Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage

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[Intervention Protocol]

Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage

Sheikh Irfan Ahmed[1], Anne Ammerdorffer[2], Catherine A Moakes[3], James Cheshire[4], Ahmet Metin Gülmezoglu[2], Arri Coomarasamy[5], David Lissauer[6,7], Amie Wilson[3]

[1]Aga Khan University Hospital, Karachi, Pakistan. [2]Concept Foundation, Geneva, Switzerland. [3]Institute of Applied Health Research, University of Birmingham, Birmingham, UK. [4]Birmingham Women's Hospital, Birmingham, UK. [5]Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research (IMSR), WHO Collaborating Centre for Global Women's Health Research, University of Birmingham, Birmingham, UK. [6]Malawi-Liverpool-Wellcome Trust Research Institute, Queen Elizabeth Central Hospital, College of Medicine, Blantyre, Malawi. [7]Institute of Lifecourse and Medical Sciences, University of Liverpool, Liverpool, UK

Contact: Amie Wilson, a.wilson.5@bham.ac.uk.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

The objective of this review is to evaluate the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage.

BACKGROUND

Description of the condition

Over 208 million women around the world become pregnant each year (Singh 2010), but an estimated 10% to 20% of pregnancies end as a miscarriage (Adolfsson 2006; Linnakaari 2019; Maconochie 2007; Magnus 2019; Patki 2016; Rossen 2018). One in four women experience miscarriage in their lifetime (Alberman 1992). Miscarriage is defined as the unintended loss of pregnancy in the first 24 weeks (Giakoumelou 2016), although this is defined differently around the world with some countries reporting miscarriage up to 28 weeks of pregnancy (WHO 2021). Miscarriage, induced abortion and ectopic pregnancy collectively were estimated to be responsible for around 193,000 maternal deaths between 2003 and 2009 (Say 2014).

The language used around miscarriage is important to women and their families (WHO 2021). The term 'miscarriage' is preferred to '(spontaneous) abortion'. The change in terminology has been supported by patient organisations and clinicians for several decades (Beard 1985; Cameron 2005; Chalmers 1992; Gardner 1972; Harison 1986; Hutchon 1998; Moscrop 2013; Pridjian 1989; Silver 2011). The use of the term miscarriage is also supported by researchers and early pregnancy special interest groups, for consistency (Kolte 2015).

The common clinical signs and symptoms associated with miscarriage can vary with the type of miscarriage that a woman is experiencing and the gestational age or size of the pregnancy (NICE 2019b). A complete miscarriage is when all of the pregnancy tissue is expelled from the uterus. This is associated with heavy vaginal bleeding, severe abdominal pain and the passage of all the pregnancy tissue. Complete miscarriage does not require any interventions for treatment. Incomplete miscarriage is likely to be associated with vaginal bleeding and abdominal pain, as the pregnancy tissue has been partly expelled from the uterus (NICE 2019a). Missed miscarriage (sometimes known as delayed or silent) is when a non-viable pregnancy is identified via ultrasonography. All the pregnancy tissue is retained in the uterus, so women may have no symptoms or a small amount of vaginal bleeding (NICE 2019a).

Incomplete and missed miscarriage can be treated conservatively, medically or surgically. Expectant management involves waiting for the pregnancy tissue to pass naturally. Medical management involves medications (mifepristone plus misoprostol or misoprostol alone) to make the womb expel the pregnancy tissue. Surgical management involves the removal of the pregnancy tissue during surgery. A recent Cochrane Review (Ghosh 2021), found that medical and surgical methods of uterine evacuation to treat miscarriage were more effective than when compared with expectant management. Expectant management was found to have the lowest chance of successful uterine evacuation and the highest chance of serious complications, including the need for unplanned or emergency surgery. The evidence however, did suggest that surgical methods of uterine evacuation carried higher risks of pelvic infection when compared to medical methods of uterine evacuation or expectant management.

Uterine evacuation procedures to treat miscarriage are a common reason for hospital admission, with some hospitals in low-income settings reporting up to 70% of gynaecological hospital admissions for miscarriage surgery (Lema 1994). A survey of health facilities in Malawi in 2015 estimated that the number of cases treated for post-abortion care was over 67,000 (including both miscarriage and induced abortion), with over 15,000 of these cases being late miscarriages (Polis 2017).

Pregnancy-related infection was estimated to be responsible for 261,000 maternal deaths between 2003 and 2009, with over 99% of these deaths being in low- and middle-income countries (Say 2014). Infection after uterine evacuation procedures to treat miscarriage is reported to occur in 6% of women in high-income countries (Prieto 1995; Ramin 1995), and up to 30% of women in low-income countries (Seeras 1989). Pelvic infection is a serious complication of uterine evacuation procedures to treat miscarriage and can result in serious illness and death (Melese 2017). It can also have long-term consequences, which can increase rates of ectopic pregnancy and infertility (Cates 1985). As well as physical effects, miscarriage can also have considerable emotional and societal implications for women and their families, with the consequences of miscarriage lasting far beyond the length of the pregnancy (Conway 2000; Farren 2020; Geller 2001; Murphy 2012; Neugebauer 1997).

