

Review Article

Influenza and its treatment during pregnancy: A review

L.M. Ghulmiyyah^a, M.M. Alame^a, F.G. Mirza^a, H. Zaraket^b and A.H. Nassar^{a,*}

^aDepartment of Obstetrics and Gynecology, American University of Beirut Medical Center Beirut, Lebanon

^bDepartment of Experimental Pathology, Immunology & Microbiology, American University of Beirut Medical Center, Beirut, Lebanon

Received 20 November 2014

Revised 23 May 2015

Accepted 23 June 2015

Abstract. The influenza viral infection has dramatic effects during pregnancy on the mother and the fetus. We present a review article on the prevention and treatment recommendations of influenza infection in pregnant women, and the effects of antiviral medications on maternal-fetal outcomes. This viral infection not only leads to miscarriages, preterm deliveries and a high maternal mortality rate, but it also poses negative risks to the fetus including small-for-gestational age infants, and admissions to neonatal intensive care units. Vaccination is the most effective strategy for preventing influenza infection during pregnancy whereby can protect both maternal and fetal immunities. The safety profiles of antiviral drugs during pregnancy are limited. Available risk-benefit evidence has indicated that pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy where these medications reduce the risk of complications among pregnant women, and attenuate the teratogenic effects of the influenza infection. Post-exposure prophylaxis is not recommended for most pregnant women, but it may be prescribed in pandemic settings, particularly to non-vaccinated women. Although some *ex vivo* models for pharmacokinetic studies have revealed that the transplacental transfer of oseltamivir to fetal circuits may occur, there is no evidence of adverse fetal outcomes as a result of most in utero exposures to neuraminidase inhibitors. Due to the large number of confounding variables, large, population-based studies are needed to assess the association between in utero oseltamivir exposure and fetal outcome.

Keywords: Pregnancy, influenza, treatment, oseltamivir, pharmacokinetics

Abbreviations

H1N1pdm09 2009 pandemic influenza A/H1N1
ICU intensive care unit
HPAI highly pathogenic avian influenza
CDC Centers for Disease Control
and Prevention

SGA small-for-gestational age
ACIP Advisory Committee on
Immunization Practices
ACOG American College of Obstetricians
and Gynecologists
NAI neuraminidase inhibitor
FDA U.S. Food and Drug Administration
IV intravenous
WHO World Health Organization
JSOG Japan Society of Obstetrics
and Gynecology
OP oseltamivir phosphate

*Corresponding author: Anwar Nassar, MD, Department of Obstetrics and Gynecology, American University of Beirut Medical Center, PO Box: 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon. Tel.: +961 1 350000/Ext. 5600/5604; Fax: +961 1 370829; E-mail: an21@aub.edu.lb.

OC	oseltamivir carboxylate
C_{\max}	maximum concentration
IC ₅₀	inhibitory concentration at 50%
P-gp	phosphoglycoprotein
BCRP	breast cancer resistance protein
MDR1	multidrug resistance protein 1
ATP	adenosine triphosphate

1. Introduction

During pregnancy, the mother and her fetus are vulnerable to unwanted consequences secondary to a variety of microbial infections. Influenza virus has dramatic effects on pregnant women. The H1N1 Spanish flu pandemic in 1918, the worst disease outbreak in history, led to a large number of miscarriages, preterm deliveries, and a high maternal mortality rate of 27% [1, 2]. Similarly, a 20% maternal mortality rate was associated with the 1957 Asian flu pandemic (H2N2) [1, 3]. The 2009 pandemic influenza A/H1N1 (H1N1pdm09) resulted in higher rates of hospitalization (6.3%), intensive care units (ICU) admissions (5.9%), and deaths (5.7%) in pregnant women compared to the general population [4]. The risk of severe disease (ICU admission or death) due to influenza infection is present throughout all trimesters; nevertheless, its severity escalates with the increasing length of pregnancy [5–7]. Moreover, the preterm delivery rate (30.2%) during the 2009 pandemic influenza was significantly greater than the United States average (12.7%) [8]. Increases in illness severity and hospitalization incidence due to respiratory diseases and acute cardiopulmonary problems have also been observed during inter-pandemic periods (seasonal influenza) especially in pregnant women with comorbidities such as diabetes, heart problems, pulmonary or renal diseases, or anemia [6, 9, 10]. Abdel-Ghafar et al. reported mortalities in four out of the six pregnant women infected with the highly pathogenic avian influenza (HPAI) A/H5N1 virus, whereas the two survived women had spontaneous abortions [11].

Transplacental transmission of influenza virus is a rare event that appears to be limited to highly pathogenic influenza viruses [12, 13]. Postmortem analysis tissues obtained from a pregnant woman infected with HPAI H5N1 virus and its fetus demonstrated viremia and the spread of the virus to several tissues, including fetal lung cells [14]. The Centers

for Disease Control and Prevention (CDC) reported in 2009 that the neonates of women who delivered while hospitalized for the H1N1 infection, or after being discharged, were more likely to be admitted to a neonatal ICU and to have a 5-minute Apgar score of less than or equal to six [15]. Several studies have revealed a correlation between maternal influenza infection or hyperthermia and an increased risk of fetal eye anomalies (anophthalmos/microphthalmos), severe limb deficiencies, congenital renal anomalies, neural tube defects, cleft lip with or without cleft palate, and congenital heart defects [3, 16–23]. However, one case-control study has shown no relationship between commonly encountered maternal exposures and conotruncal heart defects [24]. Prenatal exposure to maternal influenza seems to have lifetime consequences, as demonstrated by cohorts born during the Spanish flu pandemic, who have been shown to have an over 20% increased risk of cardiovascular disease between 60 and 82 years of age [3].

