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MAJOR ARTICLE

The Impact of *Neisseria gonorrhoeae* Mono- and Coinfection on Adverse Pregnancy Outcomes

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Background. Sexually transmitted infections (STIs) have recently been linked to hypertensive disorders of pregnancy (HDP). However, the impact of *Neisseria gonorrhoeae* on risk of HDP is not well understood. This study determined the impact of gonorrhea and gonorrhea coinfection on HDP and other adverse pregnancy outcomes in a population with a high screening rate and presumed treatment.

Methods. This retrospective study included 29 821 singleton births between 2016 and 2021. The STI testing results, demographic variables, and pregnancy outcomes were identified from electronic health records. The HDP were primary outcomes of interest including gestational hypertension, preeclampsia, and superimposed preeclampsia. We further examined preeclampsia subtypes defined by severe features and gestational age of delivery (term and preterm preeclampsia). Secondary outcomes included preterm premature rupture of membranes, chorioamnionitis, and preterm delivery. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Models were adjusted for maternal age, maternal race/ethnicity, and smoking.

Results. Gonorrhea screening occurred in 95% of the population. Gonorrhea increased the odds of preterm preeclampsia (adjusted OR [ORadj.], 1.95; 95% CI, 1.02–3.73) and preterm birth (ORadj., 1.78; 95% CI, 1.22–2.60). Furthermore, gonorrhea-chlamydia coinfection was associated with preterm birth (ORadj., 1.77; 95% CI, 1.03–3.04). However, results were similar when we examined gonorrhea monoinfection (ORadj., 1.76; 95% CI, 1.04–2.97).

Conclusions. Among a diverse population of pregnant individuals, gonorrhea increased odds of preterm preeclampsia and preterm delivery Further research is needed to determine the burden of STIs on HDP, including investigations into biological effects during pregnancy.

Keywords. gonorrhea; preeclampsia; preterm birth; sexually transmitted infections.

Neisseria gonorrhoeae is a bacterial sexually transmitted infection (STI) that is known to cause pelvic inflammatory disease and can subsequently result in ectopic pregnancy and tubal factor infertility [1]. Several factors have improved prevention and control of gonorrhea and other bacterial STIs including the introduction of nucleic acid amplification tests (NAATs) in the early 1990s, which has increased diagnostic performance [2, 3]. In addition, given the asymptomatic nature and nonspecific symptoms of bacterial STIs [2, 4], national screening programs have been implemented. The Centers for Disease Control and Prevention (CDC) recommends screening for chlamydia and gonorrhea for nonpregnant (when sexually active) and pregnant women <25 years of age or women at high risk [5]. However, rates of gonorrhea have been steadily climbing with an increase of 89% from 2010 to 2018 [6]. Despite screening recommendations [6, 7], uptake during pregnancy is suboptimal, and there are reports of significant delays in treatment and antibiotic resistance [8–10]. Thus, alternative preventative strategies are needed, but this requires that we better understand how gonorrhea directly impacts specific adverse pregnancy outcomes [9, 11, 12].

A recent meta-analysis [13] suggests a moderate association between gonorrhea and preterm birth, preterm premature rupture of membranes (pPROM), and perinatal mortality, but most of these studies did not include multivariable analyses, and they were limited by low screening rates in the target population. In recent studies, chlamydia and syphilis have been linked to hypertensive disorders of pregnancy (HDP) [14–17], which include a spectrum of disorders (gestational hypertension, preeclampsia, and superimposed preeclampsia) [18]. Preeclampsia, the new onset of hypertension and systemic organ dysfunction, is an HDP that imposes a great risk of

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maternal mortality and morbidity [19]. Preeclampsia is distinguishable from superimposed preeclampsia, which occurs among individuals entering pregnancy with chronic hypertension, and gestational hypertension, which does not result in multiple organ dysfunction. Chlamydia has been associated with superimposed preeclampsia and preeclampsia with severe features, whereas syphilis has been associated with gestational hypertension [14–17]. Studies of gonorrhea and HDP are rare [14, 15], and it remains unknown whether gonorrhea has any impact on various HDP.

