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Adverse pregnancy and neonatal outcomes associated with *Neisseria gonorrhoeae, Mycoplasma genitalium, M. hominis, Ureaplasma urealyticum and U. parvum:* a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Several bacterial sexually transmitted and genital mycoplasma infections during pregnancy have been associated with poor pregnancy and perinatal outcomes. Comprehensive and systematic information about associations between sexually transmitted infections (STI) and genital infections in pregnancy and adverse perinatal outcomes is needed to improve understanding about the evidence for causal associations between these infections and adverse pregnancy and neonatal outcomes. Our primary objective is to systematically review the literature about associations between: (1) *Neisseria gonorrhoeae* in pregnancy and preterm birth; (2) *Mycoplasma genitalium* in pregnancy and preterm birth; (3) *M. hominis, Ureaplasma urealyticum* and/or *U. parvum* in pregnancy and preterm birth.

Methods and analysis We will undertake a systematic search of Medline, Excerpta Medica database and the Cochrane Library and Cumulative Index to Nursing and Allied Health Literature. Following an initial screening of titles by one reviewer, abstracts will be independently assessed by two reviewers before screening of full-text articles. To exclude a manuscript, both reviewers need to agree on the decision. Any discrepancies will be resolved by discussion, or the adjudication of a third reviewer. Studies will be included if they report testing for one or more of *N. gonorrhoeae, M. genitalium, M. hominis, U. urealyticum and/or U. parvum* during pregnancy and report pregnancy and/or birth outcomes. In this review, the primary outcome is preterm birth. Secondary outcomes are premature rupture of membranes, low birth weight, spontaneous abortion, stillbirth, neonatal mortality and ophthalmia neonatorum. We will use standard definitions, or definitions reported by study authors. We will examine associations between exposure and outcome in forest plots, using the I^2 statistic to examine between study heterogeneity. Where appropriate, we will use meta-analysis to combine results of individual studies.

Ethics and dissemination This systematic review of published literature does not require ethical committee approval. Results of this review will be published in a peer reviewed, open access journal.

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Strengths and limitations of this study

- This systematic review is, as far as we are aware, the first to address associations between adverse pregnancy and neonatal outcomes and the sexually transmitted pathogens *Neisseria gonorrhoeae* and *Mycoplasma genitalium*, and associations with other genital mycoplasmas.
- The systematic review, which covers more than one infection, will be efficient because these infections are often tested for and reported in the same study.
- This review will appraise the quality of each study according to the study design (ie, cross-sectional, case–control, cohort or clinical trial).
- The results of this review can be used to estimate the burden of disease due to these sexually transmitted and genital infections.
- A limitation of this review is that we will only be able to examine associations separately for *Ureaplasma urealyticum* and *U. parvum* in more recent studies because older studies did not distinguish between the two species.

INTRODUCTION

Several bacterial sexually transmitted infections (STI) during pregnancy have been reported to be associated with poor pregnancy outcomes.[1–3] *Chlamydia trachomatis* (CT, chlamydia), *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV, trichomoniasis) and *Mycoplasma genitalium* (MG) have all been associated with one or more of the following: premature rupture of membranes

(PROM), preterm birth and low birth weight (LBW)[1–10]; CT and NG are also recognised as causes of neonatal conjunctivitis and CT is a cause of neonatal pneumonia.[11] Other genital mycoplasmas in the reproductive tract are *M. hominis, Ureaplasma urealyticum and U. parvum.* Combined testing for these organisms is common and they are very frequently found in the vagina.[12] Routine testing and treatment of asymptomatic non-pregnant women are discouraged because the evidence that they cause disease is questionable.[13] Detection of these organisms during pregnancy has been reported in some studies, however, to be associated with spontaneous abortion, stillbirth, preterm birth, LBW and perinatal morbidity and mortality.[13–15] In a large cohort study in south Asia, *Ureaplasma* spp (*U. urealyticum* and *U. parvum* together) were the second most common organism identified in infants with signs of serious bacterial infection than from healthy babies and were more commonly isolated from sick than healthy infants.[16] Bacterial culture for *U. urealyticum* does not distinguish between two closely related species, *U. urealyticum* and *U. parvum* and associations with each of these subspecies and adverse pregnancy outcomes are not consistent.[17 18]

