OBSTETRICS

Infant outcomes among pregnant women who used oseltamivir for treatment of influenza during the H1N1 epidemic

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OBJECTIVE: This study was undertaken to examine the association between maternal oseltamivir treatment for influenza and infant outcomes during the 2009 HINI influenza pandemic.

STUDY DESIGN: This was a retrospective cohort study using a population-based maternal newborn database including women who gave birth to a singleton infant in the Canadian province of Ontario from November 2009 through April 2010. Risks of small for gestational age (SGA) (10th percentile and 3rd percentile), preterm birth (<37 weeks of gestation), very preterm birth (<32 weeks of gestation), and 5-minute Apgar score <7 associated with maternal exposure to oseltamivir were analyzed by multivariable regression.

RESULTS: A total of 55,355 women with a singleton birth were included in this study. Among them, 1237 (2.2%) women received oseltamivir for treatment or prevention of influenza during pregnancy. Women who took oseltamivir during pregnancy were less likely to have a SGA infant based on the 10th percentile for growth (adjusted risk ratio, 0.77; 95% confidence interval, 0.60–0.98). No association between maternal use of oseltamivir with SGA on 3rd percentile, preterm birth, very preterm birth, and low Apgar score was observed.

CONCLUSION: There is no evidence of an association between maternal use of oseltamivir for influenza and early birth, low Apgar at birth, and poor fetal growth.

Key words: birth outcomes, influenza, oseltamivir, pregnancy

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In March 2009, a novel H1N1 influenza A virus was identified in Mexico and spread rapidly across many countries.[1,2] Compared with nonpregnant women, pregnant women are at increased risk for related hospital admission and death associated with influenza pandemic.[3-6] During seasonal influenza epidemics and previous pandemics, pregnant women have been at increased risk for complications related to influenza infection.[7-9] The mechanical, immunological, and hormonal changes during pregnancy are likely the reasons that pregnant women are more vulnerable to viral respiratory infections such as influenza than nonpregnant women.[10,11]

Oseltamivir (Tamiflu; F. Hoffmann-La Roche Ltd., Basel, Switzerland) is an antiviral drug of the neuraminidase inhibitor class used for the treatment and prophylaxis of influenza.[12] It is hydrolyzed by the liver to its active metabolite, with an elimination half-life of about 6-10 hours.[13] The H1N1 virus is susceptible to neuraminidase inhibitors such as oseltamivir.[14,15] The efficacy and safety of oseltamivir in children aged ≥1 year and in adults has been well established,[16,17] and it was used extensively for the treatment and prevention of 2009 H1N1 influenza.[6] Only a few studies have examined the association between maternal use of oseltamivir and pregnancy outcomes[12,18-21]; however, these studies were based on small samples or self-reports from pregnant women. The benefit of treatment of pregnant women with antiviral medications is presumed to outweigh its risk; however, the limited availability of information on risk and ben-

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efits of antiviral medication during pregnancy is challenging for both health care providers and pregnant women. The aim of this study was to assess the effect of maternal oseltamivir use for treatment or prevention of influenza on infant outcomes.

Materials and Methods

This was a population-based retrospective cohort study. All hospital birth records from November 2009 through April 2010 from Better Outcomes Registry and Network (BORN) Ontario, an Internet-based birth record system, were abstracted. The BORN Ontario database contains information on maternal and prenatal characteristics, health services, obstetric information, as well as birth outcomes. Starting on Nov. 2, 2009, at the time of admission for labor or elective cesarean section, health care staff collected additional information via patient interview or from antenatal records and hospital charts regarding influenza illness, use of antiviral medications, or influenza vaccination during pregnancy using standardized questions and data collection forms. These data were entered directly into the BORN birth record system at each hospital or electronically uploaded to the BORN system in hospitals with this capability.

Statistics Canada software (PCCF+ version 5E; Statistics Canada, Ottawa, Ontario, Canada) was used to create neighborhood information on education and income based on the long form 2006 Canadian Census (administered to a 20% random sample of the population). Neighborhood family income and level of education were linked by dissemination areas using maternal postal code. These variables were presented as quintiles for analysis. Each quintile contains about one-fifth of the total Ontario population, but may not necessarily contain one fifth of the births in our study population.