Another relatively understudied area is the effect of STI coinfection on HDP. Coinfection between chlamydia and gonorrhea is frequent (~10%–40%) [20] and results in a unique endometrial transcriptional signature of T-cell signaling, protein synthesis, and mitochondrial oxidative phosphorylation, resulting in immune evasion and enhanced pathology among nonpregnant women [21]. Immune dysfunction very early in pregnancy is one pathway leading to placental-mediated diseases such as HDP [22]. In a recent, large study of US natality files, researchers found that chlamydia and gonorrhea coinfections with syphilis are associated with gestational hypertension [14]. However, the researchers were unable to examine other HDP. The separation of different HDP is important because these conditions have varying pathophysiologies, severity, and clinical management [18].

The objective of this study was to determine whether gonorrhea and gonorrhea coinfection with chlamydia was associated with HDP including preeclampsia (defined by severity and gestational age of delivery), gestational hypertension, and superimposed preeclampsia. Secondary exposures were positive diagnosis with other STIs, and secondary outcomes were preterm birth, pPROM, and chorioamnionitis. We hypothesized that gonorrhea may be associated with preeclampsia, particularly severe subtypes, and that coinfection with chlamydia may further enhance risk.

METHODS

In this retrospective cohort study, we used 29 821 records of patients with singleton pregnancies who obtained prenatal care and delivered at the University of Texas Medical Branch (UTMB) in Galveston, Texas between October 1, 2016 and August 13, 2022. All data were obtained from electronic medical records using demographic data collected, internal laboratory test codes, *International Classification of Diseases, Tenth Revision* (ICD-10) diagnostic codes, and Current Procedural Terminology (CPT) codes. This study was approved by the UTMB Institutional Review Board.

Standard protocol at UTMB for pregnant individuals includes testing all patients at their first prenatal visit for *N gonorrhoeae*, our primary exposure of interest, as well as *Chlamydia trachomatis* and syphilis, our secondary exposures of interest. In addition, patients are routinely tested for human immunodeficiency virus (HIV) and hepatitis B. In brief, vaginal swabs or urine are used to test for *C trachomatis* and *N gonorrhoeae* using NAATs [7, 23]. Blood samples are obtained to test for (1) syphilis by rapid plasma regain, (2) HIV with an antibody test, and (3) hepatitis B with hepatitis B surface antigen (HBsAg) test. Within the population under study, 94.6% were tested for gonorrhea and chlamydia, 96.2% for syphilis, 99.9% for hepatitis B, and 99.6% for HIV.

The ICD-10 codes were used to identify each adverse pregnancy outcome (Supplementary Table 1). Our primary outcomes were HDP as diagnosed by the American College of Obstetrics and Gynecology (ACOG) [24]. Preeclampsia is defined by systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg on at least 2 occasions 4 hours apart after 20 weeks gestation but before the onset of labor (or during postpartum) and proteinuria (24-hour urinary protein ≥300 mg or spot urine protein to creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥++). In the absence of proteinuria, the new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral visual symptoms can be used to diagnosis preeclampsia. Preeclampsia is heterogenous with multiple subtypes that should be explored as separate outcomes when possible [18]. Therefore, we further examined preeclampsia with severe features, which is defined as preeclampsia plus 1 or more of the following: (1) systolic blood pressure ≥160 mmHg; (2) diastolic blood pressure ≥110 mmHg; (3) proteinuria ≥5 grams/24 hours; (4) elevated liver enzymes; or (5) platelet count ≤100 000. We further examined preeclampsia defined by gestational age of delivery. Preterm preeclampsia is preeclampsia with delivery <37 weeks gestation. Although term preeclampsia is preeclampsia with term deliveries ≥37 weeks gestation. Superimposed preeclampsia occurs among those entering pregnancy with chronic hypertension that develop worsening high blood pressure and protein in the urine or other symptoms of preeclampsia. Gestational hypertension is the new onset of elevated blood pressure after 20 weeks gestation, as described above, without the development of proteinuria or evidence of systemic organ dysfunction. All women with HDP are treated according to standard protocols at UTMB.

