Genital Herpes and Its Treatment in Relation to Preterm Delivery

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To examine the risks of genital herpes and antiherpes treatment during pregnancy in relation to preterm delivery (PTD), we conducted a multicenter, member-based cohort study within 4 Kaiser Permanente regions: northern and southern California, Colorado, and Georgia. The study included 662,913 mother-newborn pairs from 1997 to 2010. Pregnant women were classified into 3 groups based on genital herpes diagnosis and treatment: genital herpes without treatment, genital herpes with antiherpes treatment, and no herpes diagnosis or treatment (unexposed controls). After controlling for potential confounders, we found that compared with being unexposed, having untreated genital herpes during first or second trimester was associated with more than double the risk of PTD (odds ratio (OR) = 2.23, 95% confidence interval (CI): 1.80, 2.76). The association was stronger for PTD due to premature rupture of membrane (OR = 3.57, 95% CI: 2.53, 5.06) and for early PTD (≤35 weeks gestation) (OR = 2.87, 95% CI: 2.22, 3.71). In contrast, undergoing antiherpes treatment during pregnancy was associated with a lower risk of PTD compared with not being treated, and the PTD risk was similar to that observed in the unexposed controls (OR = 1.11, 95% CI: 0.89, 1.38). The present study revealed increased risk of PTD associated with genital herpes infection if left untreated and a potential benefit of antiherpes medications in mitigating the effect of genital herpes infection on the risk of PTD.

acyclovir; antiviral medication; genital herpes; preterm delivery

Abbreviations: CI, confidence interval; ICD-9, International Classification of Diseases, Ninth Revision; OR, odds ratio; PPROM, preterm premature rupture of membranes; PROM, premature rupture of membranes; PTD, preterm delivery.

Preterm delivery (PTD), defined as giving birth before 37 completed weeks of gestation, is the leading cause of perinatal mortality and morbidity. In the United States and other developed countries, it is also the leading cause of many debilitating conditions among offspring, including cerebral palsy, blindness, and deafness (1, 2). In addition, it is the major cause of admission to neonatal intensive care units and a significant contributor to medical expenditure during infancy and early childhood. Each year in the United States, approximately 12% of all births (approximately half a million births) are the result of PTD, and many of those preterm infants are admitted to a neonatal intensive care unit. The economic costs associated with PTD amount to more than $26 billion each year and are rising (3–5). PTD is a global crisis as defined by the World Health Organization and the March of Dimes (6, 7). Despite decades of research, the incidence of PTD has not been reduced, in large part because of a lack of progress in understanding its underlying causes (2).

Although infection during pregnancy has long been suspected to be an important risk factor for PTD (2, 8–12), treating bacterial infections during pregnancy has not been demonstrated to be effective in reducing the rate of PTD (13–15). There is, however, little literature examining the potential impact of viral infections of the reproductive tract on PTD. Genital herpes simplex infections are reported to be prevalent in pregnant women based on seropositivity (14%–22%), although the prevalence of primary genital herpes infection during pregnancy is relatively low (≈2%) (16–19). Among the limited studies in which genital herpes infection during pregnancy was examined, the focus has been on the impact of maternal herpes infection on vertical transmission to offspring (16, 17, 20, 21). The relationship between genital
herpes infection and PTD risk is largely unknown. Consequently, the treatment effect of antiviral medications on reducing PTD risk has largely not been examined. To examine genital herpes infection and antiviral medications in relation to the risk of PTD, we conducted a multicenter study among 4 geographically and demographically diverse Kaiser Permanente regions with more than 73,000 births annually: Kaiser Permanente California, including the northern and southern California regions, Kaiser Permanente Colorado, and Kaiser Permanente Georgia.

METHODS

The present study was approved by the institutional review boards of all 4 participating Kaiser Permanente regions. All participating regions have similar comprehensive and advanced electronic medical records containing robust clinical and administrative information. The electronic medical records capture all in-patient and out-patient visits, diagnoses, and treatments; prescriptions of medications, including dispensing date and days of supply in pharmacy databases; and pregnancy outcomes, including gestational age.