We restricted our analysis to singleton, live births ≥20 weeks of gestation and ≥500 g in weight. Pregnancies that ended in miscarriage <20 weeks' gestation and terminations of pregnancy for fetal anomalies at any gestational age were excluded from the database.

Adverse infant outcomes examined in the study included small-for-gestational-age (SGA) infant (<10th percentile for birthweight) and severe SGA infant (<3rd percentile) by sex and gestational week strata using a Canadian growth standard,[22] preterm delivery (live birth at <37 gestational weeks), very preterm delivery (live birth at <32 gestational weeks), and Apgar score <7 at 5 minutes.

We first compared the distribution of baseline characteristics between women who were exposed to oseltamivir during pregnancy and those women who were not. We then analyzed risk of each adverse infant outcome associated with maternal exposure to oseltamivir by calculating unadjusted risk ratios (RRs) along with 95% confidence intervals (CIs) using logistic regression. Odds ratios with 95% CI approximate the RR for rare outcomes, and will thus be interpreted as RR. Subsequently, adjusted RR with 95% CI were estimated using multiple logistic regression. Two sets of logistic regression models were developed. In the first set of models, we adjusted for maternal age (<20, 20-24, 25-34, 35-39, and ≥40 years), parity (defined as number of previous live births and stillbirths, with values 0, 1, and ≥2), vaccination (vaccination for influenza, yes vs no), preexisting comorbidities (asthma, chronic hypertension, insulin-dependent diabetes, noninsulin-dependent diabetes, or heart disease, present vs absent), maternal smoking (yes vs no), occurrence of influenza-like illness (yes vs no), and neighborhood education and income levels (in quartiles). In the second sets of models, influenza vaccination during pregnancy was added to the model. The confounding factors to be adjusted for were selected by an expert panel consisting of obstetricians, epidemiologists, statisticians, and nursing researchers, after integrating information from a literature review[5,12,18-20,23-25] and preliminary results of the data. Supplemental analyses were performed in pregnant women who reported influenza.

All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, NC). Research ethics board approval was obtained from the Ottawa Hospital.

Results

A total of 55,355 pregnant women who gave birth to a singleton infant from November 2009 through April 2010 in hospitals in Ontario were included in the analysis. Among them, 1237 (2.2%) women had received oseltamivir therapy at some time during their pregnancy. Women who received oseltamivir therapy were more likely to have no previous live birth and be smokers, were younger, were more likely to come from low education and higher income neighborhoods, and were less likely to have high-risk medical comorbidities (Table 1).

The risks and RR for birth outcomes are shown in Table 2. The risk of SGA <10th percentile was significantly lower among women who used oseltamivir at some time during pregnancy compared with those who did not (6.9% vs 9.2%; adjusted RR, 0.77; 95% CI, 0.60–0.98). No association between maternal use of oseltamivir with SGA <3rd percentile, preterm birth <37 weeks, very preterm birth <32 weeks, and Apgar score <7 was observed, after adjusting for potential confounding factors. Results from models with or without influenza vaccination were almost identical. Supplemental analyses restricting to pregnant women who reported influenza yielded similar findings, although reduced number of study subjects resulted in statistical instability (data available upon request).

Comment

In this population-based cohort study, we found that maternal use of oseltamivir during pregnancy was associated with a lower risk of having an SGA infant based on the SGA <10th percentile. On the other hand, no association of maternal use of oseltamivir with severe fetal growth restriction (SGA <3rd percentile), preterm birth, very preterm birth, or low Apgar score was found. Our results are consistent with the findings from a few previous studies that assessed the association between maternal exposure to oseltamivir and infant outcomes.[18-21]

Only 4 previous studies could be located on this topic from a detailed MEDLINE and Embase search.[18-21] In a study of 86 women exposed to neuraminidase in-

TABLE 1
Comparison of baseline characteristics between pregnant women who used oseltamivir and those who did not during 2009 H1N1 pandemic in Ontario, Canada

