



Chlamydia Trachomatis and the Development of Preeclampsia in Pregnancy

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Abstract

Background: Preeclampsia is a major contributor to maternal and perinatal morbidity and mortality. While known risk factors include chronic hypertension, diabetes, and autoimmune disease, emerging evidence suggests a potential association between Chlamydia trachomatis infection and hypertensive disorders of pregnancy.

Objective: To evaluate whether Chlamydia trachomatis infection is associated with an increased risk of preeclampsia.

Methods: This retrospective cohort study utilized data from the TriNetX Research Network. Pregnant individuals with and without prior Chlamydia trachomatis infection were identified using ICD-10 codes. Propensity score matching was used to balance cohorts on race, comorbidities, and socioeconomic factors. Outcomes were analyzed using risk difference, risk ratio, odds ratio, Kaplan-Meier survival curves, and t-tests.

Results: Women with a history of Chlamydia infection had a slightly higher incidence of preeclampsia (3.6% vs 3.5%). The risk difference was 0.001 (95% CI, 0.000-0.003; $P=0.042$); risk ratio, 1.037; odds ratio, 1.038. Survival analysis showed no significant difference in time to onset ($P=0.164$). However, women in the Chlamydia group experienced a significantly higher mean number of preeclampsia events (4.43 vs 2.81; $P<0.001$).

Conclusion: Although the increased risk is modest, Chlamydia trachomatis infection may contribute to the development of preeclampsia through inflammatory endothelial pathways. Universal STI screening during pregnancy, particularly in high-risk populations, may offer an opportunity for early intervention and improved maternal outcomes.

Keywords: Preeclampsia; Chlamydia Trachomatis; Hypertensive Disorders of Pregnancy; Pregnancy Complications; STI Screening

Introduction

Preeclampsia, a leading cause of maternal and perinatal morbidity and mortality, is a Hypertensive Disorder of Pregnancy (HDP) that can severely impact both mother and baby. It is characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, though systemic manifestations such as low platelets or elevated liver enzymes can occur before proteinuria, leading to delayed diagnoses [1]. The pathophysiology of preeclampsia involves abnormal placentation in the first trimester, followed by an excess of anti-angiogenic factors later in pregnancy, with oxidative stress and ischemic placental factors playing significant roles [1]. Endothelial dysfunction is a central feature of the disease, often exacerbated by the heightened inflammatory response in preeclamptic women [2].

Risk factors for preeclampsia include a history of the condition, chronic hypertension, pre-gestational diabetes, antiphospholipid syndrome, obesity, advanced maternal age, and the use of assisted reproductive technologies [2]. These risk factors contribute to endothelial dysfunction [2]. Recent research has highlighted the emerging link between sexually transmitted infections, particularly *Chlamydia trachomatis*, and an increased risk of HDPs, including preeclampsia. Chlamydia infection is often asymptomatic, but its inflammatory effects on the reproductive

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system can lead to chronic damage and may predispose women to hypertensive complications during pregnancy [3].

Chlamydia trachomatis is known for its intracellular reproductive cycle, which causes localized inflammation and endothelial dysfunction. This infection has been associated with adverse pregnancy outcomes, particularly in low- and middle-income populations [4]. Identifying Chlamydia as a potential risk factor for preeclampsia in high-risk populations could lead to important changes in screening and prevention protocols. In addition to reducing the risk of pregnancy complications, emphasizing the need for universal screening and timely intervention will improve maternal and neonatal outcomes.

Ethical Considerations

This retrospective study is exempt from informed consent as the data evaluated is a secondary analysis of existing data. This study did not involve interaction with or intervention for human participants, and personal information has been de-identified according to the HIPAA Privacy Rule's de-identification standard.

Methods

Data Source and Study Population

Data for this retrospective cohort study were obtained from the TriNetX Research Network, a federated global platform containing de-identified Electronic Health Records (EHRs) from participating healthcare organizations across the United States. The query included data from January 17, 2004, through January 17, 2025. Individuals are included in TriNetX when they receive clinical care at a participating institution; thus, inclusion does not depend on insurance enrolment, and patients remain identifiable within the network even if they change insurance providers. Because TriNetX is encounter-based, care received outside participating systems may not be captured, and gaps in clinical histories may occur.