Comprehensive and systematic information about associations between STI, other genital infections in pregnancy and adverse pregnancy and perinatal outcomes is needed to improve understanding about the evidence for causal associations, to contribute to estimates of the global burden of STI and to determine the potential impact of preventive interventions. For example, associations between syphilis in pregnancy and preterm birth, LBW, stillbirth and systemic congenital infection are well-established, the burden of disease has been estimated and a global strategy for elimination of congenital syphilis is in place.[19–21] For other STI and reproductive tract infections, the consistency and causal nature of associations are not as clear. Much of the published work on STI, reproductive tract infections and their association with adverse birth outcomes comes from middle-income and high-income countries, with less evidence from low-income settings which have the highest prevalence rates of STI in pregnancy.[1 22]

Systematic reviews that synthesise findings from different studies can help to examine the consistency and risk of bias of the body of evidence. To date, systematic reviews about adverse pregnancy outcomes have examined associations with CT,[23] TV[24] and MG.[25] For CT, there are published and ongoing reviews. Silva *et al*[23] reported on 12 studies published up to January 2010 and found that CT infection during pregnancy was associated with an increased risk of preterm labour, LBW and perinatal mortality. A protocol in the online database PROSPERO shows that another systematic review about CT and adverse pregnancy outcomes is ongoing.[26] For TV, a systematic review by Silver *et al*[24] included 11 studies published up to May 2013 and found that antenatal TV infection was associated with increased risk of preterm birth, PROM and small for gestational age infants. For MG, a systematic review by Lis *et al*[25] included nine studies published up to June 2014 and found that MG was associated with preterm birth and spontaneous abortion. Nucleic acid amplification tests (NAATs) for MG are only now becoming widely available, so a new systematic review of evidence about MG is warranted.[25] For NG and adverse pregnancy and neonatal outcomes we are unaware of any systematic reviews. Multiplex NAATs now include targets for *M. hominis*, *U. urealyticum* and *U. parvum*. We are unaware of a systematic review that has synthesised quantitative data about associations between these genital mycoplasmas and adverse pregnancy outcomes. *M. hominis*, in particular, is strongly associated with bacterial vaginosis (BV) which itself is strongly associated with adverse pregnancy outcomes.[15] The use of antibiotic therapy for treating BV in pregnancy has been found to eradicate BV during pregnancy but did not reduce the risk of preterm birth, or preterm, prelabour rupture of membranes.[27] It would be useful to examine whether or not co-existing BV modifies any association between genital mycoplasmas and adverse pregnancy outcomes. STIs and genital mycoplasmas can co-occur and the use of multiplex NAATs means that findings about multiple organisms are increasingly presented together.[13 28] A single search strategy that includes terms for different pathogens and outcomes could make the work of a systematic review more efficient.

Objectives

The overall aim of this systematic review is to examine associations between selected infections in pregnancy and adverse pregnancy and/or neonatal outcomes. We have the following specific objectives:

1. To determine whether NG infection during pregnancy increases the risk of preterm birth.
2. To determine whether MG infection during pregnancy increases the risk of preterm birth.
3. To determine whether infection with the genital tract infections *M. hominis*, *U. urealyticum* and *U. parvum* during pregnancy increase the risk of preterm birth.
4. To examine associations between each of the named infections during pregnancy and other adverse pregnancy or neonatal outcomes: LBW, PROM, spontaneous abortion; perinatal mortality; ophthalmia neonatorum.

METHODS AND ANALYSIS

We wrote the systematic review protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines[29] (online supplementary file 1), adapting it where necessary to our review of observational research studies. If we need to amend the protocol, we will update the PROSPERO record with the date of each amendment, accompanied by a description of the change and the rationale.

Eligibility criteria

Studies will be selected if they report one or more pregnancy, perinatal or neonatal outcome in women with NG, MG, *M. hominis, U. urealyticum* and/or *U. parvum*.

Study design

We will include any study design with data that allows comparison between women with and without one of the included infections. Eligible study designs include case–control, cross-sectional, cohort studies and clinical trials. Individual case reports, case series without a control group and opinion articles will not be included.

Participants

Women who have been tested during pregnancy for NG, MG, *M. hominis, U. urealyticum* or *U. parvum* using a laboratory diagnostic test, for example culture or NAAT, and for whom pregnancy and/or neonatal health outcomes are reported.

Infections

For studies that report more than one of the eligible infections, we will only include studies for which we can extract data separately for each infection, with the exception of *U. urealyticum*. We will assume that studies reporting on *U. urealyticum* alone have not differentiated between *U. urealyticum* and *U. parvum*. We assume that studies published after 2000 and reporting separate results for *U. urealyticum* and *U. parvum* have conducted tests that distinguish between these organisms.

