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Review Article

Influenza in pregnancy

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The 2009 pandemic served as a strong reminder that influenza-induced disease can have a great impact on certain at-risk populations and that pregnant women are one such important population. The increased risk of fatal and severe disease in these women was appreciated more than 500 years ago, and during the last century, pregnant women and their newborns have continued to be greatly affected by both seasonal and pandemic influenza. In this review, we briefly discuss the data collected both before and after the 2009 pandemic as it relates to the impact of influenza on pregnant women and their fetuses/newborns, as well as risk variables, clinical features, clues to pathophysiologic mechanisms, and approaches to treatment and prevention.

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Introduction

The 2009 H1N1 influenza pandemic offered an opportunity to re-examine the health effects of infection using approaches not available during previous influenza pandemics, including that of 1968. An important epidemiologic feature of virtually all influenza pandemics and seasonal epidemics of any degree of severity is the existence of specific groups of people at elevated risk for severe complications and death; these include the very young, the very old, patients with underlying chronic respiratory and cardiovascular conditions, and pregnant women and the fetuses they carry.[1,2] That pregnant women are at increased risk of severe and fatal influenza-associated disease was appreciated more than 500 years ago and has been repeatedly confirmed since. In the last century, increased influenza risk for pregnant women has been reported in multiple clinical and epidemiological studies undertaken during pandemic years as well as during seasonal influenza epidemics.[3–6]

Here, we briefly review data collected both before and after the 2009 pandemic about the impact of influenza on pregnant women and their fetuses/newborns, as well as risk variables, clinical features, clues to pathophysiologic mechanisms, and approaches to treatment and prevention.

The nature and magnitude of influenza risk to pregnant women, fetuses, and newborns

Although appreciated for centuries, the impact of pandemic influenza on pregnant women and their unborn children was first examined systematically during the 1889, and more substantially during the 1918 pandemics. The 1918 'Spanish flu' killed 675 000 persons in the United States, with an overall case fatality rate of 1–2%.[7] Numerous studies indicated that pregnant women were at greatly elevated risk of severe disease and death, with overall fatality rates calculated to be as high as 27%,[4–6] and as high as 50% or higher in pregnant women who developed secondary bacterial pneumonia.[5] The 1957 and 1968 influenza pandemics caused significantly lower overall mortality, 70 000 and 30 000 US deaths in the first year respectively,[8] but pregnant women again accounted for significant and disproportionate numbers of deaths.[4,9]

In recent decades, circulation of seasonal H3N2 and H1N1 viruses has resulted in an average of approximately 24 000 influenza-associated annual US deaths,[3] and more than 200 000 hospitalizations,[10] typically associated with underlying co-morbidities such as cardiopulmonary diseases or immunocompromising states.[11,12] As was the case during past pandemics, pregnancy during these seasonal epidemics has also been associated with increased illness severity and risk of death. In studies lacking complete virologic confirmation, pregnant women were more likely to be hospitalized for respiratory illnesses than non-pregnant women, especially during influenza season;[6,13] and pregnant women with influenza were three to four times more likely to be hospitalized for an acute cardiopulmonary condition[6] and eight times more likely if they had one pre-existing underlying comorbidity.[13] Moreover, it has been repeatedly documented that risk increases as the pregnancy progresses, with up to fivefold higher influenza-associated hospitalization rates in women infected with influenza during the third trimester.[13]

The 2009–2010 pandemic has provided another opportunity to examine pregnancy as a risk factor for influenza severity.[14–18] Increased A(H1N1)pdm09-associated hospitalizations, intensive care unit (ICU) admissions, complications, and mortality during pregnancy were documented worldwide. Pregnancy was identified globally as one of the strongest risk factors for influenza-associated ICU admission, in some studies constituting a larger risk factor than influenza associated with cardiac failure, diabetes, or obesity.[19–22]

Although pregnant women make up only about 1% of the US population at any point in time, during the 2009–2010 pandemic, pregnant women accounted for up to 6·3% of influenza-associated hospitalizations, 5·9% of ICU admissions, and 5·7% of deaths.[23] Among US women between 18 and 29 years of age, pregnancy accounted for up to 29% of influenza-associated hospitalizations and up to 16% of deaths.[24–27] In European women, influenza during pregnancy accounted for <10% of A(H1N1)pdm09 fatalities.[28]