			Antiviral use during pregnancy				
	Total n = 55,355		None n = 54,118		Oseltamivir n = 1237		
Characteristics	n	%	n	%	n	%	*P* value
Maternal age, y							
<20	2066	3.7	2007	3.7	59	4.8	
20-24	7423	13.4	7225	13.4	198	16.0	
25-34	34,070	61.5	33,331	61.6	739	59.7	.0128
35-39	9625	17.4	9427	17.4	198	16.0	
≥40	2170	3.9	2127	3.9	43	3.5	
Missing	1	0.0	1	0.0	0	0.0	
Parity							
0	24,223	43.9	23,738	44.0	485	39.3	
1	19,581	35.5	19,123	35.4	458	37.1	.0023
≥2	11,415	20.7	11,124	20.6	291	23.6	
Missing	136	0.2	133	0.2	3	0.2	
Month of delivery							
November 2009	9404	17.0	9196	17.0	208	16.8	
December 2009	8702	15.7	8497	15.7	205	16.6	
January 2010	9928	17.9	9699	17.9	229	18.5	.0597
February 2010	9421	17.0	9244	17.1	177	14.3	
March 2010	8883	16.0	8694	16.1	189	15.3	
April 2010	9017	16.3	8788	16.2	229	18.5	
Smoking							
No	47,005	88.4	46,040	88.5	965	82.8	
Yes	6190	11.6	5989	11.5	201	17.2	< .0001
Missing	2160	3.9	2089	3.9	71	5.7	
Had influenza							
No	53,105	96.8	52,610	98.0	495	43.2	
Yes	1734	3.2	1083	2.0	651	56.8	< .0001
Missing	516	0.9	425	0.8	91	7.4	
Vaccinated for influenza							
No	31,640	58.1	30,997	58.2	643	53.6	
Yes	22,779	41.9	22,223	41.8	556	46.4	.0014
Missing	936	1.7	898	1.7	38	3.1	
Medical comorbidities[a]							
No	49,998	92.6	48,942	88.1	1056	92.7	
Yes	3969	7.4	3826	11.9	143	7.3	< .0001
Missing	1388	2.5	1350	2.5	38	3.1	

Xie. Infant outcomes and oseltamivir use during pregnancy. Am J Obstet Gynecol 2013. *(continued)*

TABLE 1
Comparison of baseline characteristics between pregnant women who used oseltamivir and those who did not during 2009 H1N1 pandemic in Ontario, Canada *(continued)*

			Antiviral use during pregnancy				
	Total n = 55,355		None n = 54,118		Oseltamivir n = 1237		
Characteristics	n	%	n	%	n	%	*P* value
Income quartiles							
1 (Lowest)	13,515	25.0	13,231	25.1	284	23.5	
2	13,600	25.2	13,256	25.1	344	28.5	
3	13,601	25.2	13,335	25.3	266	22.0	.0066
4 (Highest)	13,285	24.6	12,972	24.6	313	25.9	
Missing	1354	2.4	1324	2.4	30	2.4	
Education quartiles							
1 (Lowest)	13,743	25.4	13,350	25.3	393	32.6	
2	13,585	25.2	13,278	25.2	307	25.4	
3	13,500	25.0	13,228	25.1	272	22.5	< .0001
4 (Highest)	13,173	24.4	12,938	24.5	235	19.5	
Missing	1354	2.4	1324	2.4	30	2.4	

[a] High-risk medical comorbidities include: mothers with asthma, chronic hypertension, insulin-dependent diabetes, noninsulin-dependent diabetes, and heart disease.

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hibitors (81 with oseltamivir only, 2 with zanamivir, and 3 with both oseltamivir and zanamivir) compared with unexposed women from the same population, no increased risks of low Apgar score, preterm birth, congenital malformations, or death among infants with exposure to oseltamivir was observed.[20] However, in that study, no SGA case was identified in the exposed group, thus no effect measure could be estimated.[20] Another study found that maternal antiviral exposure was not associated with preterm birth, stillbirth, and major or minor malformations.[19] Data from 2 Japanese teratogen information services including 90 women with oseltamivir exposure in the first trimester. In these 90 cases, 1 case of congenital malformation was identified.[18,21]