Description of the intervention

Antibiotic prophylaxis can be defined as the administration of "antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications" (National Centre for Biotechnology Information 2021). Prophylactic antibiotics are given for certain surgical procedures to reduce infection after surgery, including vacuum aspiration for abortion care (Low 2012; WHO 2015). For uterine evacuation procedures to treat miscarriage, the administration of prophylactic antibiotics would mean that women are given antibiotics around the time of uterine evacuation even if they are not known to have genital tract infections.

Studies have demonstrated that almost 50% of women in some regions are prescribed prophylactic antibiotics for uterine evacuation procedures to treat miscarriage (Fawcus 1997), and that prophylactic antibiotics may improve outcomes (Melese 2017). In this review, prophylaxis will be defined by the administration of antibiotics to prevent infection.

A Cochrane Review, May 2007, examined the evidence on antibiotics for incomplete abortion, and, with the inclusion of a single study, (Seeras 1989), concluded there was "not enough evidence to evaluate a policy of routine antibiotic prophylaxis to women with incomplete abortion". This review stated the "real and urgent need to find out whether antibiotics should routinely be used in cases of incomplete miscarriages".

The World Health Organization (WHO) recommends electric or manual vacuum aspiration as uterine evacuation procedures to treat miscarriage before 12 to 14 weeks (WHO 2015). Vacuum aspiration is also called suction curettage or dilatation and suction, and uses a vacuum source to remove pregnancy tissue. Vacuum aspiration does not require electricity and can be used with a hand-held vacuum syringe (manual vacuum aspiration) or electric pump.

Sharp metal curettage to remove pregnancy tissue after dilatation of the cervix (if required) used to be common practice for

uterine evacuation to treat miscarriage (WHO 1995). A sharp metal curettage (also known as dilatation and curettage) was used to remove the pregnancy tissues from the uterus, however, sharp curettage is associated with a higher incidence of pelvic infection when compared to vacuum aspiration (Tuncalp 2010), and is no longer recommended due to the increased incidence of such complications and associations with Asherman's syndrome (intrauterine adhesions; FIGO 2011). Many clinicians in low-income settings use sharp metal curettage because they are not trained in vacuum aspiration or do not have the necessary equipment to perform vacuum aspiration.

Uterine evacuation procedures to treat miscarriage beyond 12 weeks usually involve pre-procedure cervical dilatation with medications or osmotic dilators, or both (WHO 2016), and evacuation with a combination of vacuum aspiration and specialised forceps (also known as dilatation and evacuation or D&E). Uterine evacuation procedures to treat miscarriage of more advanced pregnancies can be more complex and associated with greater risk of complications (Tuncalp 2010). Uterine evacuation procedures to treat miscarriage have been reviewed previously (Tuncalp 2010), indicating that vacuum aspiration is safe, quick to perform, and less painful than sharp curettage, and is recommended for use in the management of incomplete miscarriage, but the findings were based on data from a single study.

Perhaps because of the lack of evidence of effectiveness of prophylactic antibiotics for uterine evacuation procedures to treat miscarriage, there is inconsistency in clinical practice and international guidelines (ACOG 2015; Fawcus 1997; NICE 2019a, WHO 2017). Some guidelines do not recommend prophylaxis, reflecting the lack of evidence (NICE 2019a, WHO 2017), whereas other guidelines support their use, based on extrapolation of findings from other indications (ACOG 2015). This review will not address prophylactic antibiotics for medical management of miscarriage.

How the intervention might work

Uterine evacuation procedures to treat miscarriage can introduce pathogens that cause infection when a surgical instrument is inserted through the cervical canal into the uterine cavity to remove the pregnancy tissue (ACOG 2018). The most common micro-organisms that cause infection in the reproductive tract are enterococci, streptococci, staphylococci, Gram-negative bacilli and anaerobes (Kok 2000). When chlamydia and gonococcus exist in the vagina, they can move up into the uterus during uterine evacuation and cause infection (Workowski 2021).

Antibiotics work by killing existing bacteria (bactericidal) or inhibiting the replication of bacteria (bacteriostatic). The types of antibiotics used prophylactically should be effective against these common micro-organisms and include the following: ampicillin, cephazolin, clindamycin, vancomycin, azithromycin, and the aminoglycosides (ACOG 2018). Antibiotic prophylaxis before certain operations has been shown to reduce the risk of infections.

