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

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ABSTRACT

Objective To examine associations between *Neisseria gonorrhoeae* (NG) infection during pregnancy and the risk of preterm birth, spontaneous abortion, premature rupture of membranes, perinatal mortality, low birth weight and ophthalmia neonatorum.

Data sources We searched Medline, EMBASE, the Cochrane Library and Cumulative Index to Nursing and Allied Health Literature for studies published between 1948 and 14 January 2020.

Methods Studies were included if they reported testing for NG during pregnancy and compared pregnancy, perinatal and/or neonatal outcomes between women with and without NG. Two reviewers independently assessed papers for inclusion and extracted data. Risk of bias was assessed using established checklists for each study design. Summary ORs with 95% CIs were generated using random effects models for both crude and, where available, adjusted associations.

Results We identified 2593 records and included 30 in meta-analyses. Women with NG were more likely to experience preterm birth (OR 1.55, 95% CI 1.21 to 1.99, n=18 studies); premature rupture of membranes (OR 1.41, 95% CI 1.02 to 1.92, n=9); perinatal mortality (OR 2.16, 95% CI 1.35 to 3.46, n=9); low birth weight (OR 1.66, 95% CI 1.12 to 2.48, n=8) and ophthalmia neonatorum (OR 4.21, 95% CI 1.36 to 13.04, n=6). Summary adjusted ORs were, for preterm birth 1.90 (95% CI 1.14 to 3.19, n=5) and for low birth weight 1.48 (95% CI 0.79 to 2.77, n=4). In studies with a multivariable analysis, age was the variable most commonly adjusted for. NG was more strongly associated with preterm birth in low-income and middle-income countries (OR 2.21, 95% CI 1.40 to 3.48, n=7) than in high-income countries (OR 1.38, 95% CI 1.04 to 1.83, n=11).

Conclusions NG is associated with a number of adverse pregnancy and newborn outcomes. Further research should be done to determine the role of NG in different perinatal mortality outcomes because interventions that reduce mortality will have the greatest impact on reducing the burden of disease in low-income and middle-income countries.

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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 4–6] 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,[19] 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,[21] case-control and cohort studies,[22] 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 I^2 statistic to examine the level of between-study heterogeneity other than that due to chance.[23]

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.[24] 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