Secondary outcomes included pPROM and chorioamnionitis. Preterm birth was defined as a gestational age at delivery of <37 weeks of gestation. Data on type of delivery (vaginal vs cesarean) were also obtained.

Maternal ethnicity/race (Hispanic or Latina, Non-Hispanic White, Non-Hispanic Black, Other, and Unknown), language (English, Spanish, and Other), and citizenship (yes, no, and unknown) were obtained from electronic health records. Maternal age at delivery was calculated by using the delivery date subtracted by the mother's birth date and categorized into 3 groups (<26, 26–35, and 36+ years of age). Drug and alcohol use were

obtained from medical records, but prevalence was too low to include in analyses. The Exihauser Comorbidity Index was calculated through the SAS Macro published by the Manitoba Centre for Health Policy by using the mother's diagnosis codes within 1 year before the delivery. We then categorized the sum of Elixhauser Comorbidity Index for each patient into 4 groups (0, 1, 2, 3+). Tobacco use was identified through ICD-10 codes Z87.891, Z72.0, F17.2, and O99.33. Obesity/overweight was identified through ICD-10 code E66.

Statistical Analysis

Frequencies of maternal demographics described above were calculated for our cohort. We decided a priori to adjust all models for maternal age, ethnicity/race, and smoking because these factors are associated with STIs and HDP [19, 25–28]. We considered adjusting for other STIs in the models, but this resulted in multicollinearity, given the high correlation among STIs. To assess the associations between *N gonorrhoeae* and our primary and secondary outcomes, we used multivariable logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Associations among *C trachomatis*, syphilis, HIV, hepatitis B, and adverse pregnancy outcomes were also determined (Supplementary Materials). As a secondary analysis, we examined the association between *N gonorrhoeae* and *C trachomatis* coinfection and adverse pregnancy outcomes using the same methods described above. To account for small sample size, we used the penalized likelihood approach, when necessary, because this approach addresses issues of separability and reduces bias. We attempted to examine associations between those who had a second infection in the third trimester of pregnancy, but the sample was too small for analysis. Finally, to assess the effect of unmeasured confounding, E-values were calculated [29]. The E-value is the minimum strength of association, on the odds ratio scale with outcome population prevalence <15%, that an unmeasured confounder would need to have with both exposure and outcome to fully explain away the observed exposure-outcome association, conditional on covariates included in the model. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Patient Consent Statement

This study was a retrospective medical chart review, and we were not in contact with human subjects to obtain consent. No personal identifiers were obtained from medical records. The UTMB Institutional Review Board approved this research.

RESULTS

Population Demographics and Rates of Maternal Outcomes

Most patients were between the ages of 26 and 35 years (48%) and approximately 60% were of Hispanic ethnicity (Table 1).

Table 1. Demographics Characteristics of the Study Population

Patient Characteristic	N (%)
Total births	29 821
Age Category	…
<26	12 262 (41.1%)
26–35	14 181 (47.6%)
36+	3378 (11.3%)
Patient Ethnicity (Ethnicity + Race)	…
Hispanic	17 742 (59.5%)
Non-Hispanic White	7330 (24.6%)
Non-Hispanic Black	3496 (11.7%)
Other	1167 (3.9%)
Unknown	86 (0.3%)
Primary Language	…
English	20 166 (67.6%)
Spanish	9370 (31.4%)
Other	285 (1.0%)
US Citizenship	…
Yes	17 830 (59.8%)
No	11 971 (40.1%)
Unknown	20 (0.1%)
Elixhauser Comorbidities	…
0	14 153 (47.5%)
1	12 245 (41.2%)
2	2656 (8.9%)
3+	767 (2.6%)
Tobacco Use	…
Yes	2200 (7.4%)
No	27 621 (92.6%)
Obesity/Overweight	…
Yes	12 327 (41.3%)
No	17 494 (58.7%)

NOTES: Tobacco use was identified by *International Classification of Diseases, Tenth Revision* (ICD-10) codes: Z87.891, Z72.0*, F17.2*, and O99.33*. Obesity/overweight was identified by ICD-10 code: E66 for patients within 12 months before delivery.