The morbidity and mortality consequences of influenza infection are accompanied by increased burden on pregnant patients and healthcare systems. The purpose of this paper is to review the recent recommendations regarding influenza prevention and treatment in pregnant women, examine the safety information of the most commonly used antiviral agent “oseltamivir” on fetal outcomes, and review “oseltamivir” pharmacokinetics profile during pregnancy.

2. Prevention and treatment recommendations for pregnant women

2.1. Vaccination

The first fundamental aspect of prenatal care is the prevention of influenza infections. Vaccination is the first and most effective preventive step to protect both the mother and the new born [25]. Passive transfer of anti-influenza antibodies, from vaccinated pregnant women to the fetus provide protection extended from the neonatal period up to 6 months of age [26–31]. Cohort analysis has revealed that flu vaccination during pregnancy reduces the likelihood of prematurity during local, regional, and widespread influenza outbreaks. It has also been shown that infants born to vaccinated mothers have higher birth weights and are less likely to be born small-for-gestational-age (SGA) [32, 33].

The CDC, the Advisory Committee on Immunization Practices (ACIP), and the American College of Obstetricians and Gynecologists (ACOG) recommend that all women who are pregnant or who might be pregnant during the influenza season receive the influenza vaccine because of the increased risks of serious illnesses and complications from infection [25, 34]. The intramuscular administration of an inactivated influenza vaccine is safe during pregnancy and can be given at any time of the year (optimally in October and November), and during any trimester [3]. Differently, live attenuated influenza vaccines (nasal sprays) are not recommended in pregnant females [25].

2.2. Drug therapy

The second essential element in prenatal care is the prevention or reduction of influenza complications. Studies have shown that the risk of maternal death due to pneumonia complications after influenza infection is reduced by both early antiviral drug use and ICU admission [4, 5, 35].

2.3. Antiviral agents

Two antiviral classes are available for prophylaxis or treatment of influenza infection. Adamantanes (amantadine, and rimantadine) are M2-channel blockers that prevent the release of infectious viral nucleic acid into the host cell, and interrupt viral assembly during replication. Because M2 membrane protein is only present in the influenza A genus, efficacy of adamantanes is limited to this genus [36]. Yet, their clinical utility has been diminished due to widespread resistance among influenza A viruses [37–39]. Neuraminidase inhibitors (NAIs e.g. oral oseltamivir, and inhaled zanamivir) prevent the enzymatic cleavage of sialic acid receptors, thereby preventing the release of progeny virions from the infected cells. Likewise, viral replication and propagation to other host cells is blocked [40, 41]. In addition to these two NAIs, on December 19, 2014, the U.S. Food and Drug Administration (FDA) approved the first intravenous (IV) NAI, peramivir, administered as a single IV dose to treat influenza infection in adults age 18 years and older [42].

The use of any therapeutic agent during pregnancy should be carefully considered by weighing the benefits that would be obtained from its use versus its risks or adverse events. Antiviral agents can lessen symptoms, shorten the disease duration by one or two

days, prevent serious flu complications (pneumonia, respiratory failure, ICU admissions, and death), and decrease the inflammatory responses [5, 32, 43–46]. A large birth cohort study performed by Xie et al. examined the association between maternal oseltamivir use and infant outcome during the 2009 H1N1 pandemic [47]. Out of 55,355 pregnant women, 1237 (2.2%) took oseltamivir for influenza treatment or prevention. There was a significantly lower risk of SGA (<10th percentile) in the maternal group who used oseltamivir at some time during pregnancy. This was a result of reducing the respiratory, circulatory, and febrile symptoms of influenza, thereby providing adequate oxygen and nutrients to the growing fetus. Regarding the risks, a population-based case-control study has shown that the use of antiviral medications was more common in mothers of children with clubfeet than those without major malformations [48]. Nonetheless, despite the strong association observed, no information on the specific antiviral drugs used was presented to allow estimation of drug-specific risks. Overall, the available evidence suggests that antiviral influenza medications can attenuate the teratogenic effects of the virus, and that pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy [23, 49–53].

2.4. Treatment recommendations

The ACIP considers that pregnant women are at high risk of influenza complications and has placed them into a group requiring empiric treatment upon exposure to the virus [53]. Similarly, the CDC recommends treatment with antiviral medications for pregnant women (and those up to 2 weeks postpartum) with suspected or confirmed influenza [53]. During the 2009 H1N1 pandemic, the World Health Organization (WHO), the CDC, and the Japan Society of Obstetrics and Gynecology (JSOG) recommended the use of NAIs (oseltamivir or zanamivir) in infected pregnant patients [43, 54–56].

During the later stages of pregnancy, the diaphragmatic excursion, which is limited by the gravid uterus, may impair the necessary distribution of inhaled zanamivir through the respiratory tract [31]. As a result, oral oseltamivir is currently the preferred anti-influenza agent for use in pregnant women since it is systemically absorbed, and it would be more consistently delivered to virus-infected respiratory tract tissues than inhaled zanamivir [53]. More extensive

clinical studies and safety analysis should be performed involving oseltamivir use during pregnancy [57, 58].