Both seasonal and pandemic influenza has a significant impact on the fetus as well as the mother. In recent years of seasonal influenza virus circulation, infection during pregnancy has been associated with an approximate fivefold increase in perinatal mortality, including miscarriages, stillbirths, and early neonatal diseases and death.[29,30] There has been a threefold increased risk of premature and often complicated birth in pregnant women hospitalized with A(H1N1)pdm09.[31] Infants who were delivered during their mother's hospitalization for A(H1N1)pdm09 were more likely to be pre-term and have low birth weight, while infants delivered following the mother's hospitalization had increased likelihood of being small for their gestational age.[18] Part of this risk seems to have resulted from a nearly doubling of Cesarean section deliveries in influenza-infected mothers, in many cases being performed on an emergent basis due to worsening maternal status.[16,23] Such premature births due to spontaneous delivery or Cesarean section were presumably associated with maternal infection and not infection of the fetus.[23] Adverse effects on the fetus of ICU-treated mothers, some of who received mechanical ventilation or ECMO, must also be great, but have not yet been clearly measured.

Pathophysiologic mechanisms

The pathophysiologic mechanisms underlying increased influenza risk to pregnant women and their fetuses are unclear. Increased exposure to the virus due to contact with children (who have higher rates of infection and higher levels of shedding[32]) as well as reluctance to treat pregnant women with category C drugs has been suggested as an explanation for increased infection rates leading to increased occurrence of complicated and severe disease.[32] However, during recent years in which information on preventing exposure to influenza and optimal early diagnosis and management of pregnant women have become routine, there has been no evidence of decreasing risk of severe influenza complications in pregnant women, suggesting that high incidence of severe disease cannot be explained solely by higher incidence of infection.

Significant anatomic and physiologic changes during normal pregnancy include changes that increase the risk of respiratory failure and complicate the treatment of respiratory illness.[33,34] These changes include elevation of the diaphragm to accommodate the uterus, increased respiratory rate, increased intra-abdominal pressure, decreased chest compliance, and as a consequence, increased risk of aspiration.

Decreased functional residual capacity due to a greater expiratory volume can lead to alveolar collapse. Because increased tidal volume is necessary to meet increased oxygenation needs, minute ventilation is increased, leading to falling arterial CO_2 partial pressure and compensated metabolic acidosis. These cardiopulmonary changes and the increased respiratory rate needed to compensate for the metabolic acidosis make pregnant women more susceptible to respiratory compromise, predispose to the development of pulmonary edema, and make such complications more difficult to treat.[34] Pulmonary edema may also subject pregnant women to secondary bacterial pneumonias; autopsy studies during the 1918 pandemic suggested to contemporary physicians that pulmonary edema presented an environment conducive to secondary bacterial growth and the severe pneumonias that accounted for most post-influenza deaths,[7] a possibility that has not been disproven. Pregnant women with underlying cardiovascular co-morbidities are at especially high risk of respiratory failure due to influenza infection,[35] as are pregnant women with co-morbidities such as hypertension or cardiac disease. Potentially compromising anatomic and physiologic changes become more significant as pregnancy progresses, coinciding temporally with increased influenza morbidity and mortality seen in the third trimester.[13]

Pregnancy has been considered an immunomodulating and even an immunosuppressive state.[22,36,37] Cell-mediated autoimmune diseases such as multiple sclerosis and rheumatoid arthritis may remit during pregnancy,[38–44] and disruption or reduction in pregnancy-associated immunomodulation has been linked to fetal death.[36,37] Dramatic changes in expression of cytokines including IL12p70, TNFα, IFNγ, IP-10, eotaxin, G-CSF, GM-CSF, IL-15, MCP-1, and VEGF occur during pregnancy and the levels of these cytokines vary throughout the trimesters.[45] Some cytokines are suppressed (e.g. IFNγ and VEGF), while others (e.g. the proinflammatory cytokines TNFα and G-CSF)

are increased throughout pregnancy. Cytokine changes play a role in the development of maternal fetal tolerance and occur in a complex interplay with changes in Th1 and Th2 responses, NK cell function, and antigen presentation.