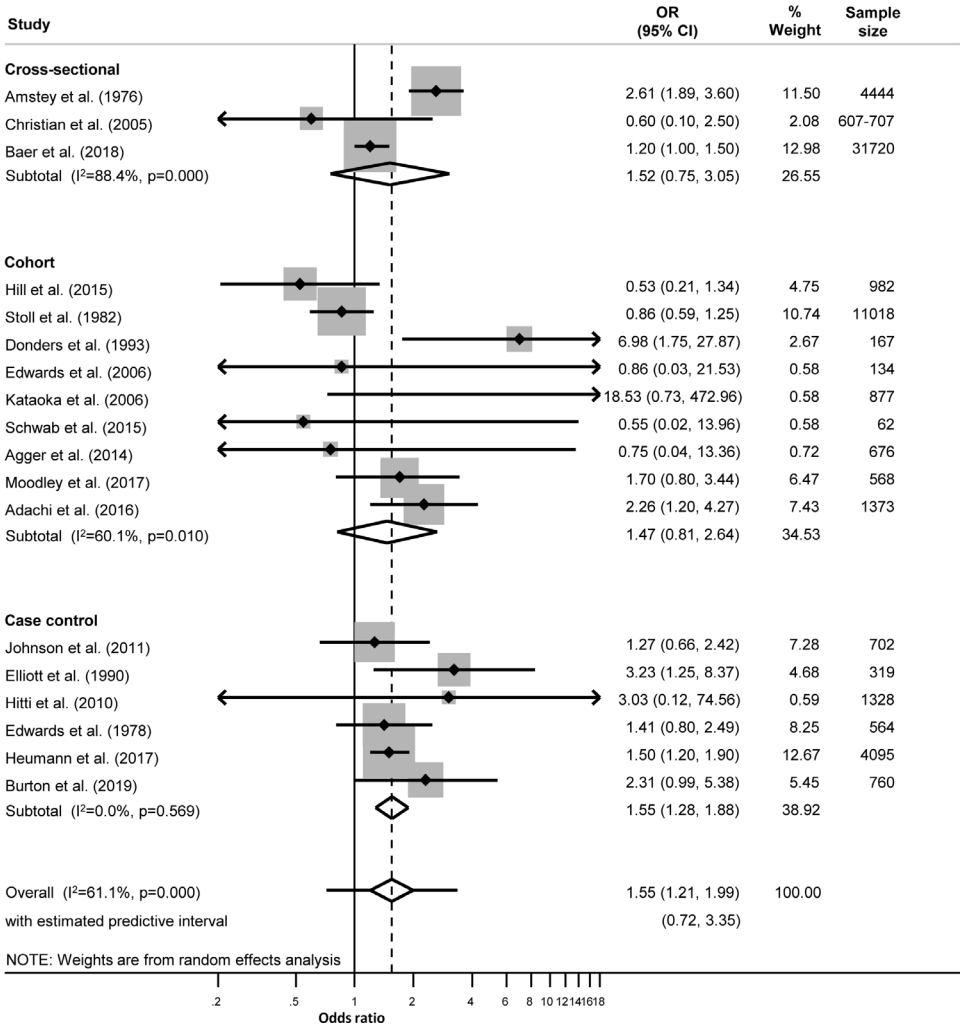

Figure 1 Unadjusted effect sizes for *Neisseria gonorrhoeae* during pregnancy and preterm birth.

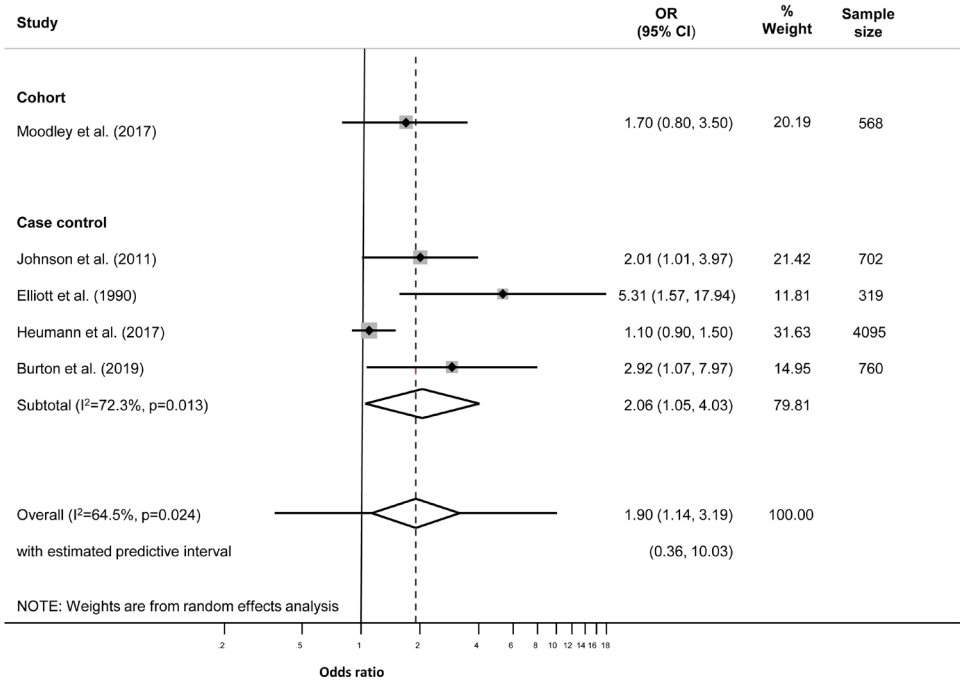

Figure 2 Adjusted effect sizes for *Neisseria gonorrhoeae* during pregnancy and preterm birth.

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,[4–8 27–29 31–43] 3 reported spontaneous abortion,[34 41 44] 12 reported PROM,[6 8 26 29–31 34 40 41 43 45 46] 9 reported perinatal mortality outcomes,[7 8 28 30 34 35 41 47 48] 8 reported LBW[4 6 7 35 37 40 42 49] and 7 reported ophthalmia neonatorum[7 9 26 42 50–52] (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[36] to 31 720.[43] 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] 2 collected specimens intrapartum;[46 51] 5 post partum;[6 9 38 42 49] 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.[31] Most studies reported specimen type (26), with 24 collecting endocervical and/or vaginal swabs.[5 6 9 26 27 30–34 36–39 41 44–52] Twenty-nine reported type of laboratory test.[4–9 26 27 29–39 41 42 44–47 49–52]

Twenty studies reported provision of treatment at the time of NG diagnosis: 8 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 46 48] and 1 study did not provide treatment[50] (online supplemental tables S9-S11).

Most studies (29) tested for other STI and genital infections: 6 tested for BV,[4 6 33 36 47 52] 25 tested for CT,[4–7 9 27–36 38–40 42 43 45–47 50 52] 9 tested for HIV,[4 6 7 35 44 47–49 52] 5 tested for MG,[27 32–34 38] 14 tested for syphilis[4–7 26 33 39 40 43 44 47–49 52] and 10 tested for TV[4 27 28 33 35 38 39 46 47 52] (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] 7 met all/ most or some (++/+),[6 29 35 38 40 43 47] 10 studies met some (+) criteria,[8 27 32 33 44–46 48 49 52] 7 met some or few/no criteria (+/−),[9 28 34 37 39 50 51] and 7 met few or no checklist criteria (−)[5 26 30 31 36 41 42] (table 1, online supplemental tables S12-S14). There was evidence of publication bias and other small study effects (Egger's test, p=0.008) for the association between NG and preterm birth (online supplemental figure S2).

