

## Safety of influenza vaccination during pregnancy

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The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine influenza vaccination for all women who are or will be pregnant during the influenza season.<sup>1</sup> The basis for this unambiguous recommendation is clear. During seasonal influenza epidemics, during previous pandemics, and with the ongoing influenza A (H1N1) pandemic, pregnancy places otherwise healthy women at increased risk for serious complications from influenza.<sup>1-4</sup> Vaccination continues to be the most effective method for preventing severe influenza illness and its sequelae.<sup>5-9</sup> Despite robust epidemiologic evidence for increased influenza-related fatality in pregnancy, pregnant women have historically had the lowest vaccine coverage rates of all adults recommended to receive seasonal influenza vaccination.<sup>10</sup> The current pandemic of influenza has once again reminded us that pregnant women are at particularly high risk for morbidity and mortality from influenza and that they are a population that should be vaccinated.

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends routine influenza vaccination for all women who are or will be pregnant during the influenza season. During seasonal influenza epidemics, during previous pandemics, and with the current influenza A (H1N1) pandemic, pregnancy places otherwise healthy women at increased risk for serious complications from influenza, including death. Inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy. No study to date has demonstrated an increased risk of either maternal complications or adverse fetal outcomes associated with inactivated influenza vaccination. Moreover, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received influenza vaccine during pregnancy. In this article, we review the evidentiary basis for the recommendation of vaccination of all women who will be pregnant during the influenza season and safety data of influenza vaccination during pregnancy.

**Key words:** H1N1, influenza vaccine, pregnancy, safety

### ★ EDITORS' CHOICE ★

From April 15 through May 18, 2009, 34 confirmed or probable cases of novel influenza A (H1N1) in pregnant women were reported to the CDC; 32% of these women required hospitalization.<sup>4</sup> Pregnant women were >4 times more likely to be hospitalized for novel influenza A (H1N1)-related complications than those infected in the general population,

and accounted for 13% of all deaths from pandemic influenza A (H1N1) during this time period. Most of the pregnant women who died as a consequence of pandemic influenza A (H1N1) were healthy prior to their influenza illness.<sup>4</sup> As a result of this and earlier evidence, CDC has placed pregnant women in the highest-priority group to receive vaccination once the novel influenza A (H1N1) vaccine becomes available.<sup>11</sup>

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Serious influenza-related illnesses in pregnant women will undoubtedly continue to escalate as the influenza A (H1N1) pandemic proceeds. Physicians and other health care providers play a crucial role in the decision-making process with regard to influenza vaccination. They can explore the determinants of vaccine refusal and alleviate fears by addressing real and perceived concerns regarding immunizations during pregnancy. In this article, we review the evidentiary basis for the recommendation of vaccination of all women who will be pregnant during the influenza season and safety data of influenza vaccination during pregnancy.

### Evolution of US immunization recommendations

The serious consequences of influenza infection during pregnancy have been recognized for almost a century. In a series of 1350 pregnant women reported during the 1918 pandemic, about 50% developed pneumonia, and of these women, more than half died, with a case fatality rate of 27%.<sup>2,12</sup> The highest mortality was seen in the third trimester. During the pandemic of 1957, nearly half of all women of childbearing age who died were pregnant.<sup>3,13-15</sup>

Over the years, as data regarding the deleterious effects of influenza on the pregnant female have mounted, and in the absence of evidence linking influenza vaccination during pregnancy to any serious negative consequences for the mother or fetus, the recommendations for influenza vaccination during pregnancy have expanded. Since 2004, ACIP has encouraged pregnant women, regardless of gestational age, to receive routine inactivated influenza vaccination.<sup>1,16</sup> The American College of Obstetricians and Gynecologists considers the influenza vaccine an "essential element of prenatal care."<sup>17,18</sup>

### Risks of influenza infection in pregnancy

Pregnancy is associated with biochemical, mechanical, hemodynamic, as well as immunologic changes in the mother that become most pronounced by the third trimester. These changes include

decreased lung capacity and tidal volume, along with increased cardiac output and oxygen consumption.<sup>19-21</sup> Adaptive humoral immunity remains generally intact with augmentation of the T-helper-type 2 antibody-mediated response.<sup>22</sup> This is in contrast to the selective suppression of T-helper-type 1 cell-mediated immunity that likely protects the developing fetus from maternal cytotoxic-T-lymphocyte activity, but as a consequence, impairs maternal response to infection.<sup>22-24</sup> Although pregnant women do not have a higher incidence of seasonal influenza than the general population, the combination of impaired cell-mediated immunity as well as physiologic changes that accompany pregnancy leave women increasingly vulnerable to serious influenza-related complications.