The effect of immunomodulatory changes of pregnancy upon influenza infection is unclear, but some studies suggest effects on disease progression.[38–43] Replication of influenza viruses is significantly higher in peripheral blood mononuclear cells (PBMCs) incubated with third trimester serum. When incubated with influenza viruses, PBMCs from third trimester pregnant women show reduced antiviral gene expression.[45] Such observations are consistent with the possibility that immune changes of pregnancy might exacerbate influenza disease, but may not fully explain increased risk of death in influenza-infected pregnant women. Because physiologic and anatomic risk factors for severe influenza in pregnancy are poorly understood, they constitute an important area of research emphasis.

Prevention and treatment of influenza in pregnancy

Prevention strategies

Prevention of influenza infection in pregnant women and their newborns begins with efforts to limit exposures, including hand washing, respiratory hygiene and cough etiquette, and implementation of infection control precautions and environmental procedures in the healthcare settings that these individuals frequent.[46] Pregnant women with suspected influenza should not be left in waiting rooms with uninfected pregnant women and should be triaged quickly for rapid examination, diagnosis, and treatment.[46,47] If hospitalized, droplet precautions should be instituted, and all persons coming within three feet of the woman should wear a surgical mask. Education of family members as well as pregnant women is a very important component of prevention. This becomes even more important once the baby is born, as proper hand hygiene prior to handling the baby is an essential component of prevention of transmission to the newborn.[47]

Antiviral treatment

During the 2009 pandemic, the Centers for Disease Control and Prevention (CDC) recommended for the first time that antiviral drugs be given to all pregnant women with influenza and prophylactically to those with significant influenza exposures.[48] Two classes of influenza antivirals are licensed: the adamantane M2 ion channel inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Adamantanes were the primary antiviral therapy for influenza infections until 2005–2006, when widespread H3N2 resistance emerged.[49] The A(H1N1)pdm09 viruses are also adamantane resistant.[50] Neuraminidase inhibitors have thus become the current antivirals of choice for influenza, especially for seasonal H3N2 and A(H1N1)pdm09 infections. However, neuraminidase inhibitor resistance[51–53] may eventually become a significant problem in A(H1N1)pdm09 viruses, just as it did following rapid development of widespread resistance in seasonal H1N1 viruses in 2008.[54]

All of the licensed influenza antiviral agents are classified as category C drugs in pregnancy, meaning that no clinical studies have been performed in pregnant women and that animal studies either have not been carried out or have shown an adverse fetal effect in at least one species.[48] Retrospective studies generally have found minimal risk to mother and fetus,[55–57] although low levels of oseltamivir drug metabolites are transferred transplacentally.[58,59] One study reported a slight increase in risk of late, transient newborn hypoglycemia,[60] but another raised no safety concerns in pregnant women who received either neuraminidase inhibitors or adamantanes.[57,61] Taken together, these data suggest that current antivirals are likely to be safe in pregnancy, but further study is needed.

Efficacy of antiviral agents during pregnancy, and especially in severely ill pregnant women, is unknown. Clinical studies in non-pregnant women indicate maximal efficacy when given early in infection or used for prophylaxis, before development of severe disease.[62] Optimal dosing for pregnant women is not known, and although bioavailability of neuraminidase inhibitors does not change during the trimesters of pregnancy,[63] data suggest that it is reduced in comparison with non-pregnant women, theoretically limiting efficacy at recommended dosages.[64] Despite incomplete data, recommendations for post-exposure prophylaxis and early initiation of treatment of pregnant women suspected of influenza infection are important components of strategies to reduce morbidity and mortality.

Vaccination

As natural influenza infection induces robust maternal antibody responses with transplacental transfer of anti-influenza IgG antibodies,[65] a similar response can potentially also be achieved by vaccination of pregnant women with inactivated influenza vaccine (TIV), which is licensed for use during pregnancy in the United States. TIV elicits equivalent antibody titers in pregnant and non-pregnant women,[66–68] and influenza-specific maternal transplacental antibody transfer occurs in up to 99% of pregnant women after TIV administration.[67–69] Live attenuated influenza vaccines (LAIV), such as FluMist, are not currently recommended in pregnant women, as safety and efficacy have not been established.[70]

Vaccine-elicited immune responses in pregnant women are clinically important in both mother and child,[71–74] leading to a reduction in perinatal incidence of influenza

infection for at least 8 weeks after birth[72] and reduction in severity of all perinatal respiratory illnesses combined in studies with incomplete virologic confirmation.[73] A randomized controlled influenza TIV vaccination trial of 340 pregnant women, featuring incomplete virologic diagnosis, reported a 63% reduction in laboratory-confirmed influenza, a 36% reduction in all febrile respiratory illnesses, and a 29% decrease in all respiratory illness in infants.[74] More recently, maternal influenza vaccination has been demonstrated to reduce influenza-associated hospitalizations in infants under 6 months old by 45–48%.[75] Maternal vaccination is also cost-effective in reducing expenses of treatment/monitoring for medically attended respiratory illness in both pregnant woman and their infants.[71,76]