Compared with previous studies in this area, our study has several strengths. Our study was based on all singleton infants in Ontario from November 2009 through April 2010. As a result, selection bias was less likely to occur. We used the 2009 through 2010 dataset from the Niday Perinatal Database, through BORN Ontario, an Internet-based provincial birth record system. Most pregnant women are not covered by the provincial PharmaCare plan but by private insurers through employers. As a result, we are unable to obtain complete drug information through prescriptions. Although we have not been able to evaluate the reliability of maternal self-report of use of antivirals, an earlier study by our group demonstrated high quality of BORN Ontario data holdings.[26] Our study was the largest among the few studies that have assessed infant outcomes associated with maternal use of oseltamivir during pregnancy. The rich perinatal data in the database allowed for adjustment for a number of potential confounding factors. We used 2 sets of regression models with and without influenza vaccination during pregnancy and therefore we were able to examine the effect of antiviral drugs independent of influenza vaccination status.

Limitations of our study should be recognized. First, information on oseltamivir treatment during pregnancy was collected at time of admission for delivery and only a "yes" or "no" answer was recorded. As a result, no dose response or analysis by time of exposure during pregnancy could be performed. The exposure time is critical for certain outcomes such as neural tube defects because >12 weeks of gestation, neural tube is closed. For other outcomes such as growth, exposure during late gestation can still play an important role. As a result, we believe that the lack of information on timing of oseltamivir exposure during pregnancy would not invalidate our study findings. We also do not know why women were prescribed oseltamivir because the database does not contain information on the indication for taking antiviral medication (ie, whether for treatment of influenza illness or for prophylaxis). According to professional guidelines, the appropriate use of this type of antiviral medication in pregnancy is to treat or prevent influenza: it is recommended that pregnant women with known or suspected influenza receive antiviral medications as early as possible in the course of their illness.[27] In our data, 56.8% women who took oseltamivir reported influenza illness while 43.2% did not report influenza. However, because we collected data at only

one point during pregnancy, some women may have influenza during pregnancy but not at the time of data collection. Despite this data limitation, sensitivity analysis restricted to pregnant women who reported influenza yielded similar results, suggesting that our findings are robust. Second, we were unable to evaluate congenital anomalies due to large number of missing data on this data element in the BORN database and due to lack of information on the timing of antiviral drug use. We were also not able to analyze data on fetal deaths, because the small number of events in the exposed group of this study population prevented us from having access to the information (cell sizes <6 are suppressed due to privacy regulations). Although this study was much larger than all other similar studies, it remains underpowered except for SGA <10th percentile due to the low prevalence of the exposure. Even for SGA <10th percentile, the statistical significance of the observed association was only marginal. Finally, because of measurement error or unmeasured or unknown risk factors, residual confounding is a concern, and we could not rule out the possibility that it may have affected the observed differences in our study outcomes.

Confounding by indication has been considered an insurmountable obstacle in observational studies assessing intended treatment effects.[28] The argument is that the sicker the patients, the more likely for them to use drugs. In observational studies, if an increased risk associated with drug use is found, it is difficult to discern whether this reflects the fact that users of the medication were severe cases, so they were in need of the medications, or whether it reflects the exposure to the medication. In our study, a decreased risk or no statistically significant result was instead observed. As a result, confounding by indication is less likely to be a concern.

We do not know the mechanism of maternal oseltamivir effect on infant outcomes such as SGA. If any such protective effect truly exists, it may be related to the indirect effects of antiviral treatment on reducing influenza symptoms of the treated women.[5,29] For example, women who were treated with antiviral drugs may have had less severe respiratory, circulatory, or febrile manifestation of influenza symptoms than untreated women with influenza, thus providing adequate oxygen and nutrients to the growing fetus.

It is unlikely from pharmacological and fetal physiological points of view that oseltamivir has a direct effect on fetus. Oseltamivir is readily absorbed by the gastrointestinal tract and is systemically distributed in the body, converted rapidly by hepatic esterase into the active metabolite oseltamivir carboxylase, and then excreted via the kidneys.[30] Worley et al[31] examined the transplacental transfer of oseltamivir using an ex vivo placental model and found that oseltamivir phosphate and oseltamivir carboxylate were not readily transferred from mother to fetus at normal therapeutic doses.