For both seasonal and pandemic influenza infections, in addition to the administration of oseltamivir, hydration and regular antipyretic agents are recommended because the CDC has stated that fever in pregnant women should be treated, and acetaminophen appears to be the best option [3, 53, 59, 60].

2.5. Dose and treatment duration

Pregnant women are recommended to receive the same antiviral dosage as non-pregnant women. In adults, for the treatment of acute uncomplicated influenza, the FDA has approved an oral 75 mg twice daily dosage of oseltamivir and a 10 mg twice daily dosage of inhaled zanamivir for 5 days. Longer treatment durations may be required for hospitalized patients with severe infections [61].

2.6. Best initiation time

The short incubation period of the influenza virus (1–4 days) necessitates early antiviral initiation to either increase the probability of treatment success or lower the risk of severe disease development [4, 62]. Studies have shown that antiviral drugs are most effective when initiated within the first 48 hours of symptom onset, but starting these drugs later can still be helpful [25, 53, 58, 63, 64]. Siston et al. found that the initiation of treatment within less than 3 days of illness onset is the best for preventing respiratory failure and death among infected pregnant women during any trimester, and that treatment within 2 days of influenza symptoms onset has been associated with fewer ICU admissions compared to treatment at more than 4 days after symptom onset [5]. Correspondingly, the CDC recommends that antiviral medications with NAI should be started as soon as possible without waiting for a laboratory confirmation of the influenza infection [53]. These medications can be taken during any trimester of pregnancy, and all pregnant women should be offered antiviral therapy regardless of the duration of their symptoms [51, 53].

2.7. Post-exposure chemoprophylaxis

Influenza risk is lowered but not eliminated by post-exposure chemoprophylaxis. The improper use of

antiviral medications may promote resistance. Decisions to perform chemoprophylaxis should take into consideration the complication risk of the exposed patient, type and duration of close contact, clinical judgment, and advice from local authorities [65]. Potential side effects, compliance, cost, and drug availability should also be considered [62]. It has been noted that during an influenza pandemic, in contrary to seasonal influenza, the post-exposure prophylactic use of antiviral medications during pregnancy is a cost-effective intervention that prevents or reduces risk of influenza complications including maternal hospitalization, mortality, and preterm birth [66].

Even though the efficacy of NAIs for post-exposure prophylaxis in pregnant women remain uncertain, their use is likely to be recommended in pandemic settings, particularly to non-vaccinated pregnant women [63, 67]. Generally, chemoprophylaxis is recommended in high-risk individuals who usually suffer from severe influenza irrespective of the promptness of the treatment [63]. The CDC has recommended the consideration of administration of prophylactic antiviral medications (for 10 days in duration) within 48 hours of the most recent exposure for different groups of pregnant women, which include those who have (1) cared for or lived with a person with confirmed, probable, or suspected influenza; (2) been in a setting where there was a high likelihood of contact with the respiratory droplets and/or body fluids of a person with confirmed, probable, or suspected influenza; or talked face-to-face with a person with suspected or confirmed influenza illness [53, 55].

Due to its limited systemic absorption (4–20%) into the bloodstream, that lowers its placental bioavailability, and local action in the respiratory tract inhaled zanamivir (10 mg once daily) may be the preferred antiviral chemoprophylactic agent unless a patient is at risk for respiratory problems (such as severe asthma and pneumonia), in which case oseltamivir (75 mg once daily) is the alternative [3, 53, 61, 63].

3. Oseltamivir safety profile during pregnancy

Birth defects may occur due to drug exposure, especially during the embryonic period that lies between three to eight weeks from conception [68]. The safety profiles of influenza antiviral drugs during pregnancy are limited [41, 57, 69, 70]. Indeed, the FDA considers the teratogenic risks of NAIs as “Pregnancy

Category C,” which means that their use may be associated with fetal risk because animal reproduction studies have shown that they adversely affect the fetus [71]. Yes, data from animal studies for determining the risk of a drug to the fetus, although valuable, are not always applicable to humans and may not be predictive of the human response. Due to ethical considerations, controlled prospective human studies are generally not performed on pregnant women. For now, knowledge about the teratogenicity of drugs relies mainly on case reports, case-control studies, or cohort studies [71].

3.1. *Animal studies*

Animal studies have suggested that potential fetal adverse effects of oseltamivir may exist. Studies of the effect of oral oseltamivir on embryo-fetal development were conducted in rats and rabbits at doses of up to 100 and 50 times, respectively, of those administered to humans. Both of these species demonstrated fetal exposure to the drug in pharmacokinetic studies. In the rat study, higher dosages (1500 mg/kg/day) were reported to confer minimal maternal toxicity (the prolongation of parturition). In the rabbit study, slight and marked maternal toxicities were successively observed due to 150 and 500 mg/kg/day dosages. Dose-dependent increases in the incidence rates of a variety of minor skeletal abnormalities were observed at high oseltamivir doses. Still, the individual incidence rate of each skeletal abnormality did not exceed that of the historical control for each species [68]. Considering the isolated nature of this finding, it is unlikely that this drug is sufficiently toxic to produce a teratogenic effect [60, 72].