There is some evidence to support the use of antibiotic prophylaxis for surgical abortion procedures (Low 2012; Sawaya 1996). Current WHO guidance advocates the use of appropriate prophylactic antibiotics for all women, before or during the procedure (WHO 2017). This recommendation is based on a Cochrane Review of 19 randomised studies showing that prophylactic antibiotics reduce pelvic infection when given for surgical abortion (Low 2012).

As the procedures to conduct uterine evacuation for abortion and to treat miscarriage are the same, it can be hypothesised that prophylactic antibiotics could reduce pelvic infection among women undergoing uterine evacuation procedures to treat miscarriage. Identifying populations experiencing miscarriage who have not sought an intervention to end their pregnancy can be complicated, particularly in settings where abortion access is limited by legal restrictions. Women presenting for medical care to treat miscarriage could be experiencing complications from an incomplete abortion obtained in a safe or unsafe setting. The cause of miscarriage can be unclear, especially in countries where abortion is illegal or access to abortion is heavily restricted. This review aims to estimate the effectiveness of antibiotic prophylaxis among women obtaining a surgical abortion procedure when presenting with a miscarriage, regardless of its cause.

Prophylactic antibiotics for uterine evacuation procedures to treat miscarriage may be effective in reducing maternal death and serious illness caused by infection. Prophylactic antibiotics may play a role in reducing the long-term consequences of pelvic scarring caused by infection, such as ectopic pregnancy and infertility, and may be economically beneficial to the health system as a cost-effective intervention (Goranitis 2019).

Why it is important to do this review

Infection is a serious consequence of uterine evacuation procedures to treat miscarriage and can result in serious illness and death (Melese 2017). Clinical evidence and guidance are clear that antibiotic treatment is needed for women experiencing miscarriage with signs and symptoms of infection (Udoh 2016), because of this we will not include studies that evaluate the use of antibiotics in women with confirmed or suspected septic miscarriage. However, it is less clear whether antibiotic prophylaxis is effective or necessary at the time of uterine evacuation procedures to treat miscarriage.

This Cochrane Review is an update of the Cochrane Review 'Antibiotics for incomplete abortion' by, May 2007, but this protocol uses the term miscarriage rather than incomplete abortion. Since the Cochrane Review by May 2007 there have been further randomised studies (Lissauer 2019; Titapant 2012), including a large, multi-centre, randomised, placebo-controlled study conducted on the use of prophylactic antibiotics before miscarriage treatment with surgical abortion (Lissauer 2019).

Given that miscarriage surgery is common and infective complications are frequent and serious, contributing to the high numbers of preventable maternal deaths around the world, prophylactic antibiotics, may offer a simple and affordable intervention to reduce maternal death and disability. If antibiotic prophylaxis proves to be ineffective or causes serious adverse events, unnecessary use of antibiotics could be minimised, which is essential given the growing problem of antibiotic resistance. Therefore, the policy, practice and cost implications arising from this review will be important.

OBJECTIVES

The objective of this review is to evaluate the effectiveness of routine antibiotic prophylaxis to women undergoing uterine evacuation procedures to treat miscarriage.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) that directly compare antibiotics with placebo or no treatment, including those of parallel design, factorial studies and multi-arm RCTs. We will include studies that randomise at the individual or cluster level. We will include full-text studies, conference abstracts (if sufficient data are provided) and unpublished data. We will include studies irrespective of their publication status and language of publication. We will exclude non-randomised studies.

Types of participants

This review will include all types of miscarriage, of any gestational age, treated with 'surgical' uterine evacuation. We will include studies that enrol women attending healthcare facilities, who present with miscarriage. There will be no gestational age limit. We appreciate that studies may include participants who present for miscarriage treatment following an unreported safe or unsafe abortion but do not present with physical or clinical evidence indicating prior interventions; they would receive standard clinical treatment for miscarriage and we will therefore include this population in this review. We will report if studies state any evidence of prior interventions found in women after randomisation. We will exclude studies that explicitly include both women having uterine evacuation procedures to treat miscarriage and women having surgical abortion, unless the groups are reported separately throughout the study, as there is clear guidance that women having surgical abortion should be given antibiotic prophylaxis (WHO 2017). We will include studies that include women with prior medical management, but who require further management with uterine evacuation. We will report prior interventions (such as medical management) in the table of characteristics. We will exclude studies that include only women with miscarriage who are experiencing signs and symptoms of infection, as there is clear guidance stating that antibiotics should be given (WHO 2017), or studies that include only women undergoing surgical abortion or unsafe abortion, as there is clear guidance stating that antibiotics prophylaxis should be given (WHO 2017).