We included pregnant women aged 15-45 years with a documented pregnancy episode and a delivery event. Pregnancies were identified using ICD-10 O-codes and CPT delivery procedure codes. Women were excluded if (1) gestational age could not be determined, (2) the pregnancy outcome was unknown or miscoded, or (3) exposure or outcome data were incomplete. If a woman had multiple pregnancies in the dataset, only the first eligible pregnancy was included to avoid within-person clustering and differential exposure classifications across pregnancies.

Exposure Definition

Chlamydia trachomatis exposure was defined using ICD-10 A56.xx codes. To ensure appropriate temporality, exposure was restricted to diagnoses within 12 months prior to conception or during the first trimester. Chlamydia diagnoses occurring after the onset of preeclampsia were excluded to prevent reverse causality and maintain accurate temporal sequencing. Women without any ICD-10 code for chlamydia comprised the unexposed cohort. Because TriNetX does not uniformly capture laboratory testing frequency, the unexposed group may include both women who were tested and found negative as well as some who may not have been tested; this is addressed in the limitations.

Outcome Definition

The primary outcome was preeclampsia, identified using ICD-10-CM codes O14.00, O14.10, O11, and O10.91, which include mild,

severe, and unspecified subtypes. ICD-10 coding for pregnancy-related hypertensive disorders and sexually transmitted infections has been shown in prior validation studies to have a positive predictive value of 85-95% in large EHR databases. The complete list of all ICD-10 codes used for exposure, outcomes, and covariates is provided in Appendix A.

Covariates

Potential confounders were selected a priori based on established associations with preeclampsia. These included maternal age, race/ethnicity, obesity, chronic hypertension, pre-existing diabetes mellitus, gestational diabetes, tobacco use, and other hypertensive disorders of pregnancy. All covariates were identified using ICD-10 codes or structured EHR fields.

Propensity Score Matching

Because women with chlamydia infection may differ systematically from uninfected women in demographic, clinical, and behavioral characteristics, Propensity Score Matching (PSM) was used to minimize selection bias and baseline imbalance. Propensity scores were estimated using logistic regression, incorporating all confounders listed above. A 1:1 nearest-neighbor PSM algorithm without replacement and with a caliper of 0.1 standard deviations of the logit of the propensity score was applied. Covariate balance between groups was assessed using Standardized Mean Differences (SMDs), with $SMD < 0.1$ considered acceptable. All matching procedures were performed using the built-in analytic functions within the TriNetX platform.

Statistical Analysis

After matching, measures of association - including Risk Ratio (RR), Risk Difference (RD), and Odds Ratio (OR) with corresponding 95% confidence intervals (CIs) - were calculated to compare the risk of preeclampsia between exposed and unexposed women. Because this was a cohort study, the risk ratio was the primary measure of association; odds ratios were computed for completeness and comparability with prior studies. Kaplan-Meier survival curves and log-rank tests were used for time-to-event assessments when applicable. All statistical tests were two-sided, and significance was defined as $p < 0.05$. Analyses were conducted within the TriNetX analytics environment, which automatically employs validated statistical modules for cohort creation, matching, and outcome assessment (Figure 1).

Results

Following propensity score matching, 170,512 women with documented Chlamydia trachomatis infection were matched 1:1 to 170,512 unexposed controls, yielding a final matched cohort of 341,024 pregnancies for analysis. Table 1 summarizes the number of individuals in each cohort, number of outcomes, and corresponding risk estimates.

Risk of preeclampsia in the exposed cohort was 0.036 (3.6%), compared with 0.035 (3.5%) in the matched unexposed cohort. The risk difference was 0.001 (95% CI: 0.000 to 0.003; $z=2.033$; $p=0.042$). The risk ratio was 1.037 (95% CI: 1.001 to 1.074), and the odds ratio was 1.038 (95% CI: 1.001 to 1.077). All estimates are presented with corresponding confidence intervals for transparency and completeness.