3.2. *Human studies*

There has been no evidence of an association between antepartum antiviral exposure and adverse outcomes, as shown by most retrospective cohort studies [36, 47]. Besides, prospective studies have not shown significant increases in preterm deliveries, low birth weight, growth restriction, or overall malformation risks in infants exposed to NAIs [63, 73]. A prospective study performed by Saito et al. found that therapeutic oseltamivir doses do not produce adverse fetal outcomes such as congenital malformations, birth weight less than 2500 g or stillbirth, nor adverse maternal effects including miscarriage, preterm delivery, or any other transient abnormalities during the neonatal

period like neonatal death, necrotizing enterocolitis, intraventricular hemorrhage, and seizures [43]. These results support the safety of the use of oseltamivir during pregnancy.

Svensson et al. found that infants, who were exposed to NAIs in fetal life, possess an increased risk of late transient hypoglycemia [73]. This finding was also observed in the study by Saito et al., in which hypoglycemia occurred in three (0.5%) out of 620 infants exposed to oseltamivir in utero and in one (2%) out of 50 zanamivir-exposed infants [43]. However, considering the data reported by Svensson and Saito together, the hypoglycemia frequency (1%) in the neuraminidase-exposed group would be lower than that in the unexposed group in Svensson's report (1.2%) [43, 73]. Significant association between oseltamivir utilization in pregnant women and adverse fetal outcomes, such as pregnancy loss, preterm delivery, low birth weight, neonatal pathology, and congenital malformations have been reported [60]. Among the reported malformations were one skeletal malformation and one congenital heart defect involving two women exposed to oseltamivir during their 4th and 1st month (organogenesis) of pregnancy, respectively. However, the latter mother had been exposed to several other drugs during pregnancy (salicylic acid, paracetamol, tuaminoheptane, escitalopram, and oxememazine during the first trimester; and paracetamol, amoxicillin, budesonide, tixocortol, and several homeopathics during the third trimester) and thus the resulting malformations cannot be solely attributed to oseltamivir.

4. **Pharmacokinetics of oseltamivir**

To understand the effects of medications on the fetus, one must understand the kinetics of drug molecules during pregnancy as well as the physiology of the placenta.

4.1. *Non-pregnant women*

Oseltamivir is administered as a prodrug oseltamivir phosphate (OP) and is rapidly converted by the hepatic enzyme carboxylesterase-1 to the active ingredient oseltamivir carboxylate (OC) [40, 41]. Oral OP is well absorbed from the gastrointestinal tract having a bioavailability of at least 75%, and reaching a peak serum concentration within 1 hour [37]. The active

metabolite OC has an excellent ability to penetrate into tissues, such as those of the lungs, nasal mucosa, and middle ear [37, 74]. It has an elimination half-life of 6–10 hours, and the excretion of the active ingredient occurs mainly (99%) via the kidneys because it does not undergo further phase I metabolism by cytochrome P450 mixed-function oxidases nor phase II metabolism by glucuronosyltransferases [18, 37, 74].

The renal clearance of OP and OC exceeds the glomerular filtration rate indicating that renal tubular secretion via organic anion transporter-1 is also involved in the elimination of these compounds [74]. Organic anion transporters are also present in the placenta suggesting possible interactions of OP and OC with placental transporters as well [75].

4.2. Pregnant women

4.2.1. Pharmacokinetic changes and dosing considerations of oseltamivir

During pregnancy, physiological changes that occur may affect the pharmacokinetics of therapeutic agents, influencing their absorption, distribution, metabolism, and excretion. This predicts the need for adjustment of medication doses in pregnant women compared to the general population. Because safety and ethical concerns exclude pregnant women from the drug development process, different oseltamivir dosing recommendations have been proposed based on the known physiological changes.

The glomerular filtration rate is increased by 50% during pregnancy, leading to increases in creatinine clearance and renal plasma flow that cause drugs primarily excreted by the kidneys (such as oseltamivir) undergo greater renal elimination [40]. This confers the need for dose up-titration to reach therapeutic concentrations and avoid sub-therapeutic antimicrobial levels that may contribute to a lack of effectiveness and to the development of drug resistance. Saleeby et al. recommended the doubling of the oseltamivir dosage and the duration of its administration, from 75 mg twice daily for 5 days to 150 mg twice daily for 10 days, in acutely ill H1N1-infected pregnant women requiring mechanical ventilation [76]. Begi et al. studied the pharmacokinetics of OP and OC in pregnant women compared to non-pregnant controls, revealing that the maximum concentration (C_{max}) was higher in non-pregnant women, and the apparent half-life did not significantly differ between the groups. This study also found that pregnant women have significantly lower

OC blood concentrations (30%), suggesting that the dosage be increased to 75 mg three times daily in influenza-infected pregnant patients to reach comparable drug concentrations as those in non-pregnant women. Likewise, an increase in drug exposure and a higher trough level of OC aids in more efficient inhibition of viral replication in different tissue compartments in critically ill patients [77]. On the other hand, Greer et al. suggested that although the first OP dose contributes to a lower maximum concentration of OC in pregnant women compared with the steady state concentration reached in non-pregnant women, the overall level of exposure achieves the required inhibitory concentration at 50% (IC_{50}), which is adequate to treat H1N1pdm09 infections. Pregnancy does not appear to significantly change the timing of either the absorption or conversion of OP to OC. In addition, the half-life of OC in pregnant women, which is similar to that in non-pregnant women, does not differ among the three trimesters [40].