We conducted a member-based cohort study. The study population included all live births delivered during the study period from 3 Kaiser Permanente regions: site A (1997–2010), site B (2001–2010), and site C (2000–2009). Because of the local data provision rules, a fourth region (site D) provided information on all births for 2001–2010 by mothers who were exposed to any antiviral medications during pregnancy and a random sample of the remaining births (no in-utero exposure to antiviral medications) with a ratio of 1:15; for each birth with in-utero exposure to antiviral medication, 15 births without the exposure were randomly selected.

Untreated genital herpes infection

To examine the potential effect of untreated herpes infection and also control for confounding by indication when examining the effect of antiviral treatment, we identified subjects who had a clinical diagnosis of genital herpes infection during pregnancy to provide a baseline risk of PTD associated with genital herpes infection. All pregnant women who had a clinical diagnosis of herpes infection (International Classification of Diseases, Ninth Revision (ICD-9) codes 054.0–054.9) and did not receive any antiviral medications during pregnancy were identified. Those with a specific diagnosis of genital herpes (ICD-9 code 054.1x) were classified as having genital herpes. Those with other herpes infection codes, mostly unspecified herpes infection (ICD-9 codes 054.x except 054.1), were classified as likely having genital herpes. Although physicians in the Kaiser Permanente system rarely enter the codes for oral herpes, it is still possible that some of the women who had these codes did not have genital herpes. Thus, the diagnosis of genital herpes in this group is less certain.

Users of antiviral medications

Of the antiviral medications approved by the Food and Drug Administration that were identified through our pharmacy database, the majority (88%) were antiviral medications. Among the users of antiviral medications during pregnancy, more than 99% used acyclovir; less than 1% used famciclovir. To ensure that we sampled only true in-utero exposure, women who used only topical creams (1.6%) were excluded. On the basis of the medication dispensing date and days’ supply overlapping with pregnancy, as well as linkage of the pharmacy data to pregnancy data, we identified the timing and duration of medication use during pregnancy. To ensure that the antiviral treatment was indeed for herpes infection, we omitted women (<1%) who received antiviral medications without a diagnosis of genital herpes infection (ICD-9 codes 054.0–054.9) so that we could better control for confounding by indication (herpes infection). Previous studies have shown that approximately 95% of Kaiser Permanente members obtained their prescription medications from Kaiser Permanente pharmacies because of drug coverage (22).

Unexposed control group

The remaining pregnant women who received neither antiviral medications nor a herpes diagnosis during pregnancy were classified as unexposed controls. To avoid possible misclassification, we excluded women with diagnoses of chickenpox, herpes zoster, and other possible herpes types, including oral herpes infection (0.3%). To avoid any potential influence of antiviral medications other than antiviral medications, we excluded women who used other antiviral medications (<0.5%) from the control group.

On the basis of the combination of clinical diagnosis of genital herpes infection and treatment with antiviral medications during pregnancy, 3 cohorts were established: 1) women with untreated herpes infections (i.e., women with a diagnosis of herpes infection who did not receive treatment with antiviral medications), 2) women who received antiviral treatment (i.e., women who received antiviral medications during pregnancy and had a concurrent diagnosis of herpes infection), and 3) unexposed controls (i.e., women with no diagnosis of herpes infection and no treatment with antiviral medications).

Preterm delivery

All pregnancies and their outcomes were captured by the Kaiser Permanente electronic medical records. Gestational age at delivery was recorded and available for 99.4% of births. For the remaining births, we calculated gestational age by subtracting the date of the last menstrual period from the delivery date. We excluded women (<0.1%) for whom we did not have information on the date of last menstrual period and who had fetuses with invalid gestational ages (<20 weeks or >45 weeks) and those with inconsistent information (i.e., an ICD-9 code indicating a PTD and gestational age indicating a full-term birth) (<0.1%). Finally, because multiple births (twins, triplets, etc.) often have their own unique etiology of PTD, we restricted our study to singleton births. Because premature rupture of membranes (PROM) is more likely to be associated with subclinical infection, we subclassified PTD into PROM due to PROM (preterm PROM, or PPROM) and PTD not due to PROM to examine whether the risk associated with herpes infection and its treatment varied by these 2 PTD subtypes.
Adjustment for potential confounders

Confounders of the relationships between herpes infection or antiherspes medication treatment and PTD are largely unknown. However, we adjusted for many factors that could potentially be confounders, including maternal age, race/ethnicity, parity, and prenatal smoking; prepregnancy hypertension and diabetes; other sexually transmitted diseases during pregnancy; infant sex; calendar year; and participation site. Inclusion of covariables in the final model was based on their impact on the coefficients (≥10% changes) for genital herpes infection and treatment.