Kaplan-Meier Survival Analysis

Time-to-event analysis using a Kaplan-Meier estimator showed

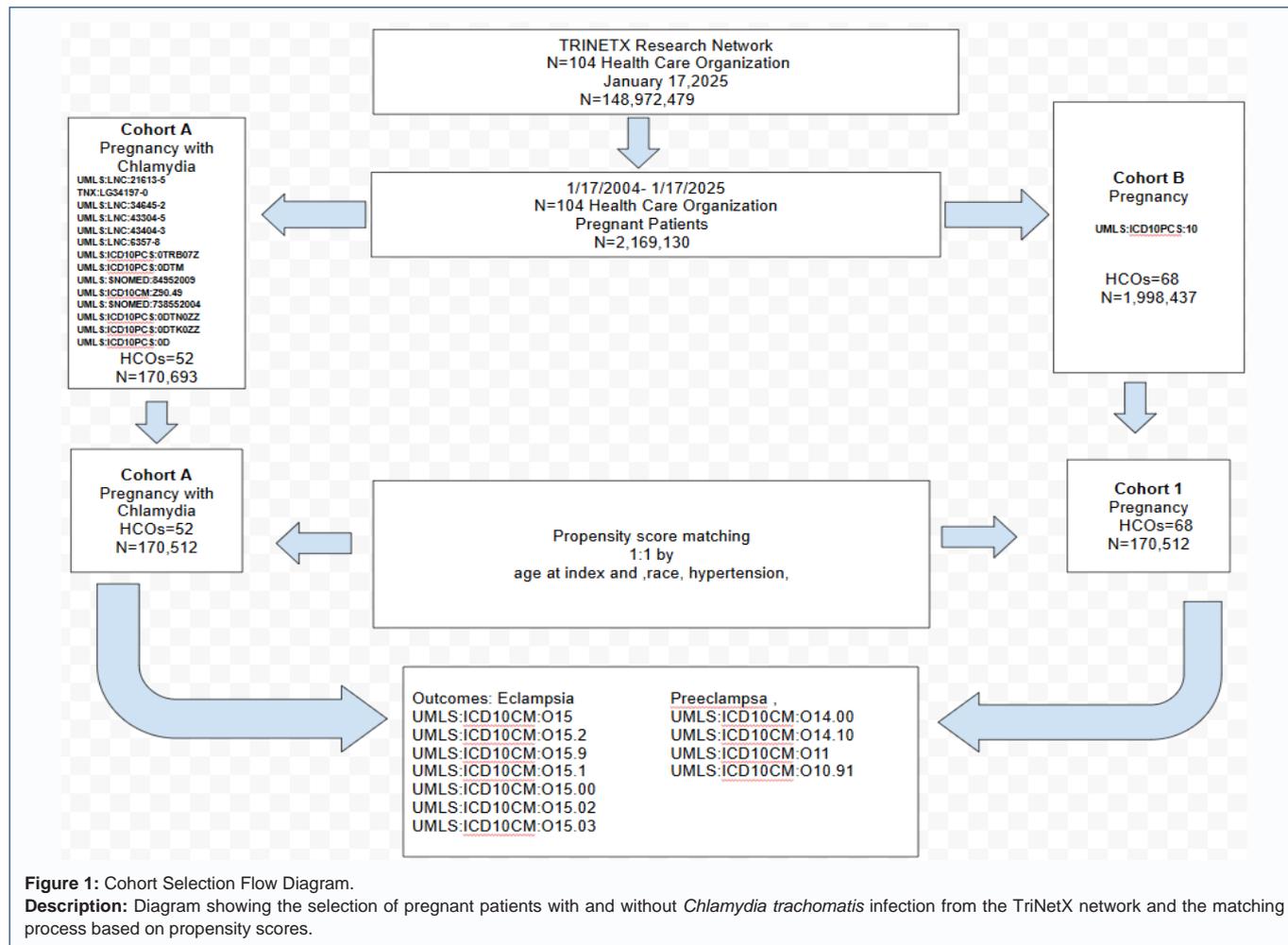


Figure 1: Cohort Selection Flow Diagram.

Description: Diagram showing the selection of pregnant patients with and without *Chlamydia trachomatis* infection from the TriNetX network and the matching process based on propensity scores.

Table 1: Risk Analysis of Preeclampsia in Chlamydia-Exposed vs. Control Cohorts.

RD=Risk difference, RR=Risk ratio, OR=Odds ratio. Reports the risk difference, risk ratio, and odds ratio for preeclampsia between matched cohorts.