Despite the aforementioned findings, in a meeting convened by the CDC in 2008 to obtain input from experts and key partners regarding the clinical management of pregnant women and related public health actions to be taken during a pandemic, experts did not recommend dosage adjustments for pregnant women because of the lack of available data addressing this issue [78].

4.3. Oseltamivir transplacental transfer in ex vivo models

Once a drug in the maternal circulation, it needs to cross the placenta to reach the fetus. This process occurs either by passive diffusion or by protein transports [71, 67]. Transplacental transfer processes are regulated by a number of variables, including molecule size, ionic state (pK_a ionization constant), lipid solubility, the extent of protein binding, maternal blood flow, the concentration in the maternal plasma, and placental metabolism [79, 80]. For passive diffusion, a drug needs to have a low molecular weight (less than 5 K daltons), not to be bound to plasma proteins, and to be in an un-ionized form [71].

To predict the safety of oseltamivir on the fetus, the extent of exposure must be determined by measuring the concentration of this drug in the fetal circulation [75]. However, existing data regarding oseltamivir transfer across the placenta are contradictory. Although OC has a relatively low molecular weight of 312.7

daltons and an extremely low protein binding rate of 3%, Worley et al., using an *ex vivo* placental model, were unable to detect it in fetal circuits following the perfusion of OP at concentrations ranging from 5-6-folds more than the therapeutic level [72, 80]. The transplacental transfer of OC was also incomplete following the perfusion of OP at very high concentrations (600–800 times more than the therapeutic level) [80]. In contrast, Berveiller et al. detected OP and OC in fetal blood after their co-perfusion in an *ex vivo* placental cotyledon model [81]. Similarly, Nanovskaya et al. performed a dual perfusion of the placental lobe to determine the bidirectional transfer of OC across the term human placenta and its distribution among the tissue, maternal, and fetal circuits. The results showed that *in vivo* fetal exposure to OC is plausible because it is able to cross the placenta in both directions, including the maternal-to-fetal and fetal-to-maternal directions [75].

4.4. Protein transporter regulatory effects

The placenta, which forms the interface between the fetal and maternal circulations, contains many protein transporters that allow the regulation of the passage of endogenous molecules and xenobiotics into the fetus [67]. These transporters include phosphoglycoprotein (P-gp) and breast cancer resistance protein (BCRP), which are considered to be the most important placental drug transporters of the microvillous membrane (maternal blood-facing) of the syncytiotrophoblast, providing fetal protection [1].

P-gp, or multidrug resistance protein 1 (MDR1), is an ATP-dependent drug efflux pump that transports hydrophilic and positively charged substrates out of cells [67, 82]. These substrates include a variety of therapeutic drugs, such as antibiotics and antiviral agents including OC [82, 83]. Although MDR1 expression has been shown to decrease with advancing gestational age, this protein transporter has been detected in the placenta during all the three trimesters [67]. Accordingly, some studies have found that low transplacental fetal permeability determines the safety of a drug, supporting the hypothesis that the fetal transfer of oseltamivir is restricted by a number of active transporters, especially P-gp functionally expressed at the placental barrier. On the contrary, Nanovskaya et al. suggested that there is no involvement of placental efflux proteins in OC transport [75]. Notably, the expression of transporters is affected by polymor-

phisms [84]. Studies have revealed genetic variation in drug transporters among different ethnic groups, which may influence fetal drug transfer between different individuals.

5. Conclusion

Fetal health is correlated with maternal health. Life-saving medications for pregnant patients should not be withheld because of reported risks to the fetus, especially when the drugs present maternal benefits that outweigh the potential fetal risks. To date, although some *ex vivo* models have revealed that the transplacental transfer of OP or OC to fetal circuits may occur, there is no evidence of adverse fetal outcomes as a result of most in utero exposures to NAIs. At the same time, there are clear maternal and fetal benefits associated with the administration of these drugs, and the CDC has suggested that pregnancy should not be considered a contraindication for the use of oseltamivir and zanamivir. Nevertheless, although oseltamivir is not a major teratogen in humans, empiric treatment decisions should take into consideration the knowledge of influenza activity in the community, the pathogenicity of the circulating influenza strain, and the general health of the pregnant woman. Due to the large number of confounding variables, large, population-based studies are still needed to better assess the association between in utero oseltamivir exposure and fetal outcomes.

Acknowledgments

None.

Disclosure statements

The authors have no conflicts of interest to declare.

References

- [1] Taubenberger J, Kash J. Influenza virus evolution, host adaptation, and pandemic formation. *Cell Host Microbe* 2010;7(6):440-51.
- [2] Kourtis A, Read J, Jamieson D. Pregnancy and infection. *N Engl J Med* 2014;370(23):2211-8.
- [3] Lim B, Mahmood T. Pandemic H1N1 2009 (swine flu) and pregnancy. *J Obstet Gynaecol India* 2011;61(4):386-93.

