Adverse pregnancy and neonatal outcomes associated with *Neisseria gonorrhoeae*: systematic review and meta-analysis

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INTRODUCTION

Sexually transmitted infections (STIs) during pregnancy have been reported to be associated with poor pregnancy outcomes. 1–3 *Neisseria gonorrhoeae* (NG) has been associated with premature rupture of membranes (PROM), 1 preterm birth (PTB), 1,4–5 low birth weight (LBW), 1,4–4 neonatal and perinatal mortality 7,8 as well as neonatal conjunctivitis. 9,10 Preterm birth and its complications are a leading cause of perinatal mortality and the majority of perinatal and neonatal deaths occur in low-resource settings.11,12 Information about associations between NG during pregnancy and adverse pregnancy and birth outcomes is therefore necessary to improve our understanding of the evidence for causality, and to determine the potential impact of preventive interventions.1,13

To date, systematic reviews about adverse pregnancy and birth outcomes have examined, and found, associations with Chlamydia trachomatis (CT), 14–16 Trichomonas vaginalis (TV) 17 and Mycoplasma genitalium (MG). 18 The objective of this study was to systematically review associations between NG infection during pregnancy and the risk of PTB, spontaneous abortion, PROM, perinatal mortality, LBW and ophthalmia neonatorum.

METHODS

The protocol for this review has been published.19 We report our findings using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (online supplemental table S1).20

Eligibility criteria

Studies reporting NG detected by culture and/or nucleic acid amplification test during pregnancy, labour or post partum were eligible for inclusion if they reported on one or more of the following outcomes: PTB, spontaneous abortion, PROM (preterm and term), LBW, perinatal or neonatal mortality, or ophthalmia neonatorum. We included clinical trials, cohort, case-control and cross-sectional studies but excluded individual case reports, case series, opinion articles and studies without a comparison group.

Information sources and search strategy

We searched Medline, Excerpta Medica database (EMBASE), the Cochrane Library and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from 1948 to 14 January 2020. We examined reference lists of included studies.
or relevant reviews for additional articles. The searches did not apply language restrictions, but we included only articles published in English or German (languages spoken fluently by review team members). Details of the search strategy are listed in online supplemental text S1.

**Study selection and data extraction**

One reviewer (LV) screened titles and abstracts (online supplemental text S2) and two reviewers screened the full text of potentially relevant articles independently (LV, DE-G). Discrepancies were resolved by discussion or by the decision of a third reviewer (NL). Data were extracted into a standardised, piloted form in a Research Electronic Data Capture (REDCap) database (Vanderbilt University, Tennessee, USA) recording study design, participant characteristics, presence or absence of NG, pregnancy, perinatal or neonatal outcomes and other STI and genital infections. Standard definitions for outcomes were used, or as defined by the authors (online supplemental tables S2-S4).

**Risk of bias in individual studies**

Two reviewers assessed the risk of bias in each study independently (LV, DE-G), using checklists for cross-sectional, case-control and cohort studies, published by the UK National Institute for Health and Care Excellence (NICE). A third reviewer (NL) resolved discrepancies. Each study was assessed qualitatively overall as having all or most (++), some (+), or few or no checklist criteria fulfilled (−).

**Data synthesis and analysis**

We used stata V.14.0 (StataCorp, College Station, Texas, USA) for all analyses. Where possible, we used the odds ratio (OR) as the measure of association for all study designs, assuming that the relative risk (RR) and OR would be similar, as the outcomes of interest are rare events. We calculated the crude OR and its 95% CI using raw data from the paper, or extracted values provided by the authors if raw data were not available. Where authors reported a multivariable analysis, we extracted the adjusted OR (aOR, 95% CI) and recorded the variables included in the model. We examined forest plots for each outcome (figures 1 and 2; online supplemental tables S3-S10), and used the I² statistic to examine the level of between-study heterogeneity other than that due to chance.