Data analysis

To take into account women who had more than 1 live birth during the study period, logistic regression for repeated measurements was used to obtain point and interval estimates of association (odds ratios and 95% confidence intervals) after controlling for confounders. Regression coefficients and associated robust standard error estimates were estimated via generalized estimating equations, accounting for the non-independence of the multiple longitudinal births per woman during the study period (23). We assumed an autoregressive working correlation structure, given that prenatal experiences for births with shorter intervals are more correlated than those of births farther apart. Alternative working correlation structures (i.e., exchangeable and unstructured) were examined in sensitivity analyses, and the results were consistent.

Because the opportunity for diagnosis and treatment of herpes in the third trimester can be affected by the occurrence of PTD, women who had infants with a higher gestational age would have a greater chance of being diagnosed with and receiving treatment for herpes infection. Because the Centers for Disease Control and Prevention recommend ascertaining and treating herpes outbreaks starting at 36 weeks of gestation, when the risk of PTD largely no longer exists (24), receiving a herpes diagnosis and treatment in the third trimester would be associated with an artificially low risk of PTD. Thus, to avoid reverse causality (low risk of PTD leads to high probability of receiving herpes diagnosis and treatment), we restricted our examination of the associations of genital herpes infection and treatment with PTD risk to women who received a herpes diagnosis or treatment in the first or second trimester only. Women whose initial (first) herpes diagnosis and treatment occurred during their third trimester were excluded (2.7%). Similarly, we excluded those (<0.15%) whose pregnancy ended before the beginning of the third trimester (≤180 days). Thus, there was no overlap between the exposure (genital herpes diagnosis and treatment) and outcome (PTD); consequently, no ambiguity in causal sequence between herpes diagnosis/treatment and PTD. Figure 1 shows the 3 study cohorts and exclusions described above. A total of 662,913 singleton live births were included in the final analyses.

RESULTS

In our study population, 4.7 per 1,000 women had a diagnosis of genital herpes during the first or second trimester of pregnancy based on ICD-9 codes in the electronic medical records. Of those, slightly more than half (56%) received antiherspes medications.

Table 1 presents the maternal and infant characteristics of the 3 cohorts based on genital herpes infection status and use of antiherspes medications during the first or second trimester. Compared with unexposed controls, women who had a herpes infection or who were being treated with antiherspes medication were more likely to be white or black.
and nulliparous and to have a diagnosis of sexually transmitted diseases during pregnancy.

To evaluate the associations of herpes infection and antiviral treatment during the first or second trimester with the risk of PTB, we examined the association of both untreated herpes infection and antiviral treatment separately for women with a diagnosis of genital herpes and women with an unspecified herpes diagnosis (possible genital herpes). After adjustment for potential confounders (maternal age, race, parity, and prenatal smoking), compared with the unexposed controls, women who had a genital herpes infection during the first or second trimester without antiviral medication (untreated genital herpes infection) had a more than 2-fold higher risk of PTB (odds ratio (OR) = 2.23, 95% confidence interval (CI): 1.80, 2.76). Possible genital herpes without medication was associated with a weaker (44%) but still statistically significant increased risk of PTB (OR = 1.44, 95% CI: 1.13, 1.84). In contrast, antiviral medication treatment was associated with reduction in the risk of PTB of more than 50% (OR = 0.49, 95% CI: 0.36, 0.68) compared with untreated genital herpes (Table 2). The reduction of PTB risk associated with antiviral treatment was somewhat smaller for treatment of possible genital herpes (OR = 0.74, 95% CI: 0.50, 1.07) (Table 2). With antiviral

