Teratology and Public Health: Working Together to Make Recommendations for Pregnant Women in the Face of Uncertainty

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Centers for Disease Control and Prevention (CDC), Atlanta, GA
July 2, 2014
Brent Lecture
Teratology Society Annual Meeting, Bellevue, WA

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure

This presenter has no financial or other interests that pose a conflict of interest.
Examples of Public Health Decisions

- Rubella vaccine to prevent congenital rubella syndrome
- Folic acid to prevent neural tube defects
- Prevention and treatment of influenza

Public Health Decisions: Weighing the Risk and Benefit

- Prospect of clinical benefit – probability of preventing harm (depends on disease risk)
- Potential risk – probability x magnitude of harm
- Benefit of intervention >>> Potential risk of harm
Rubella Vaccine to Prevent Congenital Rubella Syndrome

Rash associated with rubella

Congenital Rubella Syndrome

Rubella infection in pregnancy can lead to fetal death, preterm delivery, birth defects, spontaneous abortion, and visual, hearing and cognitive impairment
History of Congenital Rubella Syndrome

- In 1941, Gregg recognized the effects of maternal rubella on the fetus
- 1962-1965 worldwide rubella epidemic
  - 12.5 million cases of rubella in the US
  - 11,250 fetal deaths
  - 2,100 neonatal deaths
  - 20,000 infants born with congenital rubella syndrome
- Rubella vaccine developed and licensed (1969)

Decisions about Vaccination Strategies

- Vaccinate adolescent females – initially used in UK
- Vaccinate children to abolish reservoir for disease – initially used in US

Trends in Rubella and Congenital Rubella Syndrome in the US, 1966-2002

Key Changes in Recommendations

- **1969** – Recommendation for use of rubella vaccine (age 1 to puberty)
- **1978** – Expanded to include adolescents and certain adults, particularly females
- **1984** – Vaccination of certain workers; prenatal testing and postpartum vaccination of susceptible women
- **1990** – 2-dose schedule for MMR vaccine implemented
Update on Global Rubella Elimination - 1

- In 2012 – total of 94,030 rubella cases reported to WHO from 174 Member States (86% decrease from 670,894 cases reported in 2000 from 102 Member States)
Update on Global Rubella Elimination - 2

- As of December 2012, 132 of 194 WHO Member States had introduced rubella-containing vaccine
  - 3/46 (7%) in African Region
  - 35/35 (100%) in the Region of the Americas
  - 14/22 (64%) in the Eastern Mediterranean Region
  - 53/53 (100%) in the European Region
  - 5/11 (45%) in the South-East Asia Region
  - 22/27 (81%) in the Western Pacific Region

Folic Acid to Prevent Neural Tube Defects

History of Folic Acid Fortification: Key Studies

- Trial of periconceptional multivitamin (with 360 mcg folic acid) supplementation for women with previous child with an NTD
  - Rate among fully supplemented mothers was 0.6%, compared to 5.0% among unsupplemented mothers (p < 0.01)

- Trial of periconceptional multivitamin (containing 800 mcg folic acid, minerals, trace elements) supplementation for NTD occurrence prevention
  - Rate among vitamin supplement group was 0/2052, compared to 6/2104 among trace-element supplement group (p=0.029)

  Smithells et al., Lancet 1:339-40, 1980
Decisions about Folic Acid

- Supplementation vs. Fortification
- Level of Fortification
- Potential risks
  - Masking of vitamin B12 deficiency
  - Increased pregnancy loss
  - Increased risk of twinning
  - Colon cancer
  - Dementia

Crider et al., Nutrients 3:370-384, 2011

Recommendations to Prevent NTD Occurrence

- In 1992, the Public Health Service recommended that all women of childbearing age who are capable of becoming pregnant consume 400 mcg of folic acid daily
- In March 1996, FDA mandated that cereal grains labeled as "enriched" have folic acid added at level of 140 mcg/100g of product by January 1, 1998

MMWR Recomm Report 41:1, 1992
Food and Drug Administration, Federal Register 61:8781-97, 1996
**NTD-Affected Pregnancies per Year Before and After Fortification, United States**

![Graph showing the reduction in NTD-affected pregnancies before and after fortification.](chart.png)


Reduction: 27%


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**Update on Global Prevention of Folic Acid-Preventable NTDs**

![Map showing the status of global prevention efforts.](map.png)


Prevention and Treatment of Influenza

Effects of Influenza on the Pregnant Woman

- Changes in a pregnant woman’s immune, respiratory, cardiovascular and other systems place her at increased risk for influenza-associated complications
- Increased morbidity and mortality from influenza during previous pandemics
- Increased risk of complications related to seasonal influenza

Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008
Effects of Influenza on the Embryo or Fetus

• Effects of influenza on the