For outcomes reported by two or more studies of the same design, we used a random effects model to estimate a summary OR (95% CI), which is the average effect across all included studies. We first stratified these estimates by study design because there are sources of bias that could result in overestimation or underestimation of an association and these biases differ according to the study design. If the stratified estimates were similar, as visualised in forest plots, we also reported the overall
summary OR from meta-analysis, with its prediction interval for the estimated range of effect sizes across settings.\(^{24}\) Meta-analysis of the results of aORs used the same approach as for unadjusted estimates. For the outcome PTB, for which there were >10 included studies, we categorised studies as high-income and non-high-income (combining low-income and middle-income countries), based on the World Bank list.\(^{25}\) We repeated all meta-analyses using a fixed effects model as a sensitivity analysis.

Risk of bias across studies
Publication bias was examined by generating a funnel plot for outcomes that were reported by 10 or more studies.

RESULTS
In total, 2914 records were identified and 2593 screened, after exclusion of duplicates. Eighty-five full-text articles were assessed and 33 studies were included, with 30 reporting data in a format suitable for meta-analysis (online supplemental figure S1). Three studies were excluded from meta-analyses because of zero counts or missing data,\(^{26–28}\) another three studies reported on more than one outcome but had sufficient data for only one outcome (online supplemental table S5).\(^{29–31}\) The 33 studies reported on 60 outcomes. Twenty-one studies reported PTB, four–eight, 27–29, 31–43, three reported spontaneous abortion, three–four, 41–42, 45–46, nine reported perinatal mortality outcomes, eight reported LBW, and seven reported ophthalmia neonatorum (online supplemental tables S2–S4).

We included 14 cohort, 11 case-control and 8 cross-sectional studies published between 1976 and January 2020. The number of outcomes reported varied from 62 to 3172.\(^{46}\) Two-thirds (22/33) of studies took place in high-income and upper middle-income settings (table 1; online supplemental tables S2–S4); most took place in health facilities (28/33) and more than half were in urban locations (19/33). Thirteen studies reported participant’s age, 23 ethnicity, 6 smoking status and 4 reported multiple pregnancies (full descriptive details are available in online supplemental tables S6–S8).

Characteristics of specimen collection, timing and laboratory tests are reported in online supplemental tables S2–S4. Briefly, 25 studies reported the timing of specimen collection, of which 12 obtained specimens during pregnancy; 29–30, 32–34, 36–37, 43–45, 48, 50, 52. Two collected specimens intrapartum;\(^{36,51}\) 5 post partum;\(^{6,9,38,42}\) 3 during both the antenatal and postpartum period;\(^{35,39,47}\) the remaining three studies tested during pregnancy or intrapartum;\(^{41}\) intrapartum or post partum;\(^{7}\) and intrapartum and post partum.\(^{33}\) Most studies reported specimen type (26), with 24 collecting endocervical and/or vaginal swabs, five–nine, 26–27, 30–34, 36–44, 52. Twenty-nine reported type of laboratory test.\(^{4–9,26,27,30–39,41,42,44–47,49–52}\) Twenty studies reported provision of treatment at the time of NG diagnosis: eight treated all positive women,\(^{4,9,30,35,45,47,51,52}\) 12 treated some women.\(^{5,8,26,32,34,37–39,41,42,44,49}\) Provision of treatment was unclear in 12 studies,\(^{6,7,27–29,31,33,36,40,43,47,52}\) and 1 study did not provide treatment\(^{50}\) (online supplemental tables S9–S11).

Risk of bias
Based on the NICE checklists, of the 33 studies, 2 met all or most (+) checklist criteria,\(^{4,7}\) seven met all/ most or some (+/+) criteria,\(^{4,7}\) ten studies met some (+) criteria,\(^{4,7}\) nine met some or few/no criteria (−/−),\(^{4,7}\) and seven met few or no checklist criteria (−/−).\(^{4,7}\) We included 14 cohort, 11 case-control and 8 cross-sectional studies published between 1976 and January 2020. The number of outcomes reported varied from 62 to 3172.\(^{46}\) Two-thirds (22/33) of studies took place in high-income and upper middle-income settings (table 1; online supplemental tables S2–S4); most took place in health facilities (28/33) and more than half were in urban locations (19/33). Thirteen studies reported participant’s age, 23 ethnicity, 6 smoking status and 4 reported multiple pregnancies (full descriptive details are available in online supplemental tables S6–S8).