Exposures or interventions

For observational study designs, the exposures of interest are: (1) NG; (2) MG; (3) *M. hominis, U. urealyticum* and/or *U. parvum* infection, diagnosed using a recognised laboratory test. For intervention studies, the intervention of interest is antibiotic treatment for a detected NG, MG, other genital m*ycoplasma* infection or antibiotic prophylaxis. The comparator is women who did not receive antibiotic treatment for NG, MG or other genital mycoplasma infection.

Exclusion criteria

Individual case reports, case series, opinion articles and studies without a control group will be excluded.

Studies including only mycoplasma infections without differentiating between specific mycoplasmas and articles that pool different STI and mycoplasma infections together will be excluded.

Information sources

We will search Medline, Excerpta Medica database and the Cochrane Library and Cumulative Index to Nursing and Allied Health Literature to identify relevant studies in humans only. We will not apply language or date limits to the search, but will only include articles published in English or German.

Search strategy

The search strategy includes Medical Subject Headings (MeSH) and keywords related to pregnancy, infections (NG, MG, *M. hominis, U. urealyticum* and/or *U. parvum*) and pregnancy, birth and neonatal outcomes (table 1). The 'explode' function will be applied to each MeSH heading.

We will search each database from its earliest date, including online publication. To identify additional relevant studies, we will search the reference lists of included studies or relevant reviews identified during the search. LV, the lead author of this manuscript, who is also the lead person for this planned review, will conduct the search.

STUDY RECORDS

Data management

Search results will be imported into an Endnote (Clarivate Analytics 2017, Boston) library and all duplicates will be removed. We will use REDCap (Research Electronic Data Capture, Vanderbilt University, TN), a secure web application for building and managing online databases for screening and data extraction. DEG will design and pilot the forms for screening and data extraction. All extracted

Table 1 Search strategy

1. Terms for population	'pregnancy' or 'prenatal' or 'antenatal'
2. Terms for exposure	*'Neisseria gonorrhoeae'* or 'gonorrhea' or 'gonorrhoea'; *'Mycoplasma genitalium'; 'Mycoplasma hominis'; 'Ureaplasma urealyticum'; 'Ureaplasma parvum'*
3. Terms for outcomes	'birth outcome' or 'adverse birth outcome' or 'adverse pregnancy outcome' or 'perinatal morbidity' or 'perinatal mortality' or 'perinatal outcome' or 'premature birth' or 'premature delivery' or 'very preterm birth' or 'preterm birth' or 'preterm delivery' or 'premature labour' or 'preterm labour' or 'premature labor' or 'preterm labor' or 'premature rupture of membranes' or 'preterm rupture of membranes' or 'preterm premature rupture of membranes' or 'low birth weight' or 'intrauterine growth retardation' or 'intrauterine growth restriction' or 'small for gestational age' or 'gestational age' or 'stillbirth' or 'perinatal mortality' or 'perinatal morbidity' or 'perinatal death' or 'neonatal mortality' or 'neonatal morbidity' or 'neonatal death' or 'fetal death' or 'miscarriage' or 'spontaneous abortion' or 'ophthalmia neonatorum' or 'chorioamnionitis'
4.Search = #1 + # 2 + # 3	

Free text terms in the search strategy will use truncated and wildcard forms, for example, pregn*, gono*.

data will be imported into Stata V.14.0 (StataCorp LLC, TX) for analysis.

Selection process

We will conduct screening for inclusion in three stages:

1. One reviewer (LV) will review each title and decide on records that can be excluded immediately using selected criteria (online supplementary material 2). All other records advance to the next stage.
2. In the second stage, two reviewers (LV, DE-G) will independently screen all titles and abstracts against the eligibility criteria. To exclude a record, both reviewers need to agree on the decision. Any record excluded by a single reviewer is checked by the second reviewer and discrepancies will be resolved by discussion, or by the adjudication of a third reviewer.
3. In the third stage, two reviewers (LV, DE-G) will screen the full text of each record independently against the eligibility criteria. To exclude a manuscript, both reviewers need to agree on the decision. Any manuscript excluded by a single reviewer is checked by the second reviewer and discrepancies will be resolved by discussion, or by the adjudication of a third reviewer. Reasons for exclusion of any study at stage three will be recorded.

Data collection process

Two reviewers will extract data independently. The reviewers will compare their findings and resolve discrepancies through discussion, or by asking a third reviewer to adjudicate. Where necessary we will contact the authors of selected manuscripts for missing or additional information.

