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.

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 condition6 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 opportu-
nity to examine pregnancy as a risk factor for influenza
severity.14–18 Increased A(H1N1)pdm09-associated hospital-
izations, intensive care unit (ICU) admissions, complica-
tions, and mortality during pregnancy were documented
worldwide. Pregnancy was identified globally as one of the
strongest risk factors for influenza-associated ICU admis-
sion, 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, still-
births, 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.16,21 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 shedding32) 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 pre-
venting 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 respira-
tory illness.33,34 These changes include elevation of the dia-
aphragm 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 oxy-
genation needs, minute ventilation is increased, leading to
falling arterial CO2 partial pressure and compensated meta-
boic 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; autopsies
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-mor-
bidities 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 rheu-
matoid arthritis may remit during pregnancy,38–44 and
disruption or reduction in pregnancy-associated immuno-
modulation 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 oth-
ers (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 sug-
gest effects on disease progression.38–43 Replication of influ-
enza 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 antivi-
rnal 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 eti-
quette, and implementation of infection control precau-
tions 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 tri-
aged quickly for rapid examination, diagnosis, and treat-
ment.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 impor-
tant once the baby is born, as proper hand hygiene prior
to handling the baby is an essential component of preven-
tion 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 influ-
enza 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 (osel-
tamivir 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, neur-
amidase inhibitor resistance51–53 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 Ret-
rospective 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 con-
cerns in pregnant women who received either neuramini-
dase 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 espe-
cially 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 tri-
mesters of pregnancy,63 data suggest that it is reduced in
comparison with non-pregnant women, theoretically limit-
ing 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 strate-
gies to reduce morbidity and mortality.

Vaccination
As natural influenza infection induces robust maternal anti-
body responses with transplacental transfer of anti-influ-
enza 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 recom-
manded in pregnant women, as safety and efficacy have
not been established.70

Vaccine-elicted 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\textsuperscript{22} and reduction in severity of all perinatal respiratory illnesses combined in studies with incomplete virologic confirmation.\textsuperscript{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.\textsuperscript{74} More recently, maternal influenza vaccination has been demonstrated to reduce influenza-associated hospitalizations in infants under 6 months old by 45\%–48\%.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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).\textsuperscript{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\%.\textsuperscript{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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