Types of interventions

We will include studies that compare any prophylactic antibiotic regimen with no antibiotics (placebo or no treatment). This may include antibiotics administered by any route; orally, intravenously or intramuscularly; antibiotics of different classes, nitroimidazoles (e.g. metronidazole), tetracyclines (e.g. doxycycline) or beta lactams (e.g. amoxicillin); and antibiotics of differing regimes or doses (e.g. doxycycline 400 mg plus metronidazole 400 mg single dose or doxycycline 100 mg twice a day for three days). All antibiotic classes, routes, doses and regimes will be included with no limits as long as the antibiotics are given as a means of infection prevention for women undergoing uterine evacuation procedures to treat miscarriage. We will define prophylaxis by the intention of administering antibiotics before, during or shortly after surgery as a means of infection prevention. We will include studies that assess multiple interventions such as blood transfusion, medications for pain relief, or comparisons of different types of surgical miscarriage management in addition to antibiotic treatment, as long as the study groups compare an antibiotic with placebo or no treatment.

Types of outcome measures

We will not exclude studies if they report the secondary outcomes only, nor will we exclude studies in the absence of reporting outcome data. We will present outcomes in the 'Characteristics of studies' tables.

We will focus on clinical, infection-related outcomes for this review, to evaluate the effectiveness and safety of antibiotic prophylaxis. The time frame for outcome assessment will be within six weeks, in line with Centers for Disease Control (CDC) procedure-associated infections (Berríos-Torres 2017), and the peripartum period (WHO 2016). The outcomes are based on the core outcome set developed by Whitehouse and colleagues (Whitehouse 2021), and the CDC (CDC 2021). The primary outcome of uterine infection in accordance with the CDC definition may include infections anatomically localised to other parts of the reproductive tract, therefore we will present the location of the infection in the 'Characteristics of studies' tables, as presented in the primary studies.

Primary outcomes

1. Uterine infection (Whitehouse 2021), as defined by the following criteria (CDC 2021). The woman has at least two of the following signs or symptoms:
   a. fever (> 38.0 °C);
   b. pain or tenderness (uterine or abdominal, with no other recognised cause); or
   c. purulent drainage from uterus.
2. Adverse effects of treatment

Secondary outcomes

1. Antibiotic treatment to treat infection after uterine evacuation procedure for miscarriage
2. Pelvic inflammatory disease (PID)
3. Hospitalisation for treatment of infection

Search methods for identification of studies

The Fertility Regulation Group Information Specialist will conduct a search for all published, unpublished, and ongoing studies, without restrictions on language or publication status. The search strategies for each database will be modelled on the search strategy designed for MEDLINE ALL (Ovid), available in Appendix 1.

Electronic searches

We will search the following databases from their inception:

1. Cochrane Central Register of Controlled Trials (CENTRAL; current year, latest issue) in the Cochrane Library
2. MEDLINE ALL (Ovid)
3. Embase.com
4. Global Health (Ovid)
5. Scopus (conference abstracts only)

We will search the following grey literature sites:

1. Guttmacher Institute www.guttmacher.org/united-states/abortion
2. International Planned Parenthood Federation www.ippf.org/
3. Ibis Reproductive Health ibisreproductivehealth.org/
4. Women on Waves www.womenonwaves.org/
5. Marie Stopes International www.mariestopes.org/
6. Population Council www.popcouncil.org/
7. Population Services International www.psi.org/
8. Ipas www.ipas.org/

Searching other resources

We will check the bibliographies of included studies and any relevant systematic reviews that we identify for further references to relevant studies. We will contact experts and organisations in the field to obtain additional information on relevant studies. If necessary, we will contact authors of included studies for data clarification and further information.

Data collection and analysis

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth (Cochrane PCG).

At least two review authors will independently assess the studies for inclusion in the review, assess study quality, extract the data and grade the body of evidence.

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Two review authors (SI, AA) will independently screen titles and abstracts for inclusion. We will retrieve the full-text study reports or publications and two review authors (SI, AA) will independently screen the full texts and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (AW). We will list studies that initially appeared to meet the inclusion criteria but that we later excluded in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021).

Data extraction and management

We will use a standard data collection form for study characteristics and outcome data; we will pilot the form on at least one study in the review. Two review authors (SI, AA) will independently extract the study characteristics from the included studies, this may include:

1. methods: study design, number of study centres, type of study centre, study setting and location, date of study, follow-up;
2. participants: number, inclusion criteria, exclusion criteria, other relevant characteristics;
3. interventions: intervention components; dose, route, regime, co-interventions, comparison, compliance;
4. outcomes: outcomes specified and collected, time points reported;
5. notes: funding for study, notable conflicts of interest of study authors, ethical approval.

Two review authors (SI, AA) will independently extract outcome data from included studies. If any of the review authors have been involved in a study that is included in the review, they will not participate in the risk of bias assessment or data extraction (additional support will be provided by the central Cochrane team if required). We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author (AW).