Data items

Table 2 outlines data items that will be extracted, including study characteristics, participant characteristics, presence or absence of infection and pregnancy and neonatal outcomes.

OUTCOMES

There are several potential adverse outcomes of pregnancy, and perinatal or neonatal outcomes. In this review we will use standard and recommended definitions [30] or, if these are not consistently defined, use the case definitions reported by the authors. The following outcomes will be considered:

Primary outcome

- Preterm birth, defined as birth before 37 completed weeks' gestation (including extremely preterm, very preterm and moderate to late preterm).[30]

Secondary outcomes

- PROM, including preterm (before 37 completed weeks gestation) rupture of membranes.
- LBW, defined as birth weight less than 2500 g.[31]
- Spontaneous abortion (miscarriage) (or as defined by study).
- Perinatal mortality
  - Stillbirth/fetal death in utero at more than 20 weeks gestation (or as defined by study).
  - Neonatal mortality (death in the first 28 days of life).
- Ophthalmia neonatorum.

Risk of bias in individual studies

Two reviewers will assess the methodological quality and risk of bias of each study included in the review independently, using study specific checklists published by the UK National Institute for Health and Care Excellence.[32 33] The checklists enable the reviewer to appraise the internal and external validity of a study after considering key aspects relating to study design, including

Table 2 Data items to be extracted

Study characteristics	Population characteristics	NG, MG, MH, UU, UP characteristics	Birth outcomes
► Authors. ► Year of study. ► Location and setting. ► Study design. ► Inclusion criteria. ► Sample size.	► Number of participants. ► Maternal age. ► Smoking. ► Ethnic group. ► Multiple pregnancy. ► Co-infection for example, HIV or other genital infection. ► Measure of gestational age (US, FH, LMP). ► Antibiotic treatment. ► Gestation at treatment.	► Number and/or % of women with NG, MG, MH, UU, UP. ► Number and/or % of women with one or more of NG, MG, MH, UU, UP. ► Laboratory test (type). ► Specimen type (urine, vaginal swab, endocervical swab, etc). ► Specimen collection method (self/clinician collected). ► Gestation at specimen collection. ► Presence of BV.	► Premature rupture of membranes. ► Preterm birth. ► Low birth weight (<2500 g). ► Spontaneous abortion (less than 20 weeks gestation). ► Stillbirth/fetal death in utero more than 20 weeks gestation. ► Neonatal death (within first 28 days). ► Ophthalmia neonatorum.

BV, bacterial vaginosis; FH, fundal height; LMP, last menstrual period; MG, *Mycoplasma genitalium*; MH, *Mycoplasma hominis;* NG, *Neisseria gonorrhoeae*; UP, *Ureaplasma parvum*; US, ultrasound; UU, *Ureaplasma urealyticum.*

population characteristics; definition of exposure variables; outcomes assessed and methods of analyses. Based on these four aspects, an overall assessment of the internal and external validity of each study will be considered. Where the two reviewers disagree, a third reviewer will adjudicate.

Data synthesis and analysis

We will conduct separate data synthesis and analysis, first for the STI NG and MG and then for the other genital mycoplasma infections *M. hominis*, *U. urealyticum* and *U. parvum*. The stepwise approach will make our review process more efficient. We will apply the same procedures for each group of infections.

We will develop a table summarising the key characteristics of each included study, including author, study year, setting, study design, number of participants and outcomes.

For cross-sectional studies, cohort studies and clinical trials, the measure of association will usually be the risk ratio (RR, with 95% CI) and for case–control studies the measure of association will usually be the OR (with 95% CI). We will use the measure of association and 95% CI presented by the authors and we will check the calculation of the point estimate, where possible, with raw data extracted from the article. Study authors might also report effect estimates that control for potential confounding factors. Where adjusted estimates of effect obtained from multivariable regression analyses are reported, we will extract the estimate (with 95% CI) and will record the variables included in the multivariable model. We have prespecified three variables that are likely to cause confounding, resulting in an overestimation of the association between the infection of interest and pregnancy and perinatal outcomes. We will record whether each of the following variables is included in multivariable analyses: younger age, lower socioeconomic position and presence of other STI or reproductive tract infections.