Cohort	Patients in Cohort	Patients with Outcome	Risk	
Cohort 1	170,512	6,181	0.036	
Control	170,512	5,961	0.035	
95% CI			z	p
RD	0.001	(0.000, 0.003)	2.033	0.042
RR	1.037	(1.001, 1.074)	N/A	N/A
OR	1.038	(1.001, 1.077)	N/A	N/A

similar cumulative incidence patterns of preeclampsia between the exposed and unexposed cohorts. The log-rank test yielded $\chi^2=1.935$ (df=1, $p=0.164$), indicating no statistically significant difference in survival curves. The hazard ratio was 0.975 (95% CI: 0.941-1.010). Although the overall proportional hazards test was statistically significant ($\chi^2=100.002$; $p=0.000$), the hazard ratio confidence interval crossed 1.0 (Table 2).

Comparison of Outcome Instances

The database-generated metric for “instances” represents the number of coded encounters associated with preeclampsia, not the number of clinically separate events. Women in Cohort 1 had an average of 4.428 coded encounters (SD=6.155; median=2), compared

Table 2: Kaplan-Meier Survival Analysis of Time to Preeclampsia.

HR=Hazard Ratio. Comparison of survival probabilities and timing of preeclampsia occurrence using log-rank test and hazard ratio.

Test	χ^2	df	p	HR	95% CI
Log-Rank Test	1.935	1	0.164	—	—
HR & Proportionality	100.002	1	0.000	0.975	(0.941, 1.010)

with 2.808 encounters (SD=4.294; median=1) in the control cohort ($t=16.768$; df=12,140; $p<0.001$). This reflects differences in healthcare utilization rather than multiple biological episodes of preeclampsia per pregnancy (Figure 2).

The matched analysis demonstrated small numerical differences in absolute and relative risk measures. Kaplan-Meier analysis showed no significant difference in timing of preeclampsia onset. Differences in “number of instances” reflect encounter frequency rather than recurrent preeclampsia events. All interpretations of clinical meaning are provided in the Discussion section.

Discussion

Our study highlights a possible link between *Chlamydia trachomatis* infection and an increased risk of preeclampsia. Risk analysis revealed a small but statistically significant increase in the absolute risk of preeclampsia in women with chlamydia infection (Risk Difference: 0.1%, 95% CI: 0.000 to 0.003; $p=0.042$). There are modest increases in both the relative risk (RR=1.037, 95% CI: 1.001-

1.074) and odds of developing preeclampsia (OR=1.038, 95% CI: 1.001-1.077), suggesting a consistent association across measures. However, Kaplan-Meier survival analysis showed no statistically significant difference in the timing of preeclampsia onset between the infected and control cohorts (Log-Rank $p = 0.164$). This indicates that chlamydia infection does not appear to influence when preeclampsia occurs. Interestingly, the average number of preeclampsia instances was significantly higher in the infected group (Mean=4.428 vs. 2.808; $p < 0.001$), suggesting a higher burden of *Chlamydia trachomatis* among these women. Together, these findings support a potential association between *Chlamydia trachomatis* and preeclampsia.

Several studies have examined the link between *Chlamydia trachomatis* infection and adverse pregnancy outcomes, including preeclampsia, with mixed findings. Our study found a statistically significant increase in both absolute and relative risk of preeclampsia among women with chlamydia infection, consistent with prior research suggesting an elevated risk of hypertensive disorders of pregnancy, particularly when infection is untreated or diagnosed late [5, 6].

However, our Kaplan-Meier analysis showed no significant difference in the timing of preeclampsia onset, differing from prior findings that reported earlier onset associated with untreated genital infections [7]. This may reflect differences in population characteristics or the timing of infection relative to pregnancy. Notably, women with chlamydia had a higher average number of preeclampsia episodes, potentially indicating increased susceptibility to recurrent or severe hypertensive complications, consistent with studies linking chronic infection to inflammation and endothelial dysfunction [8].

Other investigations have found no significant association between chlamydia infection and hypertensive disorders after adjusting for confounders or using serological evidence of past infection [9, 10]. These discrepancies highlight the complexity of the association and suggest that the timing of infection, immune response, and access to timely treatment may influence risk.