Assessment of risk of bias in included studies

Two review authors (SI, AA) will independently assess the risk of bias for key outcomes for results of randomised studies using the Cochrane RoB 2 tool (Sterne 2019), and criteria outlined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). We will resolve any disagreement by discussion or by involving a third review author (AW). We will assess the key outcomes defined in this protocol for risk of bias. We will assess the following domains using answers to signalling questions, with overall judgments derived from the tool.

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

An additional domain is included for cluster-randomised studies as outlined in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021): 1b. bias arising from identification or recruitment of individual participants within clusters.

We will use the variants of RoB 2 for cluster-RCTs if we include any studies of this design in our review. This variant will address the following issues with bias specific to cluster-RCTs in addition to those above.

1. Bias arising from the randomisation process
2. Bias arising from the timing of identification and recruitment of participants
3. Bias due to deviations from intended interventions
4. Bias due to missing outcome data
5. Bias in measurement of the outcome

We will judge each potential source of bias as high, low, or 'some concerns' and provide a quote from the study report together with a justification for our judgment in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the risk of bias table. We will not exclude studies on the grounds of their

risk of bias but will clearly report the risk of bias when presenting the results of the studies. When considering treatment effects, we will consider the risk of bias for the studies that contribute to that outcome. We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

For dichotomous data, we will use the numbers of events in each arm of each study to estimate the effect of the intervention using risk ratio together with the appropriate associated 95% confidence interval.

Unit of analysis issues

Cluster-randomised studies

We will include cluster-randomised studies in the analyses along with individually randomised studies. Where necessary, we will adjust their standard errors using the methods described in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation co-efficient (ICC) derived from the study (if possible), from a similar study or from a study of a similar population (Higgins 2021b). If we identify both cluster-randomised studies and individually-randomised studies, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Multi-arm studies

We will include multi-arm studies that use different antibiotics, as long as the comparison is antibiotic versus placebo or no treatment. In this situation we will combine the antibiotic arms into one, and the primary comparison will remain antibiotic versus placebo or no treatment.

Factorial studies

We will include factorial studies where one or more arms contain an antibiotic (+/- other interventions) and one or more arms contain no antibiotic (i.e. placebo or no treatment, +/- other interventions). We will combine any study arms that include antibiotic and combine any study arms that do not. The primary comparison will remain antibiotic versus placebo or no treatment.

Dealing with missing data

We will contact study authors in order to verify key study characteristics and obtain missing outcome data where possible (e.g. when a study is identified as abstract only).

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will perform analyses, as far as possible, on an intention-to-treat basis. That is, we will attempt to include all participants randomised to each group in the analyses, and we will analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each study will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

To evaluate the presence of clinical heterogeneity, we will generate descriptive statistics for study characteristics and study population characteristics across all eligible studies.

If we find a sufficient number of studies, we will conduct a meta-analysis. We will assess statistical heterogeneity in each meta-analysis using Tau^2, the I^2 statistic (Higgins 2003), and Chi^2 statistic (Deeks 2011). We will describe the clinical diversity and methodological variability of the evidence in the review text and with study tables describing study characteristics including design features, population characteristics, and intervention details.

To assess statistical heterogeneity, we will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap between confidence intervals. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the I^2 statistic to quantify inconsistency among the studies in each analysis. We will also consider the P value from the Chi^2 test to assess if this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity we will report the finding and explore possible explanatory factors using prespecified subgroup analysis.

We will use a rough guideline to interpret the I^2 statistic value rather than a simple threshold, and our interpretation will take into account an understanding that measures of heterogeneity (I^2 statistic and Tau^2) will be estimated with high uncertainty when the number of studies is small (Deeks 2021).

1. 0% to 40%: heterogeneity might not be important
2. 30% to 60%: may represent moderate heterogeneity*
3. 50% to 90%: may represent substantial heterogeneity*
4. 75% to 100%: considerable heterogeneity*

*The importance of the observed value of the I^2 statistic depends on 1. magnitude and direction of effects, and 2. strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small).

Assessment of reporting biases

We will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results. If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible publication biases, interpreting the results with caution (Sterne 2011).

Data synthesis

We will undertake meta-analyses only where this is meaningful because the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

If it is reasonable to assume that each study contributing to the meta-analysis for that outcome is estimating the same underlying treatment effect (i.e. similar interventions, study populations and

settings, and similar methods used) we will conduct a fixed-effect meta-analysis. If there is clear clinical diversity between studies, which is sufficient to expect that the underlying treatment effects differ between studies, or if we detect substantial statistical heterogeneity (as described above), we will use a random-effects meta-analysis. A random-effects meta-analysis assumes that the different studies are estimating an average pooled effect from a distribution of related intervention effects.