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*
			PTB	Sp. ab.	PROM	PM	LBW	ON	
High-income group									
Agger WA, *et al*[32]	Cohort	First or second trimester; cervical	676; 0/54 (0)						+/+
Alger LS, *et al*[45]	Case-control	Second or third trimester; cervical			129; 6/45 (13)				+/+
Amstey MS, Steadman KT[41]	Cross-sectional	First or third trimester or intrapartum; cervical	4444; 56/613 (9)	5065; 24/620 (4)	4444; 52/851 (6)	5065; 15/149 (10)			–/–
Baer RJ, *et al*[43]	Cross-sectional	Second or third trimester; unclear	31 720; NR		31 720; 53/NR				+/++
Burton AE, Thomas S[39]	Case-control	First, second or third trimester; urine and vaginal	760; 18/380 (5)						+/–
Charles *et al*[26]	Cohort	NR/unclear; cervical			NR; 10/NR			2160*; 0/0 (0)	–/–
Choi SJ, *et al*[27]	Case-control	NR/unclear; vaginal	217†; 0/100 (0)						+/+
Edwards LE, *et al*[8]	Case-control	Unclear; NR/unclear	564; 22/57 (39)		564; 50/148 (34)	564; 5/11 (45)			+/+
Edwards RK, *et al*[33]	Cohort	NR/unclear; cervical	134; 0/37 (0)						+/+
Heumann CL, *et al*[40]	Case-control	NR/unclear; NR/unclear	4095; 93/353 (26)		4095; 90/416 (22)		4095; 80/266 (30)		+/++
Hill MG, *et al*[29]	Cohort	First, second or third trimester; NR/unclear	982; 5/171 (1)		933†; 0/37 (0)				+/++
Johnson HL, *et al*[4]	Case-control	NR/unclear; NR/unclear	702; 13/135 (10)				679; 8/112 (7)		++/++
Kataoka S, *et al*[34]	Cohort	First trimester; vaginal	877; 0/15 (0)	877; 0/5 (0)	877; 0/7 (0)	877; 0/1 (0)			+/–
Mann JR, *et al* [28]	Cross-sectional	Unclear; NR/unclear	7931†; 749/7931 (9)						+/–
Maxwell GL, Watson WJ[30]	Case-control	Second or third trimester; cervical			NR; 11/182 (6)	182; 1/8 (13)			–/–
Stoll BJ, *et al*[37]	Cohort	First, second or third trimester; cervical	11 018; 30/837 (4)			11 018; 14/319 (4)	11 018; 71/1754 (4)		+/–
Upper middle-income group									
Adachi K, *et al*[7]	Cohort	Intrapartum or post partum; urine	1373; 13/148 (9)			1373; 4/41 (10)	1373; 21/244 (9)	1373; 0/2 (0)	++/++
Donders GG, *et al*[5]	Cohort	NR/unclear; cervical	167; 5/29 (17)						–/–
Hitti J, *et al*[38]	Case-control	Post partum; cervical	1328; 1/661 (<1)						++/+
Moodley D, *et al*[35]	Cohort	First, second and third trimester and post partum; NR/unclear	568; 13/157 (8)			608; 9/77 (12)	550; 3/54 (6)		++/+
Nasution TA, *et al*[31]	Cross-sectional	Intrapartum or post partum; vaginal, placental swab or blood	60†; 0/30 (0)		80; 0/40 (0)				–/–
Pourabbas B, *et al*[50]	Cross-sectional	Third trimester; cervical						239; 1/29 (3)	+/–
Lower middle-income group									
Elliott B, *et al*[6]	Case-control	Post partum; cervical	319; 18/160 (11)		154; 4/46 (9)		319; 18/160 (11)		++/+
Galega FP, *et al*[51]	Cross-sectional	Intrapartum; vaginal						296; 12/12 (100)	+/–
Gichangi PB, *et al*[49]	Cohort	Post partum; cervical					203; 11/51 (22)		+/+
Gichuhi S, *et al*[52]	Case-control	Third trimester; cervical						445; 1/99 (1)	+/+
Laga M, *et al*[9]	Cohort	Post partum; cervical						781; 28/181 (15)	+/–
Mason PR, *et al*[46]	Cross-sectional	Intrapartum; cervical			105; 4/24 (17)				+/+