Approximately 40% were foreign-born individuals. Almost half (48%) had no comorbidities, whereas 41% had 1 comorbidity, and approximately one tenth had 2 comorbidities. Most were nonsmokers (93%) and 40% were either obese or overweight. The prevalence of adverse pregnancy outcomes ranged from 1.0% to 9.3% (Table 2). Of our primary outcomes, 11% had an HDP. Among HDP, 6.3% had preeclampsia, 5.4% has gestational hypertension, and 1.0% had superimposed preeclampsia. Among preeclampsia subtypes, 2.3% had preeclampsia with severe features, 2.5% had preterm preeclampsia, and 3.8% had term preeclampsia. The prevalence of preterm birth was 9.3% and chorioamnionitis 2.0%, and more than one third (35.9%) had a Cesarean section. These rates are expected because our hospital is a referral hospital and is a higher risk population.

Neisseria gonorrhoeae and Hypertensive Disorders of Pregnancy

Among the 27 984 participants who were tested for *N gonorrhoeae* during their pregnancy, 215 (0.7%) were positive

Table 2. Distribution of Maternal Outcomes Among the Study Population

Outcome	N (%)
Any Hypertensive Disorder of Pregnancy[a]	…
Yes	3291 (11.0%)
No	26 530 (89.0%)
Superimposed Preeclampsia	…
Yes	293 (1.0%)
No	29 528 (99.0%)
Gestational Hypertension	…
Yes	1615 (5.4%)
No	28 206 (94.6%)
Preeclampsia	…
Yes	1875 (6.3%)
No	27 946 (93.7%)
Preterm Preeclampsia[b]	…
Yes	732 (2.5%)
No	29 061 (97.5)
Term Preeclampsia[b]	…
Yes	1139 (3.8%)
No	28 654 (96.2%)
Preeclampsia With Severe Features	…
Yes	686 (2.3%)
No	29 135 (97.7%)
Preterm Premature Rupture of Membranes	…
Yes	601 (2.0%)
No	29 220 (98.0%)
Premature Birth, Delivery <37 Weeks Gestation	…
Yes	2781 (9.3%)
No	27 012 (90.7%)
Gestational Age Missing	28 (0.1%)
Chorioamnionitis	…
Yes	604 (2.0%)
No	29 217 (98.0%)
Type of Delivery	…
Vaginal	19 021 (64.1%)
Cesarean	10 800 (35.9%)

[a]Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, and superimposed preeclampsia.

[b]Preterm preeclampsia is defined as preeclampsia with a preterm delivery <37 weeks gestation. Term preeclampsia is defined as preeclampsia with a term delivery ≥37 weeks gestation. A total of 3 individuals with preeclampsia did not have gestational age of delivery data and could not be separated into term and preterm preeclampsia groups.

(Table 3). The frequency of HDP (gestational hypertension, preeclampsia, superimposed preeclampsia) was higher in *N gonorrhoeae*-positive than -negative participants (14.9% vs 10.9%). Similar trends were observed for individual HDP including preeclampsia (8.4% vs 6.2%) and gestational hypertension (7.4% vs 5.4%). There was little difference for superimposed preeclampsia (0.9% vs 1.0%). In multivariable analyses, confidence intervals overlapped 1, and there were no associations observed between gonorrhea and each HDP.

For preeclampsia subtypes, participants who tested positive for gonorrhea were slightly more likely to have preeclampsia with severe features (4.2% vs 2.2%) and preterm preeclampsia (4.7% vs 2.4%) but not term preeclampsia (3.7% vs 3.8%). In multivariable analyses, the odds ratio of preeclampsia with severe features was elevated, but 95% CIs overlapped 1 (adjusted OR [ORadj.], 1.80; 95% CI, .91–3.56), which may be due to the small sample for this subgroup. *Neisseria gonorrhoeae* was associated with preterm preeclampsia (ORadj., 1.95; 95% CI, 1.02–3.73). The E-value for the point estimate and confidence interval is 3.73 (1.16).