Subgroup analysis and investigation of heterogeneity

The effectiveness of antibiotic prophylaxis for uterine evacuation procedures to treat miscarriage could be influenced by several factors. These factors include gestational age at the time of the procedure (pregnancies of a greater gestation may have a higher incidence of pelvic infection due to the complexities involved with the surgical procedure), the type of surgery used (manual vacuum aspiration, suction curettage or sharp curettage; the type of miscarriage (missed or incomplete; incomplete miscarriage may be associated with a higher incidence of pelvic infection when compared to missed miscarriage), and the legal status of abortion for the study setting (legal, heavily restricted or illegal; studies conducted in settings where abortion is legal may be less likely to include cases of unsafe interventions).

We plan to carry out the following subgroup analyses to compare the effects estimated in studies that differ according to the following characteristics.

1. Gestational weeks at time of procedure (< 12 weeks, ≥ 12 weeks, unclear)
2. Type of surgery (manual vacuum aspiration, suction curettage, sharp curettage, dilation and evacuation)
3. Type of miscarriage (missed miscarriage, incomplete miscarriage)
4. Evidence of unsafe or surgical abortion (no evidence, some evidence)
5. Antibiotic class (tetracyclines, others)
6. Antibiotic regime (short course; < 3 days, longer course > 3 days; NICE 2019b)
7. Antibiotic route (oral, intravenous)

In studies of individuals that span the categories described above (e.g. different types of surgery or type of miscarriage types included in the same study), we will stratify the analyses into categories that reflect the majority of participants or will include a subgroup category of mixed populations. We will conduct interaction tests for subgroup differences and will only describe the estimates of effect for different strata if there is evidence of an interaction effect.

Sensitivity analysis

For the primary outcomes we will perform sensitivity analyses defined a priori to assess the robustness of our conclusions and explore its impact on effect sizes for the following.

1. Restricting the analyses to studies with antibiotics as a single intervention
2. Risk of bias (restricted to low risk of bias studies only): we will rank studies as 'low risk of bias' if they are double-blinded and have allocation concealment and outcome data available for nearly all participants randomised (less than 10% missing). We will consider protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses because protocol publication only became widespread in recent years.
3. Use of fixed-effect versus random-effects model

We will assess differences by evaluating the relative effects and assessment of model fit.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for the intervention comparison of any prophylactic antibiotic versus no treatment or placebo. The table will describe the results for each of the key outcomes defined in this protocol in accordance with the GRADE approach. These outcomes include pelvic infection and adverse effects of treatment. We will also present the findings from subgroup comparisons testing the effect of different treatment groups (such as antibiotic class and regime) on pelvic infection and adverse effects (e.g. short course of doxycycline versus short course of all other antibiotics).

If, during the review process, we become aware of important outcomes that we failed to list in our planned summary of findings table, we will include the relevant outcomes and explain the reasons for this is the section 'Differences between protocol and review'. Two review authors will independently assess the certainty of the evidence (high, moderate, low, and very low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias; Guyatt 2008). We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of interventions* (Schünemann 2021), and the EPOC worksheets (EPOC 2013), and use GRADEpro GDT software (GRADEpro GDT). We will resolve disagreements on certainty ratings by discussion and provide justification for decisions to down- or upgrade the ratings using footnotes in the table and make comments to aid readers' understanding of the review where necessary. We will use plain language statements to report these findings in the review (EPOC 2013).

We will consider whether there is any additional outcome information that we were not able to incorporate into meta-analyses and note this in the comments, and state if it supports or contradicts the information from the meta-analyses. If it is not possible to meta-analyse the data, we will summarise the results in the text.

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APPENDICES

Appendix 1. Model Search Strategy

Cochrane Central Register of Controlled Trials (CENTRAL; CRSWeb)

Date searched: 29 January 2021

1. (Abortion, Spontaneous OR Abortion, Incomplete OR Abortion, Missed OR Abortion, Septic OR Embryo Loss):MH AND CENTRAL:TARGET (643)
2. (("blastocyst disintegration" OR febrile abortion* OR incomplete abortion* OR infect* abortion* OR missed abortion* OR septic abortion* OR spontaneous abortion* OR tubal abortion* OR pregnancy loss OR pregnancy losses OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) AND (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabortion OR postabortal OR post-abortion OR post-abortal OR (retained AND concept*) OR (product* AND concept*)):TI OR ("blastocyst disintegration" OR febrile abortion* OR incomplete abortion* OR infect* abortion* OR missed abortion* OR septic abortion* OR spontaneous abortion* OR tubal abortion* OR pregnancy loss OR pregnancy losses OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) AND (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabortion OR postabortal OR post-abortion OR post-abortal OR (retained AND concept*) OR (product* AND concept*)):AB) AND CENTRAL:TARGET (6432)
3. #1 OR #2 (6577)
4. (Anti-Bacterial Agents OR Antibiotic Prophylaxis OR Doxycycline OR exp Tetracyclines OR Lactams OR Macrolides OR Metronidazole OR Nitroimidazoles OR Tinidazole OR Quinolones OR Oxolinic Acid OR Penicillins OR Sulfanilamide OR Infection OR Bacterial Infections):MH AND CENTRAL:TARGET (25855)
5. ((anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR infect* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* AND treat*) OR tetracycline* OR tinidazole):TI OR (anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR infect* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* AND treat*) OR tetracycline* OR tinidazole):AB) AND CENTRAL:TARGET (174803)
6. #4 OR #5 (180046)
7. #3 AND #6 (1042)