### Table 1. Characteristics of the Study Population From 4 Kaiser Permanente Regions, a 1997–2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Antiviral Medication(^b) and No Herpes Diagnosis During Pregnancy (n = 659,828)</th>
<th>Untreated Herpes in the First or Second Trimester (n = 1,343)</th>
<th>Treated Herpes in the First or Second Trimester (n = 1,742)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.(^c)</td>
<td>%</td>
<td>No.(^c)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>38,630</td>
<td>5.9</td>
<td>94</td>
</tr>
<tr>
<td>20–24</td>
<td>109,070</td>
<td>16.6</td>
<td>212</td>
</tr>
<tr>
<td>25–29</td>
<td>190,541</td>
<td>28.9</td>
<td>350</td>
</tr>
<tr>
<td>30–34</td>
<td>192,574</td>
<td>29.2</td>
<td>408</td>
</tr>
<tr>
<td>35–39</td>
<td>103,187</td>
<td>15.7</td>
<td>213</td>
</tr>
<tr>
<td>≥40</td>
<td>24,388</td>
<td>3.7</td>
<td>66</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>230,450</td>
<td>37.9</td>
<td>572</td>
</tr>
<tr>
<td>African American</td>
<td>51,673</td>
<td>8.5</td>
<td>180</td>
</tr>
<tr>
<td>Hispanic</td>
<td>213,210</td>
<td>35.0</td>
<td>387</td>
</tr>
<tr>
<td>Asian/other</td>
<td>113,492</td>
<td>18.6</td>
<td>116</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>243,422</td>
<td>41.5</td>
<td>632</td>
</tr>
<tr>
<td>1</td>
<td>195,574</td>
<td>33.3</td>
<td>308</td>
</tr>
<tr>
<td>2</td>
<td>95,201</td>
<td>16.2</td>
<td>158</td>
</tr>
<tr>
<td>≥3</td>
<td>52,250</td>
<td>8.9</td>
<td>82</td>
</tr>
<tr>
<td>Maternal smoking during index pregnancy</td>
<td>33,278</td>
<td>5.2</td>
<td>113</td>
</tr>
<tr>
<td>Maternal diabetes during index pregnancy</td>
<td>370,873</td>
<td>91.8</td>
<td>750</td>
</tr>
<tr>
<td>Other STD(^d) during index pregnancy</td>
<td>613,885</td>
<td>93.0</td>
<td>1,222</td>
</tr>
</tbody>
</table>

Abbreviation: STD, sexually transmitted disease.
\(^a\) Northern and southern California, Colorado, and Georgia.
\(^b\) Including antiviral medications.
\(^c\) The numbers in each individual category may not sum to the total number because of missing data.
\(^d\) Other than herpes.
\(^e\) For this site, there was 1:15 matching.
treatment, the risk of PTD in women with herpes was largely similar to that in the unexposed control group (Table 2). The above estimates are robust: None of the adjusted variables affected the estimates appreciably, and the observed association was consistent across all racial/ethnic groups. Restricting analyses to women without a history of PTD did not change the results. Further adjustment for participating site, other sexually transmitted diseases during pregnancy, prepregnancy hypertension, prepregnancy diabetes, infant sex, and calendar year did not change the results.

To examine the associations by subtypes of PTD, we separated women with PTD into those with a concurrent diagnosis of PPROM and those without PROM. PPROM is usually more likely to have underlying infection as a possible etiology, and sexually transmitted diseases are a risk factor for PPROM. Results in Table 3 show that the association of untreated herpes infection was stronger with PPROM PTD (OR = 3.57) than that with non-PROM PTD (OR = 1.86). Nevertheless, antiherses treatment was equally effective in eliminating the risk of herpes infection associated with both PPROM and non-PROM PTD (Table 3). Consequently, the treatment benefit of antiherses medication was also slightly greater for PPROM PTD (OR = 0.35) than for non-PROM PTD (OR = 0.57). Further dividing non-PROM PTD into spontaneous and medically indicated PTD showed that the association was slightly stronger for medically indicated PTD (Table 3).