Data from the Vaccine Adverse Event Reporting System (VAERS) on over 2 million vaccinated pregnant women detected few or no adverse effects on fetuses or infants whose mothers received influenza vaccine during pregnancy,[77] a finding supported by evidence from numerous case–control studies. Although influenza vaccine is classified as a category C agent in pregnancy, the positive safety profile has led to recommendations of the CDC, American College of Obstetrics and Gynecology (ACOG), and WHO that all pregnant women should be vaccinated with inactivated seasonal TIV.[70,78]

Despite clear benefits and a history of safety, barriers to accepting vaccination limit coverage in pregnant women. As many as 80% of pregnant women believe that vaccination can cause birth defects,[79] and for various reasons healthcare professionals are often reluctant to recommend it. In some countries, vaccination is not even routinely offered to pregnant women.[80] This is particularly unfortunate because pregnant women who are offered influenza vaccination by their healthcare providers are more likely to have positive attitudes about vaccination, and more importantly to be vaccinated (71% versus 14% in those not offered vaccination).[81] In the United States, rates of vaccination of pregnant women have greatly increased in recent years, apparently as a result of education and other increased efforts to improve vaccination acceptance. Despite this, vaccination rates of pregnant women in the United States remain barely above 50%.[82,83]

Future needs

As many basic scientific and clinical questions about influenza pathogenesis, prevention, and treatment in pregnant women are unanswered, scientific discovery remains important. Clinical studies in pregnant women evaluating the efficacy and bioavailability of both approved antivirals and those in development should be undertaken. Such studies must be supplemented by detailed investigation of the pathophysiologic mechanisms behind increased severity of influenza-related illness during pregnancy, requiring coordinated clinical/laboratory research. A thorough understanding of the risk factors for and pathophysiologic mechanisms by which pregnant women develop more severe disease after influenza infection should lead to improved treatment and prevention strategies as well as intelligent drug and vaccine design.

Conclusion

Influenza in pregnancy is a significant and under-appreciated public health problem. Its substantial morbidity and mortality impact can be mitigated by education of women and their physicians as well as by vaccination and use of available preventative and therapeutic modalities. Public health measures that increase vaccination rates are key to these efforts. It is important that physicians educate their patients regarding the increased severity of influenza infection in pregnancy and that influenza vaccination be offered to every pregnant woman, as well as every woman considering becoming pregnant. Pregnant women must also be counseled to promptly report influenza-like illnesses to their physicians, as early diagnosis and treatment are critical. Increased education of healthcare providers can be supplemented by treatment algorithms designed for busy ER, urgent care, and obstetric clinic staff. Although additional studies of the pathophysiology of influenza and the efficacy of antiviral drugs in pregnant women are needed, available data suggest that antivirals should be used promptly and early during the course of infection and not withheld until women are significantly ill or suffering complications, by which time they are less likely to be efficacious.

Reducing morbidity and mortality from influenza in pregnancy is an important public health priority, which will require a broad effort on the part of public health officials, health educators, researchers, and the healthcare system. With approximately 4 million pregnancies occurring annually in the United States, and with widespread influenza virus circulation occurring virtually every year, the serious health effects of influenza in pregnancy are likely to remain an important problem for the foreseeable future. The goal of significantly reducing influenza morbidity and mortality in pregnant women is achievable with existing knowledge and prevention/treatment approaches, but more continued efforts are needed. In addition to educating providers and supporting provider efforts to educate their patients, there is also a clear need for further research into the pathogenesis of severe influenza in pregnancy. Beyond the significant impact of annual influenza outbreaks, there is little doubt that we will eventually face future pandemic influenza viruses that could cause severe morbidity and mortality. The relative 'mildness' of the 2009 pandemic affords us time to reflect and improve and it is an important opportunity that should not be missed.

Conflict of interest

The authors have no conflict of interest to report.

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Author contributions

All of the authors contributed to this manuscript through their research of this topic and writing. Dr. Memoli was the lead and primary author of the manuscript.

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