MEDLINE ALL (Ovid) 1946 to January 28, 2021

Date searched: 29 January 2021

1 Abortion, Spontaneous/ or Abortion, Incomplete/ or Abortion, Missed/ or Abortion, Septic/ or Embryo Loss/ (23945)

2 ("blastocyst disintegration" or ((febrile or incomplete or infect* or missed or septic or spontaneous or tubal) adj3 abortion*) or (pregnancy adj3 loss) or ((embryo* or fetal or foetal or fetus* or foetus*) adj3 (death or deaths or demise or disintegrat* or loss or losses or resorption*)) or miscarriage* or postabort* or post-abort* or (retained adj3 (concept* or tissue*)) or (product* adj3 concept*)).ti,ab,kf,kw. (58781)
3 or/1-2 (70708)
4 exp Anti-Bacterial Agents/ or Antibiotic Prophylaxis/ or Doxycycline/ or exp Tetracyclines/ or exp Lactams/ or exp Macrolides/ or Metronidazole/ or exp Nitroimidazoles/ or Tinidazole/ or exp Quinolones/ or Oxolinic Acid/ or exp Penicillins/ or Sulfanilamide/ or exp Infections/ or exp Bacterial Infections/ (3134258)
5 (anti-bacterial* or antibacterial* or anti-biotic* or antibiotic* or anti-mycobacterial* or antimycobacterial* or bacteriocid* or cefoxitin or ciprofloxacin or doxycycline or fluroquinolone* or lactam* or macrolide* or metronidazole or nitroimidazole* or "oxolinic acid" or penicillin* or prophyl* or quinolone* or (screen* adj3 treat*) or tetracycline* or tinidazole).ti,ab,kf,kw,nm,rn. (904822)
6 or/4-5 (3433577)
7 (controlled clinical trial or randomized controlled trial).pt. or (groups or placebo or random* or trial).ab. or dt.fs. (5135905)
8 (exp animals/ not humans/) or (animal or animals or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or feline or goat or goats or helminths or horse or livestock or mice or mouse or ovine or pig or pigs or porcine or rabbit or rabbits or rat or rats or rattus or sheep or sow or sows or swine).ti. (5189177)
9 7 not 8 (4394990)
10 and/3,6,9 (1820)

Embase.com
Date searched: 29 January 2021
#1 'incomplete abortion'/de OR 'blighted ovum'/de OR 'fetus wastage'/de OR 'missed abortion'/de OR 'septic abortion'/de OR 'spontaneous abortion'/de (52,575)
#2 'blastocyst disintegration':ti,kw OR (((febrile OR incomplete OR infect* OR missed OR septic OR spontaneous OR tubal) NEAR/3 abortion*):ti,kw) OR ((pregnancy NEAR/3 loss):ti,kw) OR (((embryo* OR fetal OR foetal OR fetus* OR foetus*) NEAR/3 (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)):ti,kw) OR miscarriage*:ti,kw OR postabort*:ti,kw OR 'post abort*':ti,kw OR ((retained NEAR/3 (concept* OR tissue*)):ti,kw) OR ((product* NEAR/3 concept*):ti,kw) (23,406)
#3 #1 OR #2 (62,668)
#4 'antiinfective agent'/exp OR 'antibiotic prophylaxis'/de OR 'doxycycline'/de OR 'lactam'/exp OR 'macrolide'/de OR 'metronidazole'/de OR 'tinidazole'/de OR 'oxolinic acid'/de OR 'penicillin derivative'/exp OR 'sulfanilamide'/exp OR 'tetracycline derivative'/exp OR 'nitroimidazole derivative'/exp OR 'quinolone derivative'/exp OR 'infection'/mj OR 'bacterial infection'/mj OR 'intrauterine infection'/exp (4,015,881)
#5 'anti bacterial*':ti,ab,kw OR antibacterial*:ti,ab,kw OR 'anti biotic*':ti,ab,kw OR antibiotic*:ti,ab,kw OR 'anti mycobacterial*':ti,ab,kw OR antimycobacterial*:ti,ab,kw OR bacteriocid*:ti,ab,kw OR cefoxitin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR doxycycline:ti,ab,kw OR fluroquinolone*:ti,ab,kw OR lactam*:ti,ab,kw OR macrolide*:ti,ab,kw OR metronidazole:ti,ab,kw OR nitroimidazole*:ti,ab,kw OR 'oxolinic acid':ti,ab,kw OR penicillin*:ti,ab,kw OR prophyl*:ti,ab,kw OR quinolone*:ti,ab,kw OR ((screen* NEAR/3 treat*):ti,ab,kw) OR tetracycline*:ti,ab,kw OR tinidazole:ti,ab,kw (965,387)
#6 #4 OR #5 (4,327,174)
#7 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti (2,688,881)
#8 ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim) NOT [humans]/lim OR animal:ti OR animals:ti OR bovine:ti OR canine:ti OR capra:ti OR cat:ti OR cats:ti OR cattle:ti OR cow:ti OR cows:ti OR dog:ti OR dogs:ti OR equine:ti OR feline:ti OR goat:ti OR goats:ti OR helminths:ti OR horse:ti OR livestock:ti OR mice:ti OR mouse:ti OR ovine:ti OR pig:ti OR pigs:ti OR porcine:ti OR rabbit:ti OR rabbits:ti OR rat:ti OR rats:ti OR rattus:ti OR sheep:ti OR sow:ti OR sows:ti OR swine:ti (4,543,611)
#9 #7 NOT #8 (2,461,690)
#10 #3 AND #6 AND #9 (954)