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| Study | OR (95% CI) | % Weight | Sample size |
|-------|-------------|----------|-------------|
| Cohort | 1.70 (0.80, 3.50) | 20.19 | 568 |
| Case control | 2.01 (0.91, 3.67) | 21.42 | 702 |
| Johnson et al. (2011) | 5.31 (1.57, 17.94) | 11.81 | 319 |
| Elliott et al. (1990) | 1.10 (0.90, 1.50) | 31.63 | 4095 |
| Hummell et al. (2017) | 2.92 (0.95, 0.50) | 79.81 |
| Bulte et al. (2019) | 2.06 (0.05, 4.03) | 79.81 |

Overall (I²=64.5%, p=0.024) 1.90 (1.14, 3.19) 100.00

with estimated predictive interval (0.36, 10.03)

NOTE: Weights are from random effects analysis.

Figure 2 Adjusted effect sizes for Neisseria gonorrhoeae during pregnancy and preterm birth.
Table 1  Summary, characteristics of included studies by country income group

| Study                | Study design | Specimen collection timing and type | Sample size for outcome of interest; number of adverse outcomes in women with gonorrhoea/total number of women with adverse outcome (%) | NICE checklist criteria fulfilled, internal/external validity* |
|---------------------|--------------|------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------|
| **High-income group** |              |                                     |                                                                                 |                                                             |
| Agger WA, et al53   | Cohort       | First or second trimester; cervical | 676; 0/54 (0)                                                                   | ++                                                          |
| Alger LS, et al54   | Case-control | Second or third trimester; cervical | 129; 6/45 (13)                                                                  | ++                                                          |
| Armosty MS, Steadman KT55 | Cross-sectional | First or third trimester or intrapartum; cervical | 4444; 50/613 (9) | 5065; 24/620 (4) | 4444; 52/851 (6) | 5065; 15/149 (10) | --/-- |
| Baer RL, et al43    | Cross-sectional | Second or third trimester; unclear | 31 720; NR                                                                      | ++                                                          |
| Burton AE, Thomas S45 | Case-control | First, second or third trimester; urine and vaginal | 760; 18/380 (5)                                                                | +/−                                                         |
| Charles et al66     | Cohort       | NR/Unclear; cervical                | 2160*; 0/0 (0)                                                                  | --/−                                                        |
| Choi SL, et al27    | Case-control | NR/Unclear; vaginal                 | 2171; 0/100 (0)                                                                | +/+                                                         |
| Edwards LE, et al46 | Case-control | Unclear; NR/unclear                 | 564; 22/57 (19)                                                                | +/−                                                         |
| Edwards RK, et al33 | Cohort       | NR/Unclear; cervical                | 134; 0/37 (0)                                                                  | +/+                                                         |
| Heumann CL, et al46 | Case-control | NR/Unclear; NR/unclear              | 4095; 93/353 (26)                                                             | +/−                                                         |
| Hill MG, et al29    | Cohort       | First, second or third trimester; NR/unclear | 982; 5/171 (1)                   | 931; 0/37 (0)                                                 | +/++                                                        |
| Johnson HL, et al46 | Case-control | NR/Unclear; NR/unclear              | 702; 13/135 (10)                                                               | +/++                                                        |
| Kataoka S, et al48  | Cohort       | First trimester; vaginal            | 877; 0/15 (0)                                                                  | +/−                                                         |
| Mann JR, et al28    | Cross-sectional | Unclear; NR/unclear               | 7931; 749/7931 (9)                                                            | +/−                                                         |
| Maxwell GL, Watson W35 | Case-control | Second or third trimester; cervical | NR; 11/182 (6)                                                                 | --/−                                                        |
| Stoll BJ, et al37   | Cohort       | First, second or third trimester; cervical | 11 018; 14/318 (4)                  | 11 018; 71/1754 (4)                                         | +/−                                                         |
| **Upper middle-income group** |              |                                     |                                                                                 |                                                             |
| Adachi K, et al47   | Cohort       | Intrapartum or post partum; urine   | 1373; 13/148 (9)                                                               | +/++                                                        |
| Donders GG, et al46 | Cohort       | NR/Unclear; cervical                | 167; 5/23 (17)                                                                 | +/−                                                         |
| Hitti J, et al46    | Case-control | Post partum; cervical               | 132; 1/661 (<1)                                                                | +/++                                                        |
| Moodley D, et al45  | Cohort       | First, second and third trimester and post partum; NR/unclear | 568; 13/157 (8)                  | 608; 9/77 (12)                                               | +/++                                                        |
| Nasution TA, et al47 | Cross-sectional | Intrapartum or post partum; vaginal, placental swab or blood | 601; 0/30 (0)                    | 80; 0/40 (0)                                                 | --/--                                                       |
| Pourabas B, et al46 | Cross-sectional | Third trimester; cervical             | 239; 1/29 (3)                                                                  | +/−                                                         |
| **Lower middle-income group** |              |                                     |                                                                                 |                                                             |
| Elliott B, et al46  | Case-control | Post partum; cervical               | 319; 18/160 (11)                                                               | ++/+                                                        |
| Galeaga FP, et al46 | Cross-sectional | Intrapartum; vaginal               | 154; 4/46 (9)                                                                  | +/−                                                         |
| Gichangi PB, et al46 | Cohort       | Post partum; cervical               | 203; 11/51 (22)                                                                | ++                                                          |
| Gichuhi S, et al46  | Case-control | Third trimester; cervical           | 445; 1/99 (1)                                                                  | ++                                                          |
| Laga M, et al46     | Cohort       | Post partum; cervical               | 781; 28/181 (15)                                                               | ++/−                                                        |
| Mason PR, et al46   | Cross-sectional | Intrapartum; cervical             | 105; 4/24 (17)                                                                 | ++/−                                                        |