To examine whether the associations varied by early (≤35 weeks) or late (36 to <37 weeks) PTD, we conducted the analyses separately for early and late PTD cases. The observed associations between untreated herpes infection and PTD risk appeared to be stronger for early PTD (OR = 2.87) than for late PTD (OR = 1.54). Similarly, the antiherses treatment was associated with a significant reduction in the risk of early and late PTD associated with genital herpes infection: Among women who received antiherses treatment, the risk of early and late PTD was largely similar to that in the control group (Table 4).

We also examined the effect of duration of treatment during the first and second trimesters. Approximately half of those who received antiherses treatment (47%) had a prescription with a duration of 10 days or less. We did not observe a treatment effect associated with duration of the treatment (Table 5).

**DISCUSSION**

In the present multicenter cohort study based on the Kaiser Permanente member populations from 4 geographically diverse areas (northern and southern California, Colorado, and Georgia) with demographically diverse populations, we observed that 1) untreated genital herpes infection with a clinical diagnosis during the first or second trimester was associated with more than twice the risk of PTD compared with being unexposed and 2) treatment with antiherses medications was associated with removal of the risk of PTD associated with having an untreated genital herpes infection. Given that many pregnant women in the United States are seropositive for genital herpes infection (16–18) and PTD remains the leading cause of infant mortality and morbidity in the United States, our findings may have implications for

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**Table 2.** Herpes Infection and Use of Antiherses Medications During the First or Second Trimester in Relation to the Risk of Preterm Delivery From 4 Kaiser Permanente Regions.a 1997–2010

<table>
<thead>
<tr>
<th>Herpes Infection and Its Treatment</th>
<th>Total No.</th>
<th>No. of PTDs</th>
<th>%</th>
<th>Compared With</th>
<th>aORb</th>
<th>95% CI</th>
<th>aORb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>643</td>
<td>99</td>
<td>15.40</td>
<td>2.23</td>
<td>1.80, 2.76</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>1,049</td>
<td>89</td>
<td>8.48</td>
<td>1.11</td>
<td>0.89, 1.38</td>
<td>0.49d</td>
<td>0.36, 0.68</td>
<td></td>
</tr>
<tr>
<td>Possible genital herpes in the first or second trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>700</td>
<td>70</td>
<td>10.00</td>
<td>1.44</td>
<td>1.13, 1.84</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>693</td>
<td>56</td>
<td>8.08</td>
<td>1.12</td>
<td>0.86, 1.46</td>
<td>0.74e</td>
<td>0.50, 1.07</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NA, not applicable; PTD, preterm delivery.

a Northern and southern California, Colorado, and Georgia.

b Adjusted for maternal age, race, parity, and prenatal smoking. Further adjustment for participating site, other sexually transmitted diseases during pregnancy, prepregnancy hypertension, prepregnancy diabetes, infant sex, and calendar year did not change the results.

c International Classification of Diseases, Ninth Revision code 054.1x.

d The reference group comprises subjects untreated genital herpes in the first and second trimesters.

e Unknown herpes type, classified using International Classification of Diseases, Ninth Revision codes 054.0, 054.2, 054.3, 054.4x, 054.5, 054.6, 054.7x, 054.8, and 054.9.

f The reference group comprises subjects with untreated possible genital herpes in the first and second trimesters.
### Table 3. Herpes Infection and Use of Antiherpes Medication During the First or Second Trimester in Relation to the Risk of Subtypes of Preterm Delivery From 4 Kaiser Permanente Regions, a 1997–2010

