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Original Contribution

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 antiherpes medication on reducing PTD risk has largely not been examined. To examine genital herpes infection and antiherpes 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 antiherpes 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 antiherpes 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 antiherpes medications

Of the antiviral medications approved by the Food and Drug Administration that were identified through our pharmacy database, the majority (88%) were antiherpes medications. Among the users of antiherpes 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 antiherpes treatment was indeed for herpes infection, we omitted women (<1%) who received antiherpes 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 antiherpes 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 antiherpes medication 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 antiherpes medication), 2) women who received antiherpes treatment (i.e., women who received antiherpes medication treatment 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 medication).

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 infants 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 PTD 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 antiherpes 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 nonindependence 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 antiherpes medications.

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

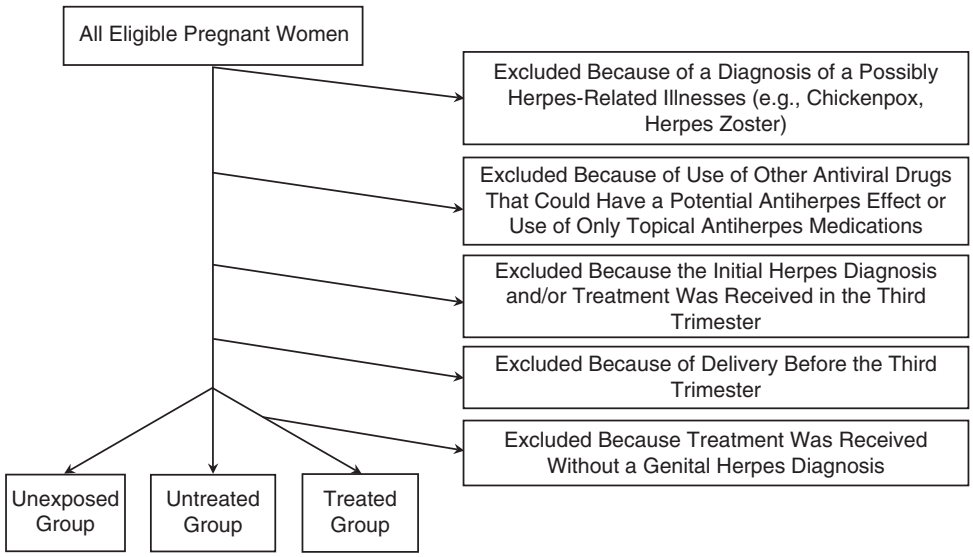

Figure 1. Study cohorts and exclusions from 4 Kaiser Permanente regions (northern and southern California, Colorado, and Georgia), 1997–2010.

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

Characteristic	No Antiviral Medication[b] and No Herpes Diagnosis During Pregnancy (n = 659,828)		Untreated Herpes in the First or Second Trimester (n = 1,343)		Treated Herpes in the First or Second Trimester (n = 1,742)	
	No.[c]	%	No.[c]	%	No.[c]	%
Age, years						
<20	38,630	5.9	94	7.0	110	6.3
20–24	109,070	16.6	212	15.8	317	18.2
25–29	190,541	28.9	350	26.1	455	26.1
30–34	192,574	29.2	408	30.4	471	27.0
35–39	103,187	15.7	213	15.9	302	17.3
≥40	24,388	3.7	66	4.9	87	5.0
Race/ethnicity						
White	230,450	37.9	572	45.6	762	47.4
African American	51,673	8.5	180	14.3	273	17.0
Hispanic	213,210	35.0	387	30.8	436	27.1
Asian/other	113,492	18.6	116	9.2	137	8.5
Parity						
0	243,422	41.5	632	53.8	848	59.0
1	195,579	33.3	303	25.8	374	26.0
2	95,201	16.2	158	13.4	150	10.4
≥3	52,250	8.9	82	7.0	65	4.5
Maternal smoking during index pregnancy						
Yes	33,278	8.2	113	13.1	134	10.8
No	370,873	91.8	750	86.9	1,103	89.2
Maternal diabetes during index pregnancy						
Yes	45,943	7.0	121	9.0	169	9.7
No	613,885	93.0	1,222	91.0	1,573	90.3
Other STD[d] during index pregnancy						
Yes	40,683	6.2	221	16.5	298	17.1
No	619,145	93.8	1,122	83.5	1,444	82.9
Prepregnancy hypertension						
Yes	13,434	2.0	14	1.0	19	1.0
No	646,394	98.0	1,329	99.0	1,723	99.0
Prepregnancy diabetes						
Yes	11,806	1.8	11	0.8	23	1.3
No	648,022	98.2	1,332	99.2	1,719	98.7
Participating site						
A	440,140	66.7	842	62.7	858	49.3
B	44,321	6.7	140	10.4	188	10.8
C	22,929	3.5	46	3.4	95	5.5
D[e]	152,438	23.1	315	23.5	601	34.5
Infant sex						
Female	321,954	48.8	667	49.7	877	50.3
Male	337,837	51.2	676	50.3	865	49.7
Calendar year						
2001 or earlier	169,441	25.7	412	30.7	178	10.2
2002	20,126	7.6	108	8.0	91	5.2
2003	50,504	7.7	80	6.0	85	4.9
2004	51,953	7.9	66	4.9	88	5.1
2005	52,386	7.9	69	5.1	102	5.9
2006	54,206	8.2	70	5.2	141	8.1
2007	56,610	8.6	109	8.1	200	11.5
2008	57,487	8.7	124	9.2	290	16.7
2009 or later	117,115	17.8	305	22.7	567	32.6