Continued
between NG and spontaneous abortion (online supplemental figure S5).

### Premature rupture of membranes

Twelve studies reported on the association between NG in pregnancy and PROM; three cohort,26 29 34–36 five case-control,30 31 34 40 45 and four cross-sectional studies.31 41 43 46 Nine studies involving 42 168 women were included in the meta-analysis.7 8 23 34 35 37 41 43 45 46 The unadjusted summary OR for NG and PROM was 1.41 (95% CI 1.02 to 1.92; I² 59.2%; prediction interval 0.64 to 3.11) (table 2, online supplemental figure S6). None of the included studies reported a multivariable analysis.

### Perinatal mortality

Nine studies involving 21 854 women examined perinatal mortality outcomes: six cohort,7 34 35 37 47 48 two case-control,30 31 and one cross-sectional study.43 Of these, two reported neonatal mortality,7 33 two perinatal mortality,8 41 three stillbirths34 35 48 and two reported on both stillbirths and neonatal mortality.7 47 The unadjusted summary OR for NG and any perinatal mortality outcome was 2.16 (95% CI 1.35 to 3.46; I² 40.3%, prediction interval 0.69 to 6.74) (table 2, online supplemental figure S7). Two studies conducted a multivariable analysis for stillbirth. Moodley et al adjusted for age, number of pregnancies, socioeconomic status, HIV-1, CT and TV infection.30 The aOR was the same as the unadjusted OR (2.2; 95% CI 1.0 to 4.9). Kupka et al adjusted for gestational age, maternal literacy, history of stillbirth, CD4 count and previous hospitalisation.34 They reported relative risks and found a stronger association in the adjusted than the unadjusted model (9.74, 95% CI 2.52 to 37.59 vs 7.58, 95% CI 1.33 to 43.28), but CIs were wide and overlapping.