The physiological overlap between *Chlamydia* infection and preeclampsia becomes particularly important when considering the mechanisms involved in both conditions. *Chlamydia trachomatis* infection can significantly impair endothelial function through immune-mediated mechanisms, leading to vascular instability - a key feature of preeclampsia. The host immune response includes the production of interferon-gamma (IFN γ), which induces the expression of Indoleamine 2,3-Dioxygenase (IDO) in host cells. IDO depletes intracellular tryptophan, an amino acid essential for *Chlamydia* replication, thereby inhibiting bacterial growth [11]. This response also alters host cell physiology, potentially disrupting endothelial function. Additionally, IFN γ activates inducible nitric oxide synthase, resulting in Nitric Oxide (NO) production - a reactive species that, when produced in excess, may contribute to endothelial dysfunction [12].

In pregnancy, proper endothelial function is critical for placental vascular development and the maintenance of maternal blood pressure. Disruption of endothelial integrity due to immune responses against infections like *Chlamydia* may impair placental vasculogenesis and angiogenesis, leading to inadequate perfusion. This vascular instability is a hallmark of preeclampsia [11]. Thus, placental *Chlamydia*-induced endothelial dysfunction - mediated by IFN γ -induced IDO expression and NO production - may contribute to reproductive complications by compromising placental

development.

Our findings suggest that even a modest increase in inflammatory burden from a *Chlamydia* infection could tip the balance toward preeclampsia, particularly in women with other risk factors.

Limitations

This study is subject to several limitations. As a retrospective analysis based on data from the TriNetX Research Network, the findings depend on the accuracy and completeness of clinical coding and documentation, which may introduce misclassification bias. Although propensity score matching was used to mitigate confounding, confounding from unmeasured variables, such as the timing, duration, and treatment status of *Chlamydia trachomatis* infection, cannot be excluded. The use of ICD-10 codes may have also limited the identification of subclinical or undiagnosed infections. In addition, the absence of laboratory confirmation and information regarding treatment adherence further restricts the interpretation of the observed associations. Lastly, while the reported risk differences did reach statistical significance, their magnitude was modest and may limit clinical applicability.

Conclusion

This study adds to growing evidence that *Chlamydia trachomatis* may be an underrecognized contributor to preeclampsia and eclampsia. While the increase in individual risk may appear modest, the widespread prevalence of *Chlamydia* among women of reproductive age makes this a potentially significant public health concern. Mechanistically, *Chlamydia* infection promotes a chronic inflammatory state and endothelial dysfunction, both of which can interfere with the remodeling of spiral arteries in the uterus and proper placental vascular development. These disruptions significantly contribute to the pathogenesis of preeclampsia, and if left unchecked, may escalate into severe complications such as eclampsia.

Early screening and treatment of *Chlamydia* during pregnancy could help preserve endothelial function and support normal placental development, reducing the likelihood of these hypertensive disorders. Given the often-asymptomatic nature of *Chlamydia* and its potential to silently contribute to dangerous pregnancy outcomes, routine sexually transmitted disease screening should be considered a key preventive measure. This approach offers a way to reduce maternal morbidity and mortality and provides a critical opportunity to intervene before vascular damage becomes irreversible. Emphasizing the importance of *Chlamydia* screening as part of routine prenatal care, as well as during annual exams for sexually active women, even before pregnancy, could play a vital role in reducing the global burden of preeclampsia. This approach may be especially beneficial for high-risk or underserved populations, where both STI rates and preeclampsia prevalence are disproportionately high [13,14].

Implications

This study identifies a modest association between *Chlamydia trachomatis* infection and increased risk of preeclampsia. The higher risk and frequency of hypertensive events suggest that even asymptomatic infection may contribute to endothelial dysfunction and adverse pregnancy outcomes. These findings support the need for routine *C. trachomatis* screening in prenatal care, particularly for high-risk populations. Early detection and treatment may reduce inflammation-related vascular injury and improve maternal health. Further research is warranted to explore the immune pathways

linking infection and hypertensive disorders. Incorporating STI history into clinical risk assessments may enhance early identification of vulnerable patients, support targeted surveillance, and inform public health strategies aimed at reducing disparities in maternal outcomes.

Declarations

Use of Generative AI

Generative artificial intelligence (AI), specifically OpenAI's ChatGPT, was used to assist in refining the language, grammar, and clarity of the manuscript. All content was reviewed, validated, and approved by the authors to ensure accuracy, originality, and adherence to ethical standards. No AI tool was used to generate data, perform analysis, or draw scientific conclusions.

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