Continued

Table 1 Continued

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*
			PTB	Sp. ab.	PROM	PM	LBW	ON	
Warr AJ, *et al*[47]	Cohort	Second and third trimester and post partum; vaginal				1221; 1/19 (5)			++/+
Schwab FD, *et al*[36]	Cohort	Second trimester; vaginal swab	62; 0/23 (0)						–/–
Temmerman M, *et al*[44]	Case-control	First, second or third trimester; cervical		387; 10/193 (5)					+/+
Low-income group									
Christian P, *et al*[42]	Cross-sectional	Post partum; urine	607–707; NR				607–707; NR	607–707; NR	–/–
Kupka R, *et al*[48]	Cohort	First, second and third trimester; cervical or vaginal				946; 1/21 (5)			+/+

*++, all or most checklist criteria fulfilled; +, some of checklist criteria fulfilled; –, few or no checklist criteria fulfilled.
†Study not included in meta-analysis.
LBW, low birth weight; NICE, National Institute of Health and Care Excellence; NR, not reported; ON, ophthalmia neonatorum; PM, perinatal mortality; PROM, premature rupture of membranes; PTB, preterm birth; Sp. ab., spontaneous abortion.

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,[5 7 29 32–37] six case-control[4 6 8 38–40] and three cross-sectional studies.[41–43] The overall unadjusted summary OR for NG and PTB was 1.55 (95% CI 1.21, 1.99; I^2 61.1%; prediction interval 0.72, 3.35) (figure 1, table 2). Eleven studies were from high-income countries[4 8 29 32–34 37 39 41 43 45] (table 1). NG was more strongly associated with PTB in non-high-income countries (OR 2.21, 95% CI 1.40 to 3.48; I^2 14.7%) than in high-income countries (OR 1.38, 95% CI 1.04 to 1.83; I^2 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; I^2 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 between NG and spontaneous abortion (online supplemental figure S5).

Table 2 Summary estimates from random effects analyses

Adverse outcome	Number of studies	Summary estimate OR (95% CI)	I^2 (%)	Prediction interval
Preterm birth				
Adjusted	5	1.90 (1.14 to 3.19)	64.5	0.36 to 10.03
Unadjusted	18	1.55 (1.21 to 1.99)	61.1	0.72 to 3.35
Low birth weight				
Adjusted	4	1.48 (0.79 to 2.77)	49.5	0.14 to 15.70
Unadjusted	8	1.66 (1.12 to 2.48)	72.7	0.51 to 5.38
Premature rupture of membrane	9	1.41 (1.02 to 1.92)	59.2	0.64 to 3.11
Spontaneous abortion*	3	NA	NA	NA
Perinatal mortality	9	2.16 (1.35 to 3.46)	40.3	0.69 to 6.74
Ophthalmia neonatorum	6	4.21 (1.36 to 13.04)	58.0	0.17 to 104.58

*Each study had a different design, therefore it was not appropriate to report a summary estimate for this outcome.
NA, not applicable.

Premature rupture of membranes

Twelve studies reported on the association between NG in pregnancy and PROM; three cohort,[26 29 34] five case-control[6 8 30 40 45] and four cross-sectional studies.[31 41 43 46] Nine studies involving 42 168 women were included in the meta-analysis.[6 8 31 34 40 41 43 45 46] The unadjusted summary OR for NG and PROM was 1.41 (95% CI 1.02 to 1.92; I^2 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[8 30] and one cross-sectional study.[41] Of these, two reported neonatal mortality,[7 30] two perinatal mortality,[8 41] three stillbirths[34 35 48] and two reported on both stillbirths and neonatal mortality.[37 47] The unadjusted summary OR for NG and any perinatal mortality outcome was 2.16 (95% CI 1.35 to 3.46; I^2 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.[35] 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.[48] 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 35 37 49] three case-control[4 6 40] 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; I^2 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 adjusted for different variables, only four provided enough details to include in meta-analysis[4 6 35 40] (online supplemental table S15). The summary aOR was 1.48

(95% CI 0.79 to 2.77; I^2 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,[7 9 26] three cross-sectional[42 50 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; I^2 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 protocol[19] 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.[53] 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)[35] 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 LBW[14 15 56] and PTB.[15 17 56] 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.[57] 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

of STIs and of adverse pregnancy outcomes is highest.[11 12] Our review also found that the strength of association between NG and PTB was greater in low-income and middle-income than in high-income settings. In summary, this review suggests that NG is causally associated with PTB and LBW. Further research should be done to determine the role of NG in different perinatal mortality outcomes because interventions that reduce mortality will have the greatest impact on reducing the burden of disease in low-income and middle-income countries.

Key messages

- 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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