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Antiherpetic medication use and the risk of gastroschisis: Findings from the National Birth Defects Prevention Study, 1997-2007

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Abstract

Background—Previous studies examining the teratogenic effects of antiherpetic medications have found no associations for birth defects overall but have not examined the risk of specific birth defects.

Methods—The National Birth Defects Prevention Study ascertains population-based cases with birth defects and live-born controls without birth defects in ten states across the United States for the purpose of identifying potential teratogenic risk factors. Mothers of cases and controls are interviewed within two years of their estimated date of delivery about demographic, medical and behavioral factors before and during pregnancy. This analysis examined the possible association between use of antiherpetic medications (acyclovir, valacyclovir or famciclovir) during early pregnancy and gastroschisis, a birth defect of the abdominal wall.

Results—The mothers of 1.1% (n=10) of 941 gastroschisis cases and 0.3% (n=27) of 8339 controls reported antiherpetic medication use during the month before conception through the third month of pregnancy. The adjusted odds ratios for such use in relation to gastroschisis were 4.68 (95% confidence interval [1.65, 13.28]) and 4.68 [1.15, 19.03] among women with and without self-reported genital herpes, respectively, when compared to women without antiherpetic use or herpes. Among women reporting no antiherpetic medication use, the odds ratio for self-reported genital herpes in relation to gastroschisis was 3.00 [1.58, 5.68].

Conclusions—Our study raises the possibility of an increased risk of gastroschisis due to either antiherpetic medication use during early pregnancy or the underlying genital herpes infection for which it was indicated.

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Details of contributors: KAA analyzed the data, prepared the initial draft and takes full responsibility for the accuracy of the data analysis. MMW conceived the project and guided the analysis and writing. MLF provided analytic support and expertise knowledge in drafting and revising the manuscript. AAM, MAC, and MTA reviewed the study design, analytic approach and revised the manuscript.

Gastroschisis is a birth defect in which abdominal contents are located outside of the body wall and can lead to serious neonatal and long-term morbidity.[1,2] The pathogenesis of gastroschisis is not known but the critical susceptibility window occurs during the first trimester.[3] The increasing prevalence of gastroschisis within the United States (US) [4-7] suggests environmental factors may be important causes of this disease.[3,8] However, the aetiology of gastroschisis remains elusive.

Previous studies have found no evidence for an increased risk of birth defects overall due to antiherpetic medication use.[9-13] However, in an exploratory analysis, one recent Danish study observed a strong but imprecise association between first trimester antiherpetic medication use and abdominal wall defects in the aggregate (prevalence odds ratio 3.58, 95% confidence interval [0.84, 15.27]).[9] Antiherpetic medications are nucleoside analogues that disrupt DNA replication and pharmacokinetic studies have shown that acyclovir crosses the placenta,[12,14,15] therefore it is possible that antiherpetic medications could affect embryogenesis, a process that involves rapid mitotic divisions and DNA replication.

We examined the association between antiherpetic medication use and the risk of gastroschisis in the National Birth Defects Prevention Study (NBDPS), which includes the largest sample of gastroschisis cases with maternal exposure information in the US.

METHODS

Since 1997, the NBDPS has been ascertaining population-based cases with birth defects and live-born controls without birth defects in 10 US states for the purpose of identifying potential teratogenic risk factors.[16] Cases were identified from birth defect registries and were classified by clinical geneticists using standardized criteria.[17] Controls were infants born without any major structural malformation and were selected randomly from the source population.

Within two years of their estimated date of delivery, mothers took part in a computer-assisted telephone interview about demographic, medical and behavioral factors during pregnancy and the three months before conception. Interviews from women with an estimated date of delivery before January 2008 were included in this analysis. Institutional review boards at the Centers for Disease Control and Prevention and at each participating center have approved the study.

Gastroschisis cases

Cases included fetuses/infants diagnosed with gastroschisis during physical examination, surgery, or autopsy, or by prenatal high resolution ultrasound with view of the umbilicus.[18]

Antiherpetic medication use

Women were asked about occurrences of and treatments for infections and sexually transmitted infections. Women who reported medication use were asked about timing and frequency of use. Antiherpetic medications included acyclovir, valacyclovir or famciclovir.