Neisseria gonorrhoeae and Other Adverse Pregnancy Outcomes

For our secondary outcomes, those with *N gonorrhoeae* had a higher frequency of preterm birth (15.4% vs 9.2%) compared those who were negative (Table 3). There was little difference in the frequency of pPROM (2.8% vs 2.0%) or chorioamnionitis (2.8% vs 2.1%). In multivariable analyses, *N gonorrhoeae* was associated with preterm birth (ORadj. 1.78, 95% CI 1.22–2.60). The E-value for the point estimate and 95% confidence interval is 2.96 (1.74).

Neisseria gonorrhoeae Coinfection and Hypertensive Disorders of Pregnancy

One hundred seven (0.4%) patients had coinfection with *N gonorrhoeae* and *C trachomatis* (Table 4). Within this group, the frequencies of HDP were only slightly higher for those with coinfection with chlamydia compared to those negative for both pathogens (12.2% vs 10.8%). Results were similar for preeclampsia (8.4% vs 6.1%). No patients developed superimposed preeclampsia in the coinfection group, and rates of gestational hypertension (4.7% vs 5.3%) were slightly lower for those with coinfection. There were no associations found in the multivariable models. It is interesting to note that those with gonorrhea monoinfection (N = 108) had elevated frequencies of HDP (17.6%), but confidence intervals overlapped 1 (ORadj., 1.53; 95% CI, .93–2.53). Trends were similar for each HDP, but associations were not significant.

Those with coinfection were only slightly more likely to have preeclampsia with severe features (2.8% vs 2.2%), preterm preeclampsia (4.7% vs 2.4%), and term preeclampsia (3.7% vs 3.8%). Although the coinfection group had elevated odds of preterm preeclampsia (ORadj., 2.25; 95% CI, .94–5.38), the 95% CIs overlapped 1. Among those with gonorrhea monoinfection, frequencies were similar to the coinfection group, except there was an increased odds of preeclampsia with severe features (5.6% vs 2.2%; ORadj., 2.41; 95% CI, 1.05–5.52).

Neisseria gonorrhea Coinfection and Adverse Pregnancy Outcomes

When secondary outcomes were examined, we found that those with coinfection had a higher frequency of preterm birth (15.9% vs 9.3%), pPROM (3.7% vs 2.0%), and chorioamnionitis (2.8% vs 2.0%). In multivariable analyses, there was no association with pPROM (ORadj., 1.83; 95% CI, .70–4.78) or chorioamnionitis (ORadj., 1.20; 95% CI, .41–3.53). Those with *N gonorrhoeae* and *C trachomatis* coinfection had increased

Table 3. Association Between Gonorrhea and Adverse Pregnancy Outcomes

Adverse Pregnancy Outcome	Gonorrhea Negative (N = 27 984)	Gonorrhea Positive (N = 215)	OR, 95% CI	Adjusted OR, 95% CI
Hypertensive disorders of pregnancy[a]	3044 (10.9%)	32 (14.9%)	1.43, .98–2.09	1.26, .86–1.85
Superimposed preeclampsia	270 (1.0%)	2 (0.9%)	1.20, .34–4.21	1.30, .37–4.58
Preeclampsia	1734 (6.2%)	18 (8.4%)	1.39, .85–2.25	1.29, .79–2.10
Gestational hypertension	1502 (5.4%)	16 (7.4%)	1.42, .85–2.37	1.19, .71–1.99
Preterm preeclampsia[b]	666 (2.4%)	10 (4.7%)	2.00, 1.06–3.79	1.95, 1.02–3.73
Term preeclampsia[b]	1066 (3.8%)	8 (3.7%)	0.98, .48–1.98	0.89, .44–1.81
Preeclampsia with severe features	619 (2.2%)	9 (4.2%)	1.93, .99–3.78	1.80, .91–3.56
Preterm birth	2566 (9.2%)	33 (15.4%)	1.81, 1.24–2.62	1.78, 1.22–2.60
pPROM	555 (2.0%)	6 (2.8%)	1.42, .63–3.21	1.25, .55–2.84
Chorioamnionitis	581 (2.1%)	6 (2.8%)	1.36, .60–3.06	1.12, .49–2.55

Abbreviations: CI, confidence interval; OR, odds ratio; pPROM, preterm premature rupture of membranes.