- [4] Mosby L, Rasmussen S, Jamieson D. 2009 pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. *Am J Obstet Gynecol* 2011;205:10-8.
- [5] Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA* 2010;303(15):1517-25.
- [6] Neuzil K, Reed G, Mitchel E, Simonsen L, Griffin M. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998;148(11):1094-102.
- [7] Rolland-Harris E, Vachon J, Kropp R, Frood J, Morris K, Pelletier L, et al. Hospitalization of pregnant women with pandemic A(H1N1) 2009 influenza in Canada. *Epidemiol Infect* 2012;140(7):1316-27.
- [8] Mendez-Figueroa H, Raker C, Anderson B. Neonatal characteristics and outcomes of pregnancies complicated by influenza infection during the 2009 pandemic. *Am J Obstet Gynecol* 2011;204(6 Suppl 1):S58-63.
- [9] Cox S, Posner S, McPheeters M, Jamieson D, Kourtis A, Meikle S. Hospitalizations with respiratory illness among pregnant women during influenza season. *Obstet Gynecol* 2006;107(6):1315-22.
- [10] Dodds L, McNeil S, Fell D, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 2007;176(4):463-8.
- [11] Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, Abdel-Ghaffar AN, Chotpitayasunondh T, Gao Z, Hayden F, Nguyen D, et al. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008;358(3):261-73.
- [12] Irving WL, James DK, Stephenson T, Laing P, Jameson C, Oxford JS, et al. Influenza virus infection in the second and third trimesters of pregnancy: A clinical and seroepidemiological study. *BJOG* 2000;107(10):1282-9.
- [13] Kanmaz HG, Erdeve O, Oğz SS, Uras N, Celen S, Korukluoglu G, et al. Placental transmission of novel pandemic influenza A virus. *Fetal Pediatr Pathol* 2011;30(5):280-5.
- [14] Gu J, Xie Z, Gao Z, Liu J, Korteweg C, Ye J, et al. H5N1 infection of the respiratory tract and beyond: A molecular pathology study. *Lancet* 2007;370(9593):1137-45.
- [15] Centers for Disease Control and Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)—United States, April 2009–August 2010. *MMWR Morb Mortal Wkly Rep* 2011;60(35):1193-6.
- [16] Busby A, Dolk H, Armstrong B. Eye anomalies: Seasonal variation and maternal viral infections. *Epidemiology* 2005;16(3):317-22.
- [17] Martínez-Frías M, García Mazario M, Caldas C, Conejero Gallego M, Bermejo E, Rodríguez-Pinilla E. High maternal fever during gestation and severe congenital limb disruptions. *Am J Med Genet* 2001;98(2):201-3.
- [18] Abe K, Honein M, Moore C. Maternal febrile illnesses, medication use, and the risk of congenital renal anomalies. *Birth Defects Res A Clin Mol Teratol* 2003;67(11):911-8.
- [19] Li Z, Ren A, Liu J, Pei L, Zhang L, Guo Z, et al. Maternal flu or fever, medication use, and neural tube defects: A population-based case-control study in Northern China. *Birth Defects Res A Clin Mol Teratol* 2007;79(4):295-300.
- [20] Moretti M, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: Systematic review and meta-analysis. *Epidemiology* 2005;16(2):216-9.
- [21] Ács N, Bánhidly F, Puhó E, Czeizel AE. Maternal influenza during pregnancy and risk of congenital abnormalities in offspring. *Birth Defects Res A Clin Mol Teratol* 2005;73(12):989-96.
- [22] Oster ME, Riehle-Colarusso T, Alverson CJ, Correa A. Associations between maternal fever and influenza and congenital heart defects. *J Pediatr* 2011;158(6):990-5.
- [23] Li M1, Liu Z, Lin Y, Chen X, Li S, You F, et al. Maternal influenza-like illness, medication use during pregnancy and risk of congenital heart defects in offspring. *J Matern Fetal Neonatal Med* 2014;27(8):807-11.
- [24] Adams M, Mulinare J, Dooley K. Risk factors for conotruncal cardiac defects in Atlanta. *J Am Coll Cardiol* 1989;14(2):432-42.
- [25] Centers for Disease Control and Prevention. Letter to providers: Influenza vaccination of pregnant women. Feb 2014, Atlanta: Department of Health & Human Services. Available from: <http://www.cdc.gov/flu/pdf/protect/pregnancy-letter-2014.pdf>.
- [26] Sumaya C, Gibbs R. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: Reactogenicity and immunogenicity in mother and infant. *J Infect Dis* 1979;140(2):141-6.
- [27] Englund J, Mbawuike I, Hammill H, Holleman M, Baxter B, Glezen W. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis* 1993;168(3):647-56.
- [28] Puck J, Glezen W, Frank A, Six H. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. *J Infect Dis* 1980;142(6):844-9.
- [29] Reuman P, Ayoub E, Small P. Effect of passive maternal antibody on influenza illness in children: A prospective study of influenza A in mother-infant pairs. *Pediatr Infect Dis J* 1987;6(4):398-403.
- [30] Steinhoff MC, Omer SB, Roy E, Arifeen SE, Raqib R, Altaye M, et al. Influenza immunization in pregnancy—antibody responses in mothers and infants. *N Engl J Med* 2010;362(17):1644-6.
- [31] Aoki FY, Allen UD, Stiver HG, Evans GA. AMMI Canada guideline. The use of antiviral drugs for influenza: A foundation document for practitioners. *Can J Infect Dis Med Microbiol* 2013;24(Suppl C Autumn):1C-15C.
- [32] Rasmussen S, Jamieson D, Uyeki T. Effects of influenza on pregnant women and infants. *Am J Obstet Gynecol* 2012;207(3 Suppl):S3-8.
- [33] Omer SB, Goodman D, Steinhoff MC, Rochat R, Klugman KP, Stoll BJ, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: A retrospective cohort study. *PLoS Med* 2011;8(5):e1000441.
- [34] ACOG Committee Opinion No. 468: Influenza vaccination during pregnancy. *Obstet Gynecol* 2010;116(4):1006-7.
- [35] Liu S, Wang J, Yang X, et al. Pandemic influenza A(H1N1) 2009 virus in pregnancy. *Rev Med Virol* 2013;23(1):3-14.
- [36] Greer L, Sheffield J, Rogers V, Roberts S, McIntire D, Wendel G. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. *Obstet Gynecol* 2010;115(4):711-6.