Covariates

Reports of “herpes” illnesses were assumed to be genital herpes; reports of “cold sores” or “oral herpes” were classified separately as oral herpes. A priori, genital herpes was considered a confounder in the analysis. Antiherpetic medication is also indicated for other types of infections, therefore any reports of these infections were investigated jointly as a potential confounder.[11] Additional potential confounders included maternal factors previously associated with antiherpetic medication use and/or gastroschisis as well as reported infections and medication use during the first trimester.[8]

Regression Analysis

We estimated the odds ratios of antiherpetic medication use in relation to gastroschisis with logistic regression models. Antiherpetic medication use during early pregnancy (the month before conception through the third month of pregnancy) was the primary exposure. Analyses examined women with and without self-reported herpes using a common reference group of women without antiherpetic medication use or herpes.

Assessment of recall bias

We performed two sensitivity analyses to explore possible recall bias. First, we explored the risk of gastroschisis in relation to antiherpetic medication use exclusively outside of early pregnancy, when there is no biologically plausible effect on the development of gastroschisis. If this estimate was elevated, it could indicate the primary model’s effect estimate might be elevated due to recall bias. Second, we repeated the analysis between early pregnancy antiherpetic medication use and gastroschisis using as controls infants with malformations other than gastroschisis, assuming mothers’ recall accuracy would be similar for both groups.

RESULTS

There were 941 gastroschisis cases and 8339 controls included in the analysis. Case mothers were more likely than controls to be young and to report periconceptional smoking, lower pre-pregnancy body mass index (BMI), illicit drug use and genital herpes (Table 1). Overall, use of antiherpetic medication during pregnancy and in the three months before conception was 1.5% (14/941) among case and 0.9% (71/8339) among control mothers. The monthly prevalence of antiherpetic medication use was higher among case than control mothers for all pregnancy months (Figure 1).

Use of antiherpetic medication during early pregnancy was associated with an increased risk of gastroschisis among women with and without self-reported genital herpes (adjusted odds ratio [AOR] 4.68, 95% confidence interval [1.65, 13.28] and 4.68, [1.15, 19.03], respectively) when compared to women with neither genital herpes nor antiherpetic medication use (Table 2). Among women reporting no antiherpetic medication use, the AOR for self-reported genital herpes in relation to gastroschisis was 3.00 [1.58, 5.68]. Models were adjusted for maternal age and BMI; additional adjustment for other potential confounders, including other infections that might be treated with antiherpetics, did not substantially change estimates of association.

Assessment of recall bias

Antiherpetic medication use exclusively outside of early pregnancy among women without genital herpes showed a possible elevated association with gastroschisis (AOR 2.69, [0.81, 8.93]); among women with genital herpes the OR for such use could not be calculated (0% among cases vs. 0.3% among controls). When the malformed controls were substituted for the non-malformed controls in the analysis, the association between early pregnancy antiherpetic medication use and gastroschisis remained elevated for both women with and without genital herpes (AOR 9.36 [3.50, 25.08] and 3.01 [0.96, 9.42], respectively) when compared to women with neither genital herpes nor antiherpetic medication use.

COMMENTS

Antiherpetic medication use during early pregnancy was uncommon but appeared to be associated with a four-fold increased risk for gastroschisis when compared to the risk among women reporting neither genital herpes nor antiherpetic medication use. Similar associations were observed for both women with and without self-reported genital herpes. That recall bias is unlikely to account for these association is supported by the fact that when the analysis was performed using malformed controls, risks remained elevated. It should be noted that antiherpetic medication use was rare in our study population (<1% prevalence), resulting in estimates of association that were imprecise and suggesting our study findings could be the result of random error. Notably, the elevated risk associated with early pregnancy antiherpetic mediation use was similar in magnitude to that associated with untreated genital herpes, suggesting that this underlying infection may be confounding the antiherpetic-gastroschisis association we observed.