<table>
<thead>
<tr>
<th>Herpes Infection and Its Treatment by Type of Preterm Birth</th>
<th>Total No.</th>
<th>No. of PTDs</th>
<th>%</th>
<th>Compared With</th>
<th>aORb</th>
<th>95% CI</th>
<th>aORb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROMc preterm deliveries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiviral medications and no herpes diagnosis during pregnancy</td>
<td>622,843</td>
<td>9,376</td>
<td>1.51</td>
<td>1.00 Referent</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated genital herpesd in the first or second trimester</td>
<td>579</td>
<td>35</td>
<td>6.04</td>
<td>3.57 2.53, 5.06</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated genital herpesd in the first or second trimester</td>
<td>983</td>
<td>23</td>
<td>2.34</td>
<td>1.29 0.85, 1.95</td>
<td>0.35</td>
<td>0.20, 0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total non-PROMc preterm deliveries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiviral medications and no herpes diagnosis during pregnancy</td>
<td>650,452</td>
<td>36,985</td>
<td>5.69</td>
<td>1.00 Referent</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated genital herpesd in the first or second trimester</td>
<td>608</td>
<td>64</td>
<td>10.53</td>
<td>1.86 1.43, 2.41</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
<td></td>
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<tr>
<td>Treated genital herpesd in the first or second trimester</td>
<td>1,026</td>
<td>66</td>
<td>6.43</td>
<td>1.07 0.83, 1.37</td>
<td>0.57</td>
<td>0.40, 0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medically indicatede non-PROMc preterm deliveries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No antiviral medications and no herpes diagnosis during pregnancy</td>
<td>623,278</td>
<td>9,811</td>
<td>1.57</td>
<td>1.00 Referent</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated genital herpesd in the first or second trimester</td>
<td>568</td>
<td>24</td>
<td>4.23</td>
<td>2.48 1.65, 3.74</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated genital herpesd in the first or second trimester</td>
<td>983</td>
<td>23</td>
<td>2.34</td>
<td>1.33 0.88, 2.02</td>
<td>0.50</td>
<td>0.27, 0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spontaneous non-PROMc preterm deliveries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiviral medications and no herpes diagnosis during pregnancy</td>
<td>640,641</td>
<td>27,174</td>
<td>4.29</td>
<td>1.00 Referent</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated genital herpesd in the first or second trimester</td>
<td>584</td>
<td>40</td>
<td>6.85</td>
<td>1.61 1.16, 2.23</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated genital herpesd in the first or second trimester</td>
<td>1,003</td>
<td>43</td>
<td>4.29</td>
<td>0.97 0.72, 1.33</td>
<td>0.62</td>
<td>0.40, 0.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NA, not applicable; PROM, premature rupture of membrane; PTD, preterm delivery.

a Northern and southern California, Colorado, and Georgia.
b Adjusted for maternal age, race, parity, and prenatal smoking. Further adjustment for participating site, other sexually transmitted diseases during pregnancy, prepregnancy hypertension, prepregnancy diabetes, infant sex, and calendar year did not change the results.
c International Classification of Diseases, Ninth Revision codes 658.1x, 658.2x, and 761.1x.
d International Classification of Diseases, Ninth Revision code 054.1x.
e International Classification of Diseases, Ninth Revision codes 73.0, 73.01, 73.09, 73.1, 73.4, and 74.x. Women with codes 644.0x, 644.1x, and 644.2x were excluded.

### Table 4. Herpes Infection and Use of Antiherpes Medication During the First or Second Trimester in Relation to the Risk of Early or Late Preterm Delivery From 4 Kaiser Permanente Regions, a 1997–2010

<table>
<thead>
<tr>
<th>Herpes Infection and Its Treatment by Gestational Age</th>
<th>Total No.</th>
<th>No. of PTDs</th>
<th>%</th>
<th>Compared With</th>
<th>aORb</th>
<th>95% CI</th>
<th>aORb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early preterm deliveriesc</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiviral medication and no herpes diagnosis during pregnancy</td>
<td>636,648</td>
<td>23,181</td>
<td>3.64</td>
<td>1.00 Referent</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated genital herpesd in the first or second trimester</td>
<td>610</td>
<td>66</td>
<td>10.82</td>
<td>2.87 2.22, 3.71</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated genital herpesd in the first or second trimester</td>
<td>1,010</td>
<td>50</td>
<td>4.95</td>
<td>1.18 0.88, 1.57</td>
<td>0.41</td>
<td>0.28, 0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Late preterm deliveriesd</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiviral medication and no herpes diagnosis during pregnancy</td>
<td>636,647</td>
<td>23,180</td>
<td>3.64</td>
<td>1.00 Referent</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated genital herpesd in the first or second trimester</td>
<td>577</td>
<td>33</td>
<td>5.72</td>
<td>1.54 1.08, 2.19</td>
<td>1.00</td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated genital herpesd in the first or second trimester</td>
<td>999</td>
<td>39</td>
<td>3.90</td>
<td>1.04 0.75, 1.43</td>
<td>0.65</td>
<td>0.40, 1.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NA, not applicable; PTD, preterm delivery.
a Northern and southern California, Colorado, and Georgia.
b Adjusted for maternal age, race, parity, and prenatal smoking. Further adjustment for participating site, other sexually transmitted diseases during pregnancy, prepregnancy hypertension, prepregnancy diabetes, infant sex, and calendar year did not change the results.
c Gestational age ≤35 weeks.
d International Classification of Diseases, Ninth Revision code 054.1x.
had mention of and 10 untreated. Results showed that all treated subjects