Influenza-related hospitalization of healthy pregnant women occurs at a rate of 1-2 per 1000.<sup>25</sup> Schanzer et al<sup>26</sup> determined this risk is 18-fold above that of healthy nonpregnant women. Pregnant women with coexisting medical conditions are at even greater risk of severe influenza-related morbidity. When pregnancy is superimposed on high-risk conditions such as asthma or diabetes mellitus, influenza infection contributes to morbidity that is 3-4 times greater than nonpregnant control subjects with similar high-risk conditions.<sup>27-29</sup>

### Safety of inactivated influenza vaccine for the pregnant woman

The lack of harmful effects of inactivated influenza vaccination on maternal health during pregnancy has been demonstrated in several studies (Table<sup>30-41</sup>). Munoz et al<sup>32</sup> performed a retrospective analysis of data from 5 influenza seasons using an electronic database of a large multispecialty clinic in the United States. Outcomes of pregnancy were compared between a cohort of 225 healthy women who received influenza vaccine during the second and third trimesters of pregnancy and a control group of 826 healthy unvaccinated women who were matched by age, month of delivery, and type of medical insurance. No serious adverse events occurred within 42 days of vaccination, and there was no difference be-

tween the groups in the rates of cesarean section, premature birth, and infant medical conditions from birth to 6 months of age.<sup>32</sup>

During the 1976-1977 influenza season, 56 women who received the inactivated influenza vaccine during the second and third trimesters of pregnancy were evaluated. No notable immediate reactions were observed, nor were there any differences between the course or outcome of pregnancies between the vaccinated women and control group of 40 nonvaccinated pregnant women.<sup>37</sup> No significant adverse reactions, including fever, moderate or severe pain, or need to visit a physician, were observed in another study in which 26 women were randomized to receive the inactivated influenza vaccine or tetanus toxoid vaccine in the third trimester of pregnancy.<sup>35</sup> Deinaud and Ogburn<sup>36</sup> evaluated 189 women immunized with the trivalent inactivated influenza vaccine during the 3 trimesters of pregnancy and noted no differences in maternal health or pregnancy outcome compared to the control group of 517 pregnant women who did not receive the vaccine. The few serological studies on pregnant women suggest that antibody response to influenza vaccine is comparable to age-matched, nonpregnant control subjects.<sup>35-37</sup>

The Vaccine Adverse Event Reporting System contains a database for reports regarding influenza vaccination during pregnancy. It is a postmarketing surveillance system with strengths and weaknesses inherent to passive surveillance systems.<sup>42</sup> Of 26 reports related to influenza vaccine in pregnant women from 2000 through 2003, 6 concerned misadministration of the influenza vaccine without negative consequences, 9 described self-limited injection site reactions, 8 were related to systemic symptoms that regressed with time, and 3 reported miscarriages.<sup>43</sup> During this time period, an estimated 2 million pregnant women received influenza vaccination.<sup>44</sup> These data suggest a low rate of adverse events associated with administration of the inactivated influenza vaccine during pregnancy.<sup>43</sup> Licensed 2009 H1N1 monovalent vaccines will be produced using the same manufacturing