Although several studies have examined the risk of birth defects overall in relation to antiherpetic medication during pregnancy and have found no association, no study has specifically focused on gastroschisis.[9-13] Studies in rats have found teratogenic effects of high doses of acyclovir administered during organogenesis but no abdominal wall defects have been noted.[19]

Explanation for our findings

In an effort to disentangle the separate effects of antiherpetic medication use and genital herpes infection, we created mutually-exclusive categories with women who reported neither exposure as the comparison group. The elevated ORs for antiherpetic medication use and for genital herpes without such use could represent positive associations for both exposures. However, it is important to consider exposure measurement in this study. While reports of genital herpes were probably correct, women not reporting genital herpes may indeed have been diagnosed with genital herpes but did not report that in the interview. Women were not specifically asked about antiherpetic medication use or genital herpes in this study and both exposures were reported by smaller proportions of women (0.9% and 1.2%, respectively) than in another case-control birth defects study, the Slone Birth Defects Study[20] (2.3% and 2.1%, respectively), which did specifically ask about medication use for genital herpes (based on an unpublished analysis by KAA and MMW). While 6% of women reported their antiherpetic medication use for indications other than genital herpes, 36% did

not describe the infection treated, though it seems unlikely that an antiherpetic would be prescribed in the absence of an indication. With likely misclassification of both our primary exposure and its indication, assessment of their separate effects is further complicated. One possibility is that the medication use is a marker of underlying infection and the elevated ORs for such use represent an association with infection only. If this is the case, then the elevated OR for use outside the etiologic window might also represent an association with the herpes infection itself, rather than recall bias.

The NBDPS includes the largest sample of gastroschisis cases with maternal exposure information in the US, utilizes specific gastroschisis classification criteria, and collects information on a variety of maternal factors both before and during pregnancy. The results of our study suggest that antiherpetic medication use during pregnancy, or the infection for which it was indicated, may be associated with an increased risk of gastroschisis. This finding points to a possible infectious cause of gastroschisis and should direct future research into that arena.[21] Specific information regarding antiherpetic medication use (including actual use patterns and indicating infection), genital herpes outbreak details, and serological testing for HSV types 1 and 2 and other herpes infections would allow for better classification of exposure and enhanced control for confounding by indication in future studies.

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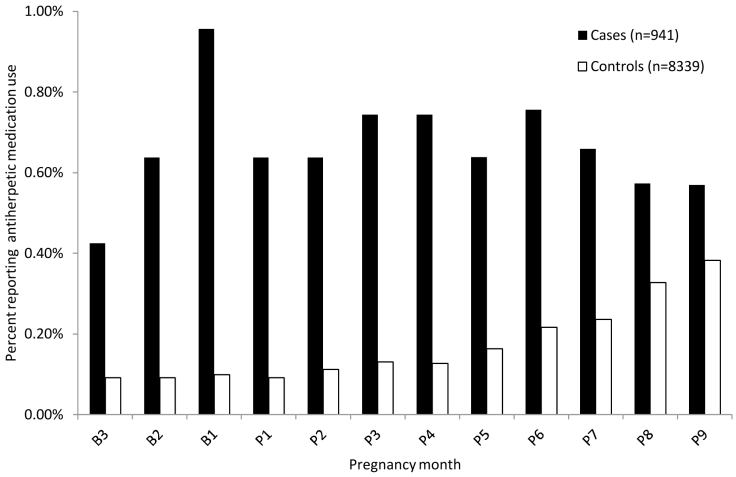

Figure 1.

Distribution of self-reported antiherpetic medication use among gastroschisis cases and controls by pregnancy month and standardized to age distribution in cases among participants of the National Birth Defects Prevention Study, 1997-2007

Abbreviations: "B"= months before conception, and "P"= months after conception

Antiherpetic medication exposure prevalence was 1.5% (14/941) among gastroschisis cases and 0.9% (71/8339) among controls.