ple of 22 women with a diagnosis of genital herpes (12 treated

treated groups, we reviewed medical charts for a random sam-
ing infection (an outbreak or past history) between treated and un-

Group for the treated group to control for potential confounding

infection as a more relevant comparison

i n i n gt h ea s s o c i a t i o no fa n t i h e r p e st r e a t m e n t ,w ei m p r o v do o ve r

on compliance with taking medications as prescribed. In exam-

study based on pharmacy data, we did not have information

We were not able to identify any published studies in which

ment is likely underestimated.

only), the observed magnitude of the association due to treat-

infections (outbreak) than the untreated group (a past history

Given that currently there is no routine screening program

identification and treatment of pregnant women with herpes

infection before third trimester to reduce PTD risk.

We were only able to identify one previous study that exam-

the relationship between genital herpes infection and PTD

The study reported an association between subclinical

shedding of herpes virus and increased risk of PTD. The re-

ported finding is consistent with the result of the present study.

We were not able to identify any published studies in which

There are some limitations to keep in mind when interpreting

our results. For example, like any pharmacoepidemiological

study based on pharmacy data, we did not have information

on compliance with taking medications as prescribed. In exam-

ining the association of antiviruses treatment, we improved over

previous studies by establishing a group of subjects with un-

reated genital herpes infection as a more relevant comparison

group for the treated group to control for potential confounding

by indication. To further determine the types of genital herpes

infection (an outbreak or past history) between treated and un-

reated groups, we reviewed medical charts for a random sample

of 22 women with a diagnosis of genital herpes (12 treated

and 10 untreated). Results showed that all treated subjects

(100%) had mention of “lesion” or “outbreak” in their medical

charts, whereas 92% of untreated subjects (11 out of 12) mentioned

herpes history only in the medical charts (the remain-
ing one described an unspecified “lesion”). Thus, the

results of the chart review confirm the common clinical prac-
tice of 1) not treating women with a past herpes history only
(without a concurrent outbreak) and 2) treating only women

with current outbreak during pregnancy. Given that the

treated group consisted of women with more severe herpes

infections (outbreak) than the untreated group (a past history

only), the observed magnitude of the association due to treat-

ment is likely underestimated.

Given that currently there is no routine screening program

for herpes infection among pregnant women in the study
population because the US Preventive Services Task Force

recommends against routine herpes screening for pregnant

women (26), our study was based on clinical diagnoses of gen-

ital herpes infection during pregnancy, which could lead to the

underdiagnosing of women with a history of genital herpes

infections who are largely asymptomatic. Thus, it is likely that

some women with a history of herpes infections but without

a clinical diagnosis might have been included in the unexposed

controls. Similarly, to the extent that the Kaiser Permanente

electronic medical records might have missed some women

with a diagnosis and treatment outside the Kaiser Permanente

system, they might also have been included in the unexposed

controls. Such nondifferential misclassification would have led
to attenuation of the observed associations. Had we been able
to remove those women from the unexposed control group, the

observed associations would have been stronger.