NOTES: Logistic regression was used to calculate ORs and CIs. Models were adjusted for maternal age, ethnicity, and smoking.

[a]Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, and superimposed preeclampsia.

[b]Preterm preeclampsia is defined as preeclampsia with a preterm delivery <37 weeks gestation. Term preeclampsia is defined as preeclampsia with a term delivery ≥37 weeks gestation. Three individuals with preeclampsia did not have gestational age of delivery data and could not be separated into term and preterm preeclampsia groups.

Table 4. Association Between Gonorrhea-Chlamydia Coinfection and Adverse Pregnancy Outcomes

Adverse pregnancy outcome	Negative (N = 25 953)	Coinfection (N = 107)	OR, 95% CI	Adjusted OR, 95% CI
Hypertensive disorders of pregnancy[a]	2801 (10.8%)	13 (12.2%)	1.14, .64–2.04	1.02, .57–1.83
Superimposed Preeclampsia	256 (1.0%)	0 (0.0%)	[b]	[b]
Preeclampsia	1591 (6.1%)	9 (8.4%)	1.48, .76–2.89	1.39, .71–2.74
Gestational hypertension	1385 (5.3%)	5 (4.7%)	0.87, .35–2.14	0.73, .29–1.80
Preterm Preeclampsia[b]	618 (2.4%)	5 (4.7%)	2.20, .93–5.23	2.25, .94–5.38
Term Preeclampsia	971 (3.8%)	4 (3.7%)	1.00, .37–2.72	0.91, .33–2.48
Preeclampsia with severe features	571 (2.2%)	3 (2.8%)	1.28, .41–4.05	1.21, .38–3.87
Preterm birth	2406 (9.3%)	16 (15.9%)	1.74, 1.02–2.97	1.77, 1.03–3.04
pPROM	518 (2.0%)	4 (3.7%)	2.13, .82–5.53	1.83, .70–4.78
Chorioamnionitis	515 (2.0%)	3 (2.8%)	1.65, .57–4.84	1.20, .41–3.53

Abbreviations: CI, confidence interval; OR, odds ratio.

NOTE: Models were adjusted for maternal age, ethnicity, and smoking.

[a]Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, and superimposed preeclampsia.

[b]Preterm preeclampsia is defined as preeclampsia with a preterm delivery <37 weeks gestation. Term preeclampsia is defined as preeclampsia with a term delivery ≥37 weeks gestation. Three individuals with preeclampsia did not have gestational age of delivery data and could not be separated into term and preterm preeclampsia groups.

odds of preterm birth (ORadj., 1.77; 95% CI, 1.03–3.04). However, trends were almost identical to those with gonorrhea monoinfection (15.7% vs 9.2%; ORadj., 1.76; 95% CI, 1.04–2.97). The E-value for the point estimate and 95% confidence interval is 2.94 (1.21).

Supplementary Tables 2–6 show data on other STIs and adverse pregnancy outcomes. Although crude analyses showed an association between chlamydia and term preeclampsia (OR, 1.25; 95% CI, 1.01–1.54) and chorioamnionitis (OR, 1.65; 95% CI, 1.28–2.12), after adjustments the 95% CIs included 1 for both outcomes (preterm preeclampsia, ORadj. = 1.20 and 95% CI = .97–1.49; chorioamnionitis, ORadj. = 1.23 and 95% CI = 0.95–1.59). For syphilis, hepatitis B, and HIV, we found no associations with any adverse pregnancy outcome.

