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## **Influenza, Vaccination, and Pregnancy**

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### **Influenza**

Influenza is an acute viral infection involving the respiratory tract. It is caused by a number of serologically distinct viral strains, such as influenza A (with many subgroups) and B, both of which cause epidemic human disease (Bridges et al., 2003). Influenza typically presents as a sudden onset of a respiratory infection with additional features of fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis (Bridges et al., 2003). In some persons, influenza can lead to more serious complications by aggravating underlying medical conditions (such as pulmonary or cardiac disease) or result in a secondary bacterial pneumonia or primary influenza viral pneumonia (Bridges et al., 2003).

The incubation period for influenza is about 1-4 days, with persons becoming infectious the day before symptoms begin through 5 days or so after the onset of the illness (Larsen, 1982). Children can be infectious for a longer period. In immunocompetent individuals, influenza usually resolves after several days, although cough and malaise can persist for 2 or more weeks.

### **Influenza during pregnancy**

Influenza has been studied to evaluate whether pregnancy increases maternal complications. Among pregnant women, an influenza-associated increased mortality has been documented during the influenza pandemics of 1918-1919 and 1957-1958 (Bridges et al., 2003). Additionally, individual case reports suggest that pregnancy (particularly the third trimester) may increase the risk for serious medical complications of influenza, possibly as a result of pregnancy associated increases in heart rate and oxygen consumption; decreases in lung capacity; and changes in immunologic function (Bridges et al., 2003, Steininger et al., 2003). For every 1,000 pregnant women vaccinated, it has been estimated that about 1-2 hospitalizations could be prevented (Bridges et al., 2003).

Influenza has also been studied during pregnancy to see whether there is a resulting increase in fetal loss. Stanwell-Smith et al. (1994) reported on a possible association of influenza A with fetal loss based on a sudden increase (within a period of three weeks) of 12 fetal losses at one health center that normally experiences 12-15 losses for the entire year. They noted that in the small number of women who miscarried or had a stillbirth, these women were significantly more likely to have experienced a flu-related illness during their pregnancy compared to control women who had delivered a liveborn (Stanwell-Smith et al., 1994). Additionally, eight out of eight women with losses and zero out of the six control women who were tested had serological evidence of a recent infection with influenza A. Although a suggestive cluster, larger studies are needed to confirm or refute this association.

Influenza has been evaluated as a possible cause of congenital malformations. In an experimental animal model, sub-lethal doses of influenza A strains were administered intranasally to pregnant mice.

However, there was no increase in congenital anomalies in the offspring (Mackenzie et al., 1977). Two Irish studies from the 1950s reported on a possible relationship between maternal influenza and human fetal malformations (primarily neural tube defects). This population has a higher frequency of neural tube defects. In the first study, a history of influenza (but not serological evidence) was obtained at delivery. Of the women that gave birth to infants with malformations, 18.4% reported an exposure to influenza compared to 3.6% of the mothers of normal infants (Coffey and Jessop, 1955). However, this type of study is susceptible to recall bias where women with infants with malformations are more likely to remember and report exposures than women whose infants have no malformations. Although the second study also reported an increased malformation rate among babies born to mothers who had influenza during pregnancy compared with those not exposed (3.6% and 1.6% respectively), the findings were still in the overall range of the expected general population risks (Coffey and Jessop, 1959).

Several more recent studies have refuted these findings (Record, 1961). For example, the population incidence of influenza infection during the first trimester was not increased among a cohort of 248 mothers who had a pregnancy with anencephaly (Saxen et al, 1990). Furthermore, additional studies that incorporated serologic evidence of infection, rather than maternal report or infection prevalence, have not identified an increased risk of malformations (Brown, 1970, Elizan et al., 1969, Warrell et al., 1981).

In summary, the available data indicates that influenza itself is unlikely to be the direct cause of congenital malformations. However, a fever greater or equal to 102 degrees F and lasting more than 24 hours during 4-6 weeks gestation has been associated with neural tube defects (Chamber et al., 1998).

Some authors have suggested an exposure to influenza during pregnancy is a neurodevelopmental risk factor for schizophrenia. For example, Mednick et al. (1988) and O'Callaghan et al. (1991) noted a significant increase in schizophrenia among individuals who were in their second trimester of fetal life during the 1957 pandemic of 'Asian' A2 influenza. However, there is no direct evidence that the subjects were exposed to influenza, rather the evidence is based on the prevalence of the infection during fetal life. The mechanism underlying this possible association is also not clear and evidence has accumulated against any association with schizophrenia (Selten and Slaets, 1994, Torrey et al., 1991). Currently, there is no conclusive evidence either in favor or against an association between schizophrenia and prenatal exposure to influenza (Cooper, 1992 and Limosin et al., 2003).

### **Vaccination**

The influenza vaccine is the primary method for preventing influenza and complications. When the vaccine and circulating viruses are antigenically similar, the vaccine is expected to prevent influenza in 70-90% of healthy adults <65 years old (Bridges et al., 2003). The primary target group for influenza vaccination includes persons who are at high risk for serious complications from influenza, such as persons aged >50 years old or persons <50 years old who have chronic underlying medical conditions.

The Advisory Committee on Immunization Practices of the Centers for Disease Control added pregnant women in the second and third trimesters to the list of high-risk groups for whom the influenza vaccination is indicated. The American College of Obstetrics and Gynecology also recommends that women who will be beyond the first trimester of pregnancy during the influenza season should be vaccinated (ACOG Committee Opinion, 2003). Administering the vaccine after the first trimester is a reasonable precaution to minimize exposures during organogenesis. However, it is considered undesirable to delay vaccinating pregnant women in the first trimester who are at high risk for pulmonary complications (ACOG Committee Opinion, 2003).

### **Vaccination during pregnancy**

Live virus vaccines are of theoretical concern since a live virus has the potential to replicate itself and infect the mother and fetus. However, the influenza vaccine contains an inactivated virus without this added theoretical concern. Additionally, available studies have not identified a pregnancy risk with exposure to the influenza vaccine at any stage of pregnancy. For example, in a study of 650 pregnancies exposed to the inactivated influenza vaccination during the first four months of pregnancy, no increase over the expected number of malformations was observed (Heinonen, 1977).

Deinard and Ogburn (1981) performed a prospective study on 176 women who were immunized with a killed virus vaccine during their pregnancy (41 in the first trimester, 58 in the second trimester and 77 in the third trimester). Pregnancy outcomes were compared with a control group that did not receive the vaccine. No significant association was found between the outcome of pregnancy, infant mortality, and infant's physical or neurological development at 8 weeks of age (Deinard and Ogburn, 1981).

Sumaya and Gibbs (1979) followed 56 women vaccinated with an inactivated influenza virus during the second and third trimesters of pregnancy. Their main focus (and conclusion) of the study was that immunization of pregnant women can provide only short term protection of the newborn infant. The authors did note that the course and outcome of pregnancy of the immunized women were similar to that of matched controls of unimmunized women.

In 2003, an intranasal, cold-adapted, live, attenuated influenza vaccine (LAIV) was approved for use in healthy individuals aged 5-49 (Harper et al., 2003). LAIV contains attenuated viruses theoretically still capable of replication. There is no animal or human data regarding the safety of LAIV in pregnancy. Because of the lack of information, the theoretical concern with live viruses in pregnancy, and the availability of an inactivated vaccine, LAIV is not recommended for pregnancy.

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