- [37] Razonable R. Antiviral drugs for viruses other than human immunodeficiency virus. *Mayo Clin Proc* 2011;86(10):1009-26.
- [38] Krumbholz A, Schmidtke M, Bergmann S, Motzke S, Bauer K, Stech J, et al. High prevalence of amantadine resistance among circulating European porcine influenza A viruses. *J Gen Virol* 2009;90(4):900-8.
- [39] Hayden F, Hay A. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. *Curr Top Microbiol Immunol* 1992;176:119-30.
- [40] Greer L, Leff R, Rogers V, et al. Pharmacokinetics of oseltamivir according to trimester of pregnancy. *Am J Obstet Gynecol* 2011;204(6 Suppl 1):S89-93.
- [41] Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu(R)) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005;55(Suppl 1):i5-i21.
- [42] Fda.gov. FDA approves Rapivab to treat flu infection. 2014 [cited 28 April 2015]. Available from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427755.htm>.
- [43] Saito S, Minakami H, Nakai A, Unno N, Kubo T, Yoshimura Y. Outcomes of infants exposed to oseltamivir or zanamivir in utero during pandemic (H1N1) 2009. *Am J Obstet Gynecol* 2013;209(2):130.e1-9.
- [44] Hayden F, Treanor J, Fritz R, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: Randomized controlled trials for prevention and treatment. *JAMA* 1999;282(13):1240.
- [45] Hiba V, Chowdhury M, Levi-Vinograd I, Rubinovitch B, Leibovici L, Paul M. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): Retrospective cohort study. *J Antimicrob Chemother* 2011;66(5):1150-5.
- [46] Lee N, Choi KW, Chan PK, Hui DS, Lui GC, Wong BC, et al. Outcomes of adults hospitalised with severe influenza. *Thorax* 2010;65(6):510-5.
- [47] Xie H, Yassen A, Xie R, et al. Infant outcomes among pregnant women who used oseltamivir for treatment of influenza during the H1N1 epidemic. *Am J Obstet Gynecol* 2013;208(4):293.e1-7.
- [48] Werler M, Yazdy M, Kasser J, et al. Medication use in pregnancy in relation to the risk of isolated clubfoot in offspring. *Am J Epidemiol* 2014;180(1):86-93.
- [49] Czeizel A, Puhó E, Ács N, Bánhidly F. High fever-related maternal diseases as possible causes of multiple congenital abnormalities: A population-based case-control study. *Birth Defects Res A Clin Mol Teratol* 2007;79(7):544-51.
- [50] Ács N, Bánhidly F, Horváth-Puhó E, Czeizel A. Population-based case-control study of the common cold during pregnancy and congenital abnormalities. *Eur J Epidemiol* 2006;21(1):65-75.
- [51] Torres M, Moayedi S. Gynecologic and other infections in pregnancy. *Emerg Med Clin North Am* 2012;30(4):869-84.
- [52] Fda.gov. Treatment of influenza during pregnancy [Internet]. 2009 [cited 23 July 2014]. Available from: <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm184917.htm>.
- [53] Prevention C. Recommendations for obstetric health care providers related to use of antiviral medications in the treatment and prevention of influenza health professionals seasonal influenza (flu) [Internet]. Cdc.gov. 2014 [cited 23 July 2014]. Available from: http://www.cdc.gov/flu/professionals/antivirals/avrec_ob.htm.
- [54] Who.int. WHO | Recommended use of antivirals [Internet]. 2009 [cited 9 August 2014]. Available from: http://www.who.int/csr/disease/swineflu/notes/h1n1_use_antivirals_20090820/en/index.html.
- [55] Cdc.gov. CDC H1N1 Flu updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season [Internet]. 2009 [cited 9 August 2014]. Available from: <http://www.cdc.gov/H1N1flu/recommendations.htm>.
- [56] Yamada T, Yamada T, Morikawa M, Cho K, Endo T, Sato S, et al. Pandemic (H1N1) 2009 in pregnant Japanese women in Hokkaido. *J Obstet Gynaecol Res* 2012;38(1):130-6.
- [57] Tanaka T, Nakajima K, Murashima A, Garcia-Bournissen F, Koren G, Ito S. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. *CMAJ* 2009;181(1-2):55-8.
- [58] The Medical Letter, Inc. Antiviral drugs for influenza. *Med Lett Drugs Ther* 2012;54(1381):1-3.
- [59] Bernstein H. Chapter 50: Maternal and perinatal infectious viral. In: Gabbe SG, editor. *Obstetrics: Normal and problem pregnancies*. 6th ed. Philadelphia: Elsevier Saunders; 2012, pp. 1122-3.
- [60] Beau A, Hurault-Delarue C, Vial T, Montastruc J, Damase-Michel C, Lacroix I. Safety of oseltamivir during pregnancy: A comparative study using the EFEMERIS database. *BJOG* 2014;121(7):895-900.
- [61] Cdc.gov. influenza antiviral medications: Summary for clinicians | health professionals | seasonal influenza (flu) [Internet]. 2014 [cited 23 July 2014]. Available from: <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#dosage>.
- [62] Burpo R. Antiviral agents in women's health: Pharmacotherapeutics of treating influenza and herpes. *J Midwifery Womens Health* 2002;47(3):182-9.
- [63] Dunstan H, Mill A, Stephens S, Yates L, Thomas S. Pregnancy outcome following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: A national prospective surveillance study. *BJOG* 2014;121(7):901-6.
- [64] Panda B, Panda A, Riley L. Selected viral infections in pregnancy. *Obstet Gynecol Clin North Am* 2010;37(2):321-31.
- [65] Cdc.gov. Antiviral agents for the treatment and chemoprophylaxis of influenza: Recommendations of the advisory committee on immunization practices (ACIP). [Internet]. 2011 [cited 2014 August 1]. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>.
- [66] Lee B, Bailey R, Waring A, Assi T, Beigi R. Antiviral medications for pregnant women for pandemic and seasonal influenza: An economic computer model. *Obstet Gynecol* 2009;114(5):971-80.
- [67] Tomi M, Nishimura T, Nakashima E. Mother-to-fetus transfer of antiviral drugs and the involvement of transporters at the placental barrier. *J Pharm Sci* 2011;100(9):3708-18.
- [68] Donner B, Niranjana V, Hoffmann G. Safety of oseltamivir in pregnancy: A review of preclinical and clinical data. *Drug Saf* 2010;33(8):631-42.
- [69] Freund B, Gravenstein S, Elliott M, Miller I. Zanamivir: A review of clinical safety. *Drug Saf* 1999;21(4):267-81.
- [70] Rasmussen S, Jamieson D, Bresee J. Pandemic influenza and pregnant women. *Emerg Infect Dis* 2008;14(1):95-100.