Table 1

Maternal and pregnancy characteristics of gastroschisis cases and controls participating in the National Birth Defects Prevention study, 1997-2007

	Gastroschisis cases (n=941)				Non-malformed controls (n=8339)			
Maternal age (years)	**< 25 n**	**%**	**≥ 25 n**	**%**	**< 25 n**	**%**	**≥ 25 n**	**%**
TOTAL	742	78.9	199	21.1	2772	33.2	5567	66.8
Maternal age at delivery								
13-19 years	363	48.9	0	0.0	856	30.9	0	0.0
20-24 years	379	51.1	0	0.0	1916	69.1	0	0.0
25-29 years	0	0.0	136	68.3	0	0.0	2290	41.1
30-50 years	0	0.0	63	31.7	0	0.0	3277	58.9
Maternal race								
Non-Hispanic White	361	48.7	122	61.3	1282	46.2	3664	65.8
Non-Hispanic Black	59	8.0	15	7.5	438	15.8	493	8.9
Hispanic	252	34.0	49	24.6	889	32.1	1032	18.5
Asian/Pacific Islander	26	3.5	4	2.0	40	1.4	205	3.7
Native American	7	0.9	0	0.0	18	0.6	24	0.4
Other [a]	37	5.0	9	4.5	105	3.8	147	2.6
Body mass index (kg/m^2)								
Underweight (12 to <18.5)	73	9.8	7	3.5	229	8.3	204	3.7
Normal (18.5 to <25)	479	64.6	122	61.3	1331	48.0	2781	50.0
Overweight/obese (≥25)	170	22.9	65	32.7	1058	38.2	2395	43.0
Missing	20	2.7	5	2.5	154	5.6	187	3.4
Periconceptional smoking								
Yes	260	35.0	74	37.2	763	27.5	777	14.0
No [b]	482	65.0	125	62.8	2005	72.3	4789	86.0
Illicit drug use before or during pregnancy								
Yes	177	23.9	36	18.1	415	15.0	520	9.3
No	565	76.1	163	81.9	2357	85.0	5047	90.7
Self-reported genital herpes								
Yes	13	1.8	9	4.5	28	1.0	70	1.3
No	729	98.2	190	95.5	2744	99.0	5497	98.7
Other indicating infections [c]								
Yes	4	0.5	0	0.0	7	0.3	10	0.2
No	738	99.5	199	100	2765	99.7	5557	99.8

[a] Includes 3 women missing maternal race information

[b] Includes 5 women missing maternal smoking information

[c] Includes oral herpes, mononucleosis and chicken pox/shingles

Table 2

Multivariable logistic regression modeling of antiherpetic medication use on the risk of gastroschisis by pregnancy exposure window among participants of National Birth Defects Prevention Study, 1997-2007

Genital Herpes Antiherpetic use exposure window[b]		Gastroschisis cases		Controls		Unadjusted		Adjusted[a]	
		n	%	n	%	OR	95% CI	OR	95% CI
All	All	941	100.0	8339	100.0				
No	No antiherpetic use	911	96.8	8213	98.5	Reference			
No	Antiherpetic use during early pregnancy	4	0.4	10	0.1	3.61	[1.13, 11.53]	4.68	[1.15, 19.03]
No	Antiherpetic use exclusively outside of early pregnancy	4	0.4	18	0.2	2.00	[0.68, 5.93]	2.69	[0.81, 8.93]
Yes	No antiherpetic use	16	1.7	55	0.7	2.62	[1.50, 4.60]	3.00	[1.58, 5.68]
Yes	Antiherpetic use during early pregnancy	6	0.6	17	0.2	3.18	[1.25, 8.10]	4.68	[1.65, 13.28]
Yes	Antiherpetic use exclusively outside of early pregnancy	0	0.0	26	0.3	Not modeled		Not modeled	

[a] The covariates for adjusted models included maternal age at delivery (13-19, 20-24, 25-29 [reference], 30-50 years) and BMI before conception (<18.5, 18.5-25 [reference], >25, missing)

[b] Early pregnancy was defined as the month before conception through the third month of pregnancy.