TABLE

## Summary of data on safety outcomes of studies of influenza immunization during pregnancy

Study	Design	Study group	Control group	Follow-up period	Maternal outcomes	Infant outcomes
Zaman et al, <sup>30</sup> 2008	Prospective, randomized, double-blind controlled trial	172 pregnant women in third trimester	168 pregnant women who received 23-valent pneumococcal polysaccharide vaccine	7 d postvaccination; mother-infant pairs followed up to 24 wk of life	No serious adverse events or differences in pregnancy outcomes	No differences in gestational age, proportion with cesarean delivery, birthweight, or APGAR score
France et al, <sup>31</sup> 2006	Retrospective, matched cohort	3160 infants born to vaccinated mothers	37,969 infants born to nonvaccinated mothers	End of influenza season	Not assessed	No difference with regard to birthweight, gestational age, or length of stay for birth hospitalization
Munoz et al, <sup>32</sup> 2005	Retrospective, matched cohort	225 pregnant women in second and third trimesters	826 nonimmunized pregnant women	42 d after immunization; birth to 6 mo of age	No serious adverse events or differences in pregnancy outcomes	No differences in outcomes of pregnancy (cesarean delivery and premature delivery) and infant medical conditions
Black et al, <sup>33</sup> 2004	Retrospective cohort	3719 pregnant women immunized	45,866 women	Until delivery	No difference in cesarean section	No difference in cesarean section or preterm delivery
Yeager et al, <sup>34</sup> 1999	Prospective cohort	319 pregnant women immunized in second and third trimesters	None	Next prenatal visit	No preterm labor or other serious events	Not assessed
Englund et al, <sup>35</sup> 1993	Randomized, controlled trial	13 pregnant women in third trimester	13 pregnant women who received tetanus toxoid vaccine	Not specified	No significant adverse reactions, including fever, moderate or severe pain, or need to visit a physician noted in either group	Similar gestational ages in both groups; no health concerns in infants examined between 1-3 mo of age
Deinard and Ogburn, <sup>36</sup> 1981	Prospective cohort	189 pregnant women (13 prior to conception; 41, 58, and 77 in first, second, and third trimesters, respectively)	517 nonvaccinated pregnant women	48 h after immunization; pregnancy outcome to 8 wk of life	No differences in maternal health, pregnancy outcome, or postpartum course	No significant differences in adverse pregnancy outcomes (congenital anomalies, neonatal mortality)
Sumaya and Gibbs, <sup>37</sup> 1979	Retrospective, matched cohort	56 women in second and third trimesters	40 nonvaccinated pregnant women	24 h after immunization	No significant immediate reactions or differences in pregnancy course	No increased fetal complications associated with vaccine
Murray et al, <sup>38</sup> 1979	Prospective, matched cohort	59 pregnant immunized women (5, 22, and 32 in first, second, and third trimesters, respectively)	27 nonpregnant vaccinated women	Not specified	No significant side effects after immunization in any women	Not assessed
Heinonen et al, 1973, <sup>39</sup> and 1977 <sup>40</sup>	Prospective cohort	2291 pregnant immunized women; up to 650 in first trimester	None	Up to 7 y of age		No suggestive associations for congenital malformations, malignancies, or neurocognitive disabilities
Hulka, <sup>41</sup> 1964	Retrospective and prospective cohort	225 pregnant immunized women (19 in first trimester)	44 nonpregnant influenza immunized; 104 pregnant and 25 nonpregnant immunized with placebo	Up to 3 d after vaccination and at delivery	Local pain at injection site and some systemic symptoms greater in women immunized with influenza vaccine	No association with fetal anomalies or miscarriage

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process as seasonal influenza vaccines, thus it is anticipated that they will have a similar safety profile with serious adverse events after vaccination uncommon.<sup>1,11</sup>

### Benefits of influenza vaccination for the neonate

Studies from the United States and Hong Kong demonstrate high rates of hospitalization among infants with influenza, especially in the age group <6 months.<sup>45-47</sup> A review of the US influenza mortality during the 2003-2004 influenza season revealed that childhood deaths associated with influenza were most frequent in infants aged <6 months.<sup>48</sup> Because of limited immunogenicity in this age group, inactivated influenza vaccine is not currently licensed for infants <6 months of age.<sup>1</sup>

Transplacental influenza antibody has been postulated to provide indirect protection in newborns, a period of increased vulnerability to influenza and its complications. Zaman et al<sup>30</sup> conducted a prospective, controlled, blinded trial that assessed the clinical effectiveness of maternal influenza vaccine in their infants. Among infants of the 172 mothers who received influenza vaccination, there were fewer cases of laboratory-confirmed influenza than among infants in the control group, with a vaccine effectiveness of 63% until at least 6 months of age. There was a 29% and 36% reduction in the rates of febrile respiratory illnesses in infants and mothers, respectively.

The advantage of endowing the fetus with maternal antibody prior to birth was also demonstrated during the influenza H1N1 epidemic of 1979. Infants born to mothers with natural serum antibody to influenza A had higher H1-specific passive antibody titers than control subjects. They also had influenza symptoms that were delayed in onset and of shorter mean duration as compared with infants of nonimmune mothers.<sup>49,50</sup> Immunization of pregnant women with influenza virus antigens evokes an antibody response that could result in the passive transfer of sufficient antibody to protect the very young infant for the duration of the influenza season.<sup>37,38</sup>

### Safety of maternal influenza vaccination for the fetus

Many pregnant women struggle with the concept of vaccination during pregnancy because of theoretical concerns regarding harm to the fetus. In the longitudinal, population-based Collaborative Perinatal Project that was conducted between 1959-1965, >2000 pregnant women received influenza vaccination, almost a third during the first trimester. The children of these women were followed up for the first 7 years of life, and maternal influenza immunization did not increase the number of stillbirths, congenital malformations, malignancies, or neurocognitive disabilities.<sup>39,40</sup>

In another longitudinal, prospective study, Deinard and Ogburn<sup>36</sup> detected no association between maternal influenza immunization and maternal, perinatal, or infant complications. No teratogenicity was documented, and the infants of vaccinated mothers did not differ from nonvaccinated offspring in physical or neurological assessments at birth and 8 weeks of life.