DISCUSSION

Our findings add to the limited literature on *N gonorrhoeae* and HDP. In a diverse population of pregnant individuals with a high prenatal STI screening rate, we found that *N gonorrhoeae* infection was associated with elevated odds of preterm preeclampsia; moreover, *N gonorrhoeae* monoinfection and *N gonorrhoeae* coinfection with *C trachomatis* increased the odds of preterm birth. Although similar trends were observed between coinfection and preterm preeclampsia, the confidence intervals lacked precision and overlapped 1. Therefore, coinfection did not seem to drive the association because we found similar trends with monoinfection. The results are significant given the prevalence of STIs and adverse pregnancy outcomes in the US population [2, 30] with high burden in racial/ethnic minorities [27, 31]. For example, studies conducted in primarily

non-Hispanic Black populations report rates of chlamydia and gonorrhea during pregnancy of 7%–9% and 1%, respectively [9, 32]. Our study population was primarily Hispanic, and studies conducted in similar populations have found chlamydia rates of 5%–8% and gonorrhea rates of 1% [33, 34]. Further research is needed to determine whether our observed associations are reproducible in other populations. Furthermore, there is a need to determine which biological mechanisms may be impacted by *N gonorrhoeae* during pregnancy.

Prenatal infection with *N gonorrhoeae* has been previously linked to preterm birth [35–38], but few studies have examined the relationship between gonorrhea mono/coinfection and HDP. In a study using 2019 US natality files, Felske et al [14] found an association between *N gonorrhoeae* and gestational hypertension as well as preterm birth. Gonorrhea/chlamydia coinfection was not associated with any adverse outcomes in that study. Similarly, Gao et al [38] used birth certificate data to observe higher rates of gestational hypertension and preterm birth among those with prenatal gonorrhea. However, birth certificate records have lower sensitivity for maternal outcomes such as gestational hypertension [39], and these studies were unable to distinguish gestational hypertension from preeclampsia. In clinical settings, preeclampsia is diagnosed as the new onset of hypertension and proteinuria or evidence of systemic organ dysfunction after 20 weeks gestation [40]. However, these symptoms do not determine severity [41] and clinical presentation remains heterogeneous. Thus, lack of consideration of subtypes often limits the ability to identify risk and predictive factors [42]. In a recent study of 38 000 prenatal records, researchers examined preeclampsia subtypes defined by severity [15] but found no association between gonorrhea and gestational hypertension, mild preeclampsia, or preeclampsia with severe features. They did find that those with gonorrhea, but without a documented CDC-recommended treatment, had an increased risk of preeclampsia with severe features. However, they were unable to examine gonorrhea coinfection due to sample size and lower frequency of gonorrhea in their population. Although we observed trends towards an association between gonorrhea and preterm preeclampsia, researchers in other studies did not include this outcome in their investigations. Additional studies will be needed to determine whether gonorrhea has any impact on the risk of preeclampsia, especially severe subtypes.

The biological mechanisms that link *N gonorrhoeae* to preterm preeclampsia are not clear. Because most are asymptomatic [2, 4], infections detected at the first prenatal visit may likely be chronic, increasing the likelihood that dysfunctional immune responses are present before or near conception. We know that uterine receptivity and decidualization (differentiation of uterine stromal cells to specialized decidual tissue) are required for implantation of a conceptus and subsequent placentation [43]. At the implantation site, interleukin (IL)-6, IL-8, IL-15, granulocyte macrophage colony-stimulating factor, and tumor necrosis factor establish an inflammatory milieu [44]. In the female genital tract, STIs may alter immune homeostasis, tubal function, and uterine receptivity. This dysfunction can result in insufficient invasion of trophoblast and ultimately placental hypoxia, endoplasmic reticulum stress, and oxidative stress [45]. Impaired placentation is more often linked to preterm preeclampsia than term preeclampsia [46]. The possible intrauterine inflammatory response could also be linked to preterm birth. Indeed infection-induced preterm birth is well documented [47]. However, the mechanism is rarely addressed in studies of gonorrhea and adverse pregnancy outcomes, which demonstrates that there is a need to understand the biological impacts of STIs during pregnancy. Existing approaches such as use of animal models and cell culture are largely limited by an inability to mimic the human experience and pinpoint when a deleterious outcome may be prevented. Thus, in future work, researchers may consider the use of innovative models such as multicell organ-on-chip to determine the impact of STIs on early pregnancy processes [48].

