INTEREST**

None of the authors have any conflicts of interest to disclose.

## **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

An additional author has been added between the publication of the review protocol and the review.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Amoxicillin-Potassium Clavulanate Combination [\*administration & dosage]; Anti-Bacterial Agents [\*administration & dosage]; Antibiotic Prophylaxis [\*methods]; Embryo Transfer [\*methods]; Pregnancy Rate

### **MeSH check words**

Female; Humans; Pregnancy