Similarly, a large retrospective, matched cohort study, which included 3160 infants born to influenza-vaccinated mothers and 37,969 infants born to nonvaccinated mothers, revealed no differences with regard to birthweight, gestational age, or length of stay for birth hospitalization.<sup>31</sup> The safety of the inactivated influenza vaccine was assessed in 7 other trials in which >4500 pregnant women were vaccinated and no significant adverse effects to the fetus were identified.<sup>30,32,33,35,37,41</sup> (Table).

It is always beneficial to have an active surveillance system in place to provide feedback of the adequacy, strengths, and weaknesses of the vaccine in question. This will be no different for the novel influenza A (H1N1) vaccine. The CDC and the Food and Drug Administration will be closely monitoring any adverse effects of the influenza A (H1N1) 2009 monovalent vaccine through the Vaccine Adverse Event Reporting System and Vaccine Safety Datalink.<sup>51</sup> The Vaccine Safety Datalink uses rapid cycle analysis to monitor specified adverse events in near real time, with appropriate compar-

ison groups. Moreover, large-scale safety monitoring studies, led by academic researchers, are being established. Ongoing proactive safety monitoring will maintain confidence in the immunization efforts related to maternal influenza vaccination and encourage continued improvements to the vaccine.

### Influenza vaccination and thimerosal

Thimerosal, a mercury-containing compound, is a preservative that has been used in some vaccines, including multivalent inactivated influenza vaccines, to reduce the likelihood of microbial growth. Concerns came to public attention in 1999 because of uncertainty regarding the applicability of guidelines for long-term exposure to methylmercury, primarily from fish consumption, to intermittent exposure to ethylmercury, a breakdown product of thimerosal. Subsequent studies have shown that ethylmercury does not accumulate and cause harm to the fetal brain like methylmercury, and mounting evidence suggests no increased risk for neurodevelopmental disorders from exposure to thimerosal-containing vaccines.<sup>52-61</sup> In 2004, the US Institute of Medicine reviewed cumulative pediatric exposure to thimerosal-containing vaccines, which led them to reject the hypothesis of a causal link between infants exposed to thimerosal-containing vaccines and autism.<sup>62</sup> The US Public Health Service and other organizations have recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines as part of a strategy to reduce mercury exposures from all sources.<sup>63</sup>

Thimerosal-free versions of the trivalent-inactivated vaccine are increasingly available and a thimerosal-free version of the novel influenza A (H1N1) vaccine will be available in the fall. Limitations in the availability of thimerosal-free influenza vaccines should not preclude administration of inactivated influenza vaccines in pregnant women.<sup>1</sup>

After reviewing the existing body of evidence with regard to thimerosal and the concerns for the developing fetus, the ACIP concludes: "The benefits of influenza vaccination for all recommended groups, including pregnant women and

young children, outweigh concerns on the basis of a theoretical risk from thimerosal exposure through vaccination. The risks for severe illness from influenza virus infection are elevated among both young children and pregnant women, and vaccination has been demonstrated to reduce the risk for severe influenza illness and subsequent medical complications. In contrast, no scientifically conclusive evidence has demonstrated harm from exposure to vaccine containing thimerosal preservative. For these reasons, persons recommended to receive TIV [trivalent inactivated influenza vaccine] may receive any age- and risk factor-appropriate vaccine preparation, depending on availability.”<sup>1</sup>

### Conclusion

Inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy. No study to date has demonstrated an increased risk of either maternal complications or untoward fetal outcomes associated with inactivated influenza vaccination. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received influenza vaccine during pregnancy. Immunization of the mother reduces 1 potential source of viral exposure to the infant, and immunization of other family members will decrease other potential sources. Health care workers caring for pregnant females can play a pivotal role in helping to protect women and newborns from this vaccine-preventable disease and should anticipate questions that expecting mothers may have regarding vaccine safety.

Over the next several months, we will likely witness a surge of infections caused by the novel influenza A (H1N1) virus. As health care workers it is essential that we encourage the vaccination of pregnant women against both the pandemic influenza A (H1N1) virus, as well as seasonal influenza. If pregnancy-related mortality data from prior influenza pandemics are a predictor of what we are to expect in the upcoming months, a signif-

icant number of deaths can be averted with influenza vaccination. ■

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