### Low birth weight

Eight studies involving at least 18 844 infants reported LBW: four cohort,7 5 5 7 34 49 three case-control6 45 and one cross-sectional study.42 The summary unadjusted OR for the association between NG and LBW was 1.66 (95% CI 1.12 to 2.48; I² 72.7%; prediction interval 0.51 to 5.38) (table 2, online supplemental figure S8). Five studies reported multivariable analyses,4 6 35 40 49 The studies used different variables, only four provided enough details to include in meta-analysis4 6 35 40 (online supplemental table S15). The summary aOR was 1.48

**Preterm birth**

Twenty-one studies reported on the association between NG in pregnancy and PTB. Eighteen studies involving at least 60 396 women were included in meta-analysis; nine cohort studies,7 7 29 32–37 three case-control4–6 8 38–40 and three cross-sectional studies.41–42 The overall unadjusted summary OR for NG and PTB was 1.55 (95% CI 1.21, 1.99; I² 61.1%; prediction interval 0.72, 3.35) (figure 1, table 1). Eleven studies were from high-income countries7 29 30 32–37 39 40 41 43 (table 1). NG was more strongly associated with PTB in non-high-income countries (OR 2.21, 95% CI 1.04 to 1.83; I² 68.6%) (online supplemental figures S3, S4).

In five studies, multivariable analysis was conducted. The variables adjusted for differed between studies (online supplemental table S15). The summary aOR for NG and PTB was 1.90 (95% CI 1.14 to 3.19; I² 64.5%); overall prediction interval 0.36 to 10.03 (figure 2, table 2).

### Spontaneous abortion

Three studies involving 6329 women reported on spontaneous abortion.34 41 44 All three were different study designs, and none reported a multivariable analysis. There was insufficient information from these studies to determine the strength of association.*
(95% CI 0.79 to 2.77; I² 64.5%; prediction interval 0.14 to 15.70) (table 2; online supplemental figure S9).

Ophthalmia neonatorum
Seven studies reported on the association between NG and ophthalmia neonatorum: three cohort,9 26 three cross-sectional10 32 51 and one case-control study.52 One was excluded from meta-analysis as there were no events. The six studies included in the meta-analysis involved at least 3741 infants. The unadjusted summary OR for NG and ophthalmia neonatorum was 4.21 (95% CI 1.36 to 13.04; I² 58%; prediction interval 0.17 to 104.58) (table 2, online supplemental figure S10). None of the included studies reported a multivariable analysis.

Sensitivity analysis
Sensitivity analysis was undertaken for all outcomes. Effect estimates from fixed effect meta-analyses were similar to those from random effects models but tended to be slightly lower (online supplemental table S16).

DISCUSSION
This systematic review included 33 studies for the qualitative analysis and 30 studies for meta-analysis. In studies that controlled for potential confounding, NG during pregnancy was associated with an increase in the adjusted odds of PTB of 1.90 (95% CI 1.14 to 3.19, five studies) and in the adjusted odds of LBW of 1.48 (95% CI 0.79 to 2.77, four studies). The odds of PROM, perinatal mortality and ophthalmia neonatorum were also increased in women with NG, but most studies of these outcomes did not provide estimates that controlled for confounding. There was insufficient evidence from studies of spontaneous abortion. The association between NG in pregnancy and PTB was stronger in studies conducted in low-income and middle-income countries than in high-income countries.

The main strength of this review was the use of a protocol19 to define the outcomes and analyses in advance and independent work by two reviewers to reduce bias in study selection, data extraction and risk of bias assessment. An additional strength is the calculation of prediction intervals for the summary estimates.24 With random effects meta-analysis, the summary OR is an average of the effect estimate and its 95% CI. The prediction interval gives information about the range of effect sizes across the settings in which studies included in the review were conducted.24 We combined effect estimates from different study designs if the stratified summary estimates were similar. The biases affecting individual studies and each observational study design differ, with some likely to overestimate the strength of association and others likely to underestimate it. Triangulation of findings across study designs is a strength of this review. Consistency in the direction and strength of effects can increase confidence in a causal interpretation, if confounding is addressed adequately.21 There are also weaknesses in the review methods. Despite searching multiple databases, our search strategy might have missed relevant studies, for example, in languages other than English or German.