Global Health (Ovid) 1973 to 2021 Week 04
Date searched: 29 January 2021
1 ("blastocyst disintegration" or ((febrile or incomplete or infect* or missed or septic or spontaneous or tubal) adj3 abortion*) or (pregnancy adj3 loss) or ((embryo* or fetal or foetal or fetus* or foetus*) adj3 (death or deaths or demise or disintegrat* or loss or losses or resorption*)) or miscarriage* or postabort* or post-abort* or (retained adj3 (concept* or tissue*)) or (product* adj3 concept*)).ti,ab. (8686)
2 (anti-bacterial* or antibacterial* or anti-biotic* or antibiotic* or anti-mycobacterial* or antimycobacterial* or bacteriocid* or cefoxitin or ciprofloxacin or doxycycline or fluroquinolone* or lactam* or macrolide* or metronidazole or nitroimidazole* or "oxolinic acid" or penicillin* or prophyl* or quinolone* or (screen* adj3 treat*) or tetracycline* or tinidazole).ti,ab. (217234)
3 and/1-2 (380)

Scopus
Date searched: 29 January 2021;
TITLE-ABS-KEY ("blastocyst disintegration" OR ((febrile OR incomplete OR infect* OR missed OR septic OR spontaneous OR tubal) PRE/3 abortion*) OR (pregnancy PRE/3 loss) OR ((embryo* OR fetal OR foetal OR fetus* OR foetus*) PRE/3 (death OR deaths OR demise OR disintegrat* OR loss OR losses OR resorption*)) OR miscarriage* OR postabort* OR post-abort* OR (retained

PRE/3 (concept* OR tissue*)) OR (product* PRE/3 concept*)) AND TITLE-ABS-KEY (anti-bacterial* OR antibacterial* OR anti-biotic* OR antibiotic* OR anti-mycobacterial* OR antimycobacterial* OR bacteriocid* OR cefoxitin OR ciprofloxacin OR doxycycline OR fluroquinolone* OR lactam* OR macrolide* OR metronidazole OR nitroimidazole* OR "oxolinic acid" OR penicillin* OR prophyl* OR quinolone* OR (screen* PRE/3 treat*) OR tetracycline* OR tinidazole) AND TITLE-ABS-KEY (groups OR placebo OR random* OR trial) AND (LIMIT-TO (DOCTYPE, "cp")) (51)

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: AW, SI, AA, CM, DL

Designing the protocol: AW, SI, AA, CM, DL

Co-ordinating the protocol: MM, AW

Designing search strategies: RP (FRG information specialist)

Writing the protocol: AW, SI

Providing general advice on the protocol: AC, AMG, DL, CM, JC

Securing funding for the protocol: N/A

Performing previous work that was the foundation of the current study: AMG, KB, WM

DECLARATIONS OF INTEREST

Sheikh Irfan: none known

Anne Ammerdorffer: none known

Catherine Moakes: CM was the Medical Statistician for the AIMS trial (ISRCTN 97143849).

James Cheshire: none known

Ahmet Metin Gülmezoglu: none known

Arri Coomarasamy: AC was the Chief Investigator for the AIMS trial (ISRCTN 97143849).

David Lissauer: DL was the Trial Manager for the AIMS trial (ISRCTN 97143849).

Amie Wilson: AW was the Trial Co-ordinator for the AIMS trial (ISRCTN 97143849).

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External sources

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