One previous study found that women with high education were more likely to get H1N1 influenza vaccination and those women also believed that vaccina-

TABLE 2
Association between maternal use of oseltamivir and infant outcomes during 2009 H1N1 pandemic in Ontario, Canada

Outcome[a]	No antiviral use (n = 53,875)	Oseltamivir use (n = 1232)
Small for gestational age (<10th percentile)		
n (%)	4975 (9.2)	85 (6.9)
Unadjusted RR (95% CI)	1.00 (Reference)	0.75 (0.61–0.92)
Adjusted RR (95% CI)	1.00 (Reference)	0.77 (0.61–0.98)
Adjusted RR (95% CI)[b]	1.00 (Reference)	0.77 (0.60–0.98)
Small for gestational age (<3rd percentile)		
n (%)	1287 (2.39)	27 (2.2)
Unadjusted RR (95% CI)	1.00 (Reference)	0.92 (0.63–1.34)
Adjusted RR (95% CI)	1.00 (Reference)	0.86 (0.54–1.38)
Adjusted RR (95% CI)[b]	1.00 (Reference)	0.83 (0.51–1.35)
Preterm birth (<37 wk)		
n (%)	3306 (6.1)	86 (7.0)
Unadjusted RR (95% CI)	1.00 (Reference)	1.14 (0.93–1.40)
Adjusted RR (95% CI)	1.00 (Reference)	1.24 (0.97–1.58)
Adjusted RR (95% CI)[b]	1.00 (Reference)	1.26 (0.99–1.61)
Very preterm birth (<32 wk)		
n (%)	379 (0.7)	8 (0.7)
Unadjusted RR (95% CI)	1.00 (Reference)	0.92 (0.50–1.86)
Adjusted RR (95% CI)	1.00 (Reference)	1.39 (0.62–3.11)
Adjusted RR (95% CI)[b]	1.00 (Reference)	1.46 (0.65–3.27)
5-min Apgar score <7		
n (%)	637 (1.2)	16 (1.3)
Unadjusted RR (95% CI)	1.00 (Reference)	1.10 (0.67–1.79)
Adjusted RR (95% CI)	1.00 (Reference)	1.20 (0.67–2.12)
Adjusted RR (95% CI)[b]	1.00 (Reference)	1.22 (0.68–2.16)

CI, confidence interval; *RR*, risk ratio.

[a] All outcomes used denominator of singleton live births and all adjusted models controlled for maternal age, parity, smoking (with missing category), occurrence of any influenza-like illness, presence of any high-risk comorbidities (with missing category), and neighborhood education and income; [b] Additionally adjusted for influenza vaccination during pregnancy.

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tion is safe for themselves and their infants.[32] Interestingly, in our sample, women with high education were less likely to take oseltamivir medication. Those women with high education may be concerned that antiviral medication may have adverse effect on fetus. Antiviral therapies play key roles in prophylaxis and treatment of influenza.[33,34] Despite the fact that influenza vaccination is considered the front line of influenza prevention,[35] vaccination could not provide full protection and only a proportion of the target population was actually vaccinated. Because oseltamivir is not considered a human teratogen, it is currently the recommended drug for influenza treatment and prophylaxis in pregnant women.[18,36] Antiviral medications should be started within 48 hours after symptom onset to maximize the effects.[5,37,38] Because of the importance of early antiviral treatment to reduce or to prevent potential complication of influenza infection during pregnancy, further research is needed to establish a safety profile and to increase women's knowledge about the use of antiviral medications during pregnancy.

Conclusion

In summary, our large birth cohort study during the 2009 H1N1 pandemic found that oseltamivir treatment for pregnant women during pregnancy might be associated with a moderately lower risk of having an SGA infant based on the SGA <10th percentile. Moreover, such treatment was not associated with any other severe forms of adverse outcomes examined in this study. Although several infant outcomes were compared simultaneously, they all share similar pathogenesis mechanisms. Consistent findings with several outcome measures or different regression models suggest that our results are interpretable, despite multiple outcomes were compared simultaneously. Our study provides further data on the relationship between oseltamivir and newborn outcomes, and should be helpful for health care providers and pregnant women alike in their decision making. Nevertheless, further research is required particularly with regard to adverse outcomes related to early pregnancy exposure. ■

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