Abbreviation: STD, sexually transmitted disease.
[a] Northern and southern California, Colorado, and Georgia.
[b] Including antiherpes 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.

and nulliparous and to have a diagnosis of sexually transmitted diseases during pregnancy.

To evaluate the associations of herpes infection and antiherpes treatment during the first or second trimester with the risk of PTD, we examined the association of both untreated herpes infection and antiherpes 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 antiherpes medication treatment (untreated genital herpes infection) had a more than 2-fold higher risk of PTD (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 PTD (OR = 1.44, 95% CI: 1.13, 1.84). In contrast, antiherpes medication treatment was associated with reduction in the risk of PTD of more than 50% (OR = 0.49, 95% CI: 0.36, 0.68) compared with untreated genital herpes (Table 2). The reduction of PTD risk associated with antiherpes treatment was somewhat smaller for treatment of possible genital herpes (OR = 0.74, 95% CI: 0.50, 1.07) (Table 2). With antiherpes

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

Herpes Infection and Its Treatment	Total No.	No. of PTDs	%	Compared With			
				Unexposed		Untreated	
				aOR[b]	95% CI	aOR[b]	95% CI
No antiviral medication and no herpes diagnosis during pregnancy	659,828	46,361	7.03	1.00	Referent	NA	NA
Genital herpes[c] in the first or second trimester							
Untreated	643	99	15.40	2.23	1.80, 2.76	1.00	Referent
Treated	1,049	89	8.48	1.11	0.89, 1.38	0.49[d]	0.36, 0.68
Possible genital herpes[e] in the first or second trimester							
Untreated	700	70	10.00	1.44	1.13, 1.84	1.00	Referent
Treated	693	56	8.08	1.12	0.86, 1.46	0.74[e]	0.50, 1.07

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.

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, antiherpes 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 antiherpes 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 antiherpes treatment was associated with a significant reduction in the risk of early and late PTD associated with genital herpes infection: Among women who received antiherpes 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 antiherpes 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 antiherpes 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

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

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

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

Herpes Infection and Its Treatment by Gestational Age	Total No.	No. of PTDs	%	Compared With			
				Unexposed		Untreated	
				aOR[b]	95% CI	aOR[b]	95% CI
Early preterm deliveries[c]							
No antiviral medication and no herpes diagnosis during pregnancy	636,648	23,181	3.64	1.00	Referent	NA	NA
Untreated genital herpes[d] in the first or second trimester	610	66	10.82	2.87	2.22, 3.71	1.00	Referent
Treated genital herpes[d] in the first or second trimester	1,010	50	4.95	1.18	0.88, 1.57	0.41	0.28, 0.61
Late preterm deliveries[e]							
No antiviral medication and no herpes diagnosis during pregnancy	636,647	23,180	3.64	1.00	Referent	NA	NA
Untreated genital herpes[d] in the first or second trimester	577	33	5.72	1.54	1.08, 2.19	1.00	Referent
Treated genital herpes[d] in the first or second trimester	999	39	3.90	1.04	0.75, 1.43	0.65	0.40, 1.06

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.

[e] Gestational age >35 weeks but <37 weeks.

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

Duration of Prescribed Antiherpes Medication	Total No.	No. of PTDs	%	aOR[b]	95% CI
Untreated genital herpes[c] in first or second trimester	643	99	15.40	1.00	Referent
Treated genital herpes[c] in first or second trimester					
≤10 days	498	38	7.63	0.46	0.31, 0.68
>10 days	551	51	9.26	0.52	0.36, 0.76

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.

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

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 examined the relationship between genital herpes infection and PTD (25). The study reported an association between subclinical shedding of herpes virus and increased risk of PTD. The reported finding is consistent with the result of the present study. We were not able to identify any published studies in which antiherpes treatment in relation to PTD risk was examined.

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 examining the association of antiherpes treatment, we improved over previous studies by establishing a group of subjects with untreated 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 untreated 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 remaining one described an unspecified "lesion"). Thus, the results of the chart review confirm the common clinical practice 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 treatment 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 genital 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. Nevertheless, the untreated and treated groups should be relatively comparable because of the underlying genital herpes infection and other factors; Table 1 also shows that the distributions 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 genital 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 antiherpes treatment, which provides further arguments supporting the observed reduced risk of PTD associated with treatment. Finally, acyclovir and other antiherpes 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 population (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 records, 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 comparing 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 genital tract infections. However, what infections are related to

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 antiherpes 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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