We will display associations first in forest plots to show the measure of association for each exposure-outcome pair, stratified by study design. We will use the I^2 test to estimate the proportion of variability in point estimates that can be attributed to between study heterogeneity for reasons other than chance.[34] As a guide, we will consider I^2 values <50% as evidence of low heterogeneity, 50%–75% as moderate heterogeneity and >75% as severe heterogeneity. We will investigate reasons for heterogeneity by stratification or, where there are enough studies, meta-regression. We will conduct sensitivity analyses to determine any effect of the following characteristics on the results: standard versus author-defined outcome definitions; low versus high risk of bias. We will conduct subgroup analyses to investigate the following possible sources of heterogeneity: country or region of study; diagnostic test (NAAT, culture, other); trimester of pregnancy when infection was detected (first, second, third); decade of study (pre-1980, 1980–1989, 1990–1999, 2000 or later); presence or absence of BV.

Where appropriate, for outcomes reported by two or more studies of the same design, we will use meta-analysis to estimate a summary RR (95% CI) or OR (95% CI). If heterogeneity is moderate or severe, we will use a random effects model.[35] The random effects model estimates the average effect across all studies and assumes that the true strength of association differs between studies. If heterogeneity is absent or low, we will use a fixed effects model. The fixed effects model assumes that the effect is similar across all studies and that variation between studies is due only to chance. We will conduct separate analyses for studies that record the presence of exposure before the outcome and studies in which exposure and outcome are measured at the same time.

We will examine the results of adjusted analyses using the same approach as for unadjusted estimates.

All data will be analysed using Stata V.14.0 (StataCorp LLC, TX).

Meta-biases

If there are more than 10 studies examining an exposure-outcome association, we will look for evidence of publication bias using funnel plots. We will examine these visually for evidence of asymmetry and use the Begg and Mazumdar rank correlation test for asymmetry.[36]

We have not planned to look for evidence of selective reporting within studies.

Confidence in cumulative evidence

We will use the Grading of Research Evidence Assessment and Development approach to assess the body of evidence, considering the observational study designs,[37] and provide a descriptive assessment of certainty in the cumulative evidence.

Patient and public involvement

Patients and/or the public were not involved in the development of this review protocol. We will publish the findings in open access publications which are available for the public to read and make use of the data.

DISCUSSION

This systematic review will fill gaps in knowledge about potential associations between STI and reproductive tract infections, and adverse pregnancy and perinatal outcomes. Our systematic review will address infections that have not previously been assessed in a systematic review (NG) and some genital mycoplasmas.

The association between STI and other genital infections, and adverse pregnancy and perinatal outcomes has been documented from a number of high- and middle-income settings.[2 5 8] We will search multiple information sources and expect to find additional studies conducted in less well-resourced settings. Additional steps to minimise bias include independent assessments by two reviewers to reduce bias in the selection of studies and extraction of data and consideration of adjusted effect

sizes and specific prespecified confounding factors in the analysis. However, we also anticipate some challenges that are specific to our review. First, we are reviewing the association between *U. urealyticum* and adverse pregnancy outcomes. *U. urealyticum* is now recognised to comprise two species, *U. urealyticum* and *U. parvum*. We will only be able to examine associations for these separate species in more recent studies, reducing the number of studies available for analysis. Second, we might not be able to determine whether trimester of pregnancy in which infection occurs results in different outcomes. Infections diagnosed in the third trimester might have been present throughout. Conversely, infections diagnosed early in pregnancy might already have been treated. We will take these factors into account when interpreting the findings.

Studies that synthesise information about complications of STI and reproductive tract infections can be used in the estimation of the burden of disease. Until now, global burden of disease estimates of the burden of disease due to bacterial STI other than syphilis only include disability resulting from pelvic inflammatory disease and infertility. Ultimately, the findings of this review could help to improve decisions about both the prevention and clinical management of NG and genital mycoplasma infections in pregnancy.

Ethics and dissemination

We will present our results at an international medical conference that focuses on the prevention and treatment of STI. We will publish the results of this review in a peer reviewed, open access medical journal.

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Contributors LMV is the guarantor of the protocol manuscript. LMV, DE-G, NL and AJV conceived the study and developed the review protocol. CSEH gave advice about the pregnancy outcomes. NL gave advice about the infection outcomes and systematic review methods. HW reviewed and advised on the statistical analyses. LV wrote the first draft of the manuscript. DE-G, NL and AJV helped to revise the manuscript. WP, RG, HW, CSEH, BS, AR and JMK contributed to the development and design of the protocol and in revising the manuscript. All authors read, provided feedback and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This systematic review does not use individual personal data and therefore does not require ethical committee approval.

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