Our searches did not find any other systematic review of the association between NG and adverse pregnancy outcomes. In narrative reviews, the findings tend to group different adverse outcomes together and to cite those from studies that find the strongest associations.1 54 The advantage of this review is the systematic inclusion of all eligible studies and examination of evidence separately for each outcome.

Our findings suggest that NG in pregnancy increases the risk of PTB and LBW. The certainty of evidence for causal associations is challenged by confounding and bias.55 In all observational study designs, confounding is an issue so the confounder-adjusted effect estimates are of most interest.53 In this systematic review, PTB and LBW were the only outcomes for which there were enough included studies to estimate a confounder-adjusted summary OR. For PTB, the summary aOR (1.90, 95% CI 1.14 to 3.19) was higher than the unadjusted OR, but the wide CI included the unadjusted summary estimate. For LBW, the 95% CI for the summary aOR (1.48, 95% CI 0.79 to 2.77) was compatible with there being no increased risk of LBW, but might reflect the small number of studies. The presence of co-infections, especially HIV, could also confound these associations. All studies reporting the outcomes PTB and LBW reported testing for other genital infections, but only Moodley et al, reporting from a high-burden setting, adjusted for co-infections (CT, TV and HIV)56 for these two outcomes. In that study, adjustment did not change the effect size. Of the other 18 studies reporting PTB and/or LBW, 15 reported co-infection with CT, four with TV and four with HIV. Each of these infections has been reported to be associated with LBW14 15 56 and PTB.15 36 Measurement bias might also have resulted in underestimation of the strength of association because, in most studies, women with NG had received treatment. These studies are measuring the outcome of treated NG, when the causal association of interest is with untreated NG.55 In this situation, cross-sectional studies that measure the presence of NG at the time of delivery are assessing the association with untreated infection. Although the onset of infection is unknown, adjusted estimates from such studies might be less biased than some cohort and case-control studies.55

For spontaneous abortion there were only three studies, with insufficient evidence to determine whether there is an association with NG. The association with ophthalmia neonatorum was strong and is known to be causal because there is evidence from randomised controlled trials that effective antiseptic or antimicrobial treatment prevents the condition.53 The association with perinatal mortality outcomes deserves further investigation to determine whether it is a consequence of PTB and LBW, or whether NG is an independent risk factor. The potential mechanisms linking NG to adverse perinatal outcomes are not well understood but NG might cause low-grade inflammation of the placenta and fetal membranes, increasing the risk of chorioamnionitis and thus PROM and PTB.58 If placental inflammation or infection of the amniotic cavity are implicated in the pathogenesis of PTB, the timing of NG infection and treatment during pregnancy might modify the risk. There was insufficient data in the included studies to formally examine the effects of these factors in the meta-analyses.

Future studies to investigate the role of NG as a cause of adverse pregnancy outcomes should be designed to address the limitations of many of the studies in this review. First, observational studies should collect data about potential confounding factors and be large enough to conduct multivariable analyses. Second, if treatment is given, the timing should be recorded so that study findings can be interpreted with this information. Third, samples should be taken for other STIs and vaginal microbiota so that the role of co-infections can be better understood. Randomised controlled trials are one way to examine the causal role of NG. Several trials of screening and treatment interventions are underway.59 60 However, it will be difficult to determine the effect of NG alone, because the interventions often include treatment for multiple infections. These trials are taking place in low-income and middle-income countries where the burden...
Women with *Neisseria gonorrhoeae* (NG) in pregnancy are more likely to experience adverse birth outcomes including preterm birth, premature rupture of membranes, low birth weight, perinatal mortality and ophthalmia neonatorum.

NG was more strongly associated with preterm birth in low-income and middle-income countries than in high-income countries.

Further studies are required to address the gap in evidence about the effects of testing and treatment of NG in pregnancy, particularly in low-income and middle-income settings.

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