- [71] Habal R. Chapter 180: Drug therapy in pregnancy. In: Rosen's emergency medicine: Concepts and clinical practice. 8th ed. Philadelphia: Elsevier Saunders; 2014, pp. 2316-7.
- [72] fda.gov. TAMIFLU® (oseltamivir phosphate) capsules and for oral suspension [Internet]. 2008 [cited 23 July 2014]. Available from: <http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm147992.pdf>.
- [73] Svensson T, Granath F, Stephansson O, Kieler H. Birth outcomes among women exposed to neuraminidase inhibitors during pregnancy. *Pharmacoepidemiol Drug Saf* 2011; 20(10):1030-4.
- [74] He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug Oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet* 1999;37(6):471-84.
- [75] Nanovskaya T, Patrikeeva S, Zhan Y, Hankins G, Ahmed M. Transplacental transfer of oseltamivir carboxylate. *J Matern Fetal Neonatal Med* 2012;25(11):2312-5.
- [76] Saleeby E, Chapman J, Morse J, Bryant A. H1N1 influenza in pregnancy: Cause for concern. *Obstet Gynecol* 2009; 114(4):885-91.
- [77] Beigi RH, Han K, Venkataramanan R, Hankins GD, Clark S, Hebert MF, et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. *Am J Obstet Gynecol* 2011;204(6):S84-S88.
- [78] Rasmussen S, Jamieson D, MacFarlane K, Cragan J, Williams J, Henderson Z. Pandemic influenza and pregnant women: Summary of a meeting of experts. *Am J Public Health* 2009;99(S2):S248-S254.
- [79] Gedeon C, Koren G. Designing pregnancy centered medications: Drugs which do not cross the human placenta. *Placenta* 2006;27(8):861-8.
- [80] Worley K, Roberts S, Bawdon R. The metabolism and transplacental transfer of oseltamivir in the *ex vivo* human model. *Infect Dis Obstet Gynecol* 2008;2008:1-5.
- [81] Berveiller P, Mir O, Vinot C, et al. Transplacental transfer of oseltamivir and its metabolite using the human perfused placental cotyledon model. *Am J Obstet Gynecol* 2012; 206(1):92.e1-92.e6.
- [82] Instiaty I, Lindegardh N, Jittmala P, et al. Comparison of oseltamivir and oseltamivir carboxylate concentrations in venous plasma, venous blood, and capillary blood in healthy volunteers. *Antimicrob Agents Chemother* 2013;57(6): 2858-62.
- [83] Iqbal M, Audette M, Petropoulos S, Gibb W, Matthews S. Placental drug transporters and their role in fetal protection. *Placenta* 2012;33(3):137-42.
- [84] Mirochnick M, Clarke D. Oseltamivir pharmacokinetics in pregnancy: A commentary. *Am J Obstet Gynecol* 2011; 204(6):S94-S95.