Our study significantly adds to the literature because few studies to date have examined associations between *N gonorrhoeae* and multiple HDP. The separation of HDP is important because of the heterogeneity across these syndromes [18]. Multiple comparisons can increase type I error when using hypothesis testing methods. We report effect estimates and confidence intervals rather than *P* values, interpreting our results with consideration of potential bias as recommended in the field. This approach also allows us to avoid increasing type II error via correction of *P* values [49, 50]. Moreover, we had very little missing data (<1% for demographic variables and adverse pregnancy outcomes) and had access to a large dataset comprising a diverse population. Gonorrhea testing was done on approximately all participants and only 5.4% were not screened. Our high screening rate is a strength compared to many other studies in which screening rates are lower (<60%) [51]. However, it is possible that those with missing screening tests could have different underlying risk factors, and if those factors affect both STI positivity rates and adverse outcomes selection bias could occur. However, the rates of adverse pregnancy outcomes among those without STI screening were similar to those included in our analyses.

Like other studies examining STIs in pregnancy, we relied on existing data because it was a retrospective cohort design. Testing for gonorrhea in our clinics can be done with vaginal swabs or urine, which have different but overlapping diagnostic performance. In a recent systematic review, researchers found that NAAT sensitivity for gonorrhea in vaginal swabs relative to the patient infection status was 64%–100% compared with 67%–94% for urine [52]. In our study, we were unable to distinguish the use of vaginal versus urine for STI diagnosis. It is possible that our study underestimated rates of gonorrhea, but prevalence is consistent with national data in similar

populations [12, 15]. We were unable to find detailed data on treatments, adherence, partner treatment, and recurrence of infection. Incomplete documented treatment has been reported in similar studies [8, 9], and significant treatment delays in pregnant individuals has been reported [9]. Because many studies of perinatal STIs have relied on retrospective designs, it is not entirely clear how treatment patterns influence risk of adverse pregnancy outcomes, but a recent study has shown that even with prompt treatment, chlamydia and gonorrhea can still result in preterm birth [53].

Retrospective analyses can also result in residual confounding, perhaps due to exclusion of social factors (sex work, homelessness, etc), mental health, and sexual behavior that were not captured in medical records. We did assess the amount of bias possible due to residual confounding through the E-value. Because E-values were primarily >2, a potential confounder would need to have a moderate association with both exposure and outcome to bias the results. Thus, residual confounding cannot be completely ruled out. We did not have extensive data on adequacy of prenatal care or timing of infection, but others have shown that associations between STIs and adverse pregnancy outcomes are consistent when stratified by these factors [15, 38]. Our population is different than the general US population. First, our population is primarily Hispanic, and we have a large portion of foreign-born individuals. Second, we are a referral hospital, and the population tends to be at higher risk for complications. The Cesarean section rate in particular was higher than national average of 32.1% but only slightly higher than the state of Texas (35.9%) [54]. There is a significant need for prospective evaluations that can (1) address consistent use of vaginal swabs for diagnosis, (2) address timing of infection and treatment, (3) incorporate data on social factors, sexual behavior, mental health, and partner infection status, and (4) determine biological pathways that may be disrupted by STIs during pregnancy.

CONCLUSIONS

Rates of gonorrhea are continuing to rise and disproportionately affect minorities. Furthermore, antibiotic resistance is a significant concern [6]. In our population, among those with gonorrhea diagnosed and treated during pregnancy, approximately 15% developed a hypertensive disorder of pregnancy with almost 5% developing preeclampsia with a preterm delivery. Similarly, 15% of individuals who tested positive for gonorrhea had a preterm delivery. Our study, in addition to recent work by others, has shown a potential link between gonorrhea and HDP as well as preterm birth [14, 15, 38], within populations that are presumed treated after screening. It may be time for a fresh examination of the impact of STIs on pregnancy health and a new focus on alternative prevention strategies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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