Although we controlled for many potential confounders,

including underlying genital herpes infection, confounding

by unmeasured factors cannot be totally ruled out. Neverthe-

less, the untreated and treated groups should be relatively

comparable because of the underlying genital herpes infec-
tion and other factors; Table 1 also shows that the distribu-
tions of risk factors for PTD are largely comparable between

the 2 groups. Because we observed an increased risk of PTD

for women with untreated genital herpes infections and at the

same time a reduced risk of PTD for women with treated gen-

ital herpes infections, it would be difficult to attribute the

findings to confounding by indication or other confounders.

Given that treated genital herpes infections were likely more

severe than untreated infections as described above, the risk

of PTD would have been higher in the treated group than in

the untreated group had the former not received the antiherp-

treatments, which provides further arguments supporting the

observed reduced risk of PTD associated with treatment.

Finally, acyclovir and other antiviruses medications can readily

cross the placental barrier, providing biological plausibility
to the observed association (27–29).

As described above, site D had a slightly different sampling

method for the unexposed cohort. However, omitting site D

from the analysis did not change the observed associations.

Several strengths of the study should be noted. First, it was

a member-based study that reduced the chance of selection

bias compared with studies based on hospital referral centers.

Second, our large study population provided a diverse popu-

lation (racially and geographically) and allowed conduct of

subgroup analyses. Third, measurements of both exposures

(i.e., diagnosis of herpes infection and its treatment) and the

outcome (i.e., PTD) were based on electronic medical rec-

ords, not self-report, thus reducing recall bias. Finally, we

were able to identify 2 separate exposure groups: women

with untreated and treated genital herpes infections. Such

identification allowed us to examine the association between

genital herpes infection and PTD without the interference of

treatment and to examine the effect of treatment by compar-
ing treated patients with untreated but infected patients, thus

controlling for confounding by indication.

A slightly stronger association of untreated genital herpes

infection with PTD due to PROM (Table 3) makes clinical

sense because PPROM is usually related to underlying gen-

ital tract infections. However, what infections are related to

Table 5. Duration of Use of Antiviruses Medications During the First and Second Trimesters and the Risk of Preterm Delivery From Kaiser Permanente Regions.a 1997–2010

<table>
<thead>
<tr>
<th>Duration of Prescribed Antiviruses Medication</th>
<th>Total No.</th>
<th>No. of PTDs</th>
<th>%</th>
<th>aORb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated genital herpes1 in first or second trimester</td>
<td>643</td>
<td>99</td>
<td>15.40</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Treated genital herpes1 in first or second trimester</td>
<td>≥10 days</td>
<td>498</td>
<td>38</td>
<td>7.63</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>&gt;10 days</td>
<td>551</td>
<td>51</td>
<td>9.26</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; PTD, preterm delivery.

a Northern and southern California, Colorado, and Georgia.
b Adjusted for maternal age, race, parity, and prenatal smoking.

Further adjustment for participating site, other sexually transmitted
diseases during pregnancy, prepregnancy hypertension, prepregnancy
diabetes, infant sex, and calendar year did not change the results.

i n i n gt h ea s s o c i a t i o no fa n t i h e r p e st r e a t m e n t ,w ei m p r o v do o ve r

PPROM remains largely unknown. Genital herpes infection could be an underlying risk factor of PPROM that has been overlooked. A stronger association with PPROM further supports the argument for genital herpes infection being related to PTD risk.

We also observed a stronger association of untreated genital herpes infection with early PTD than with later PTD. Early PTD has been reported to be more likely associated with reproductive tract infections, especially subclinical infections (10, 11). Subclinical infections have long been suspected to be an important risk factor for PTD (12, 30, 31). However, no specific infectious agents have been identified. Our findings shed new light on the possible types of infections and an underlying pathway contributing to PTD risk.

In conclusion, our study revealed an increased risk of PTD associated with untreated genital herpes infection during first or second trimester of pregnancy and a potential benefit of antitherpes medications in mitigating the risk of PTD associated with genital herpes infection. Given the nature of new findings, the results need to be replicated in other studies. If confirmed, identifying and treating those with genital herpes infection may lead to reduction of PTD risk among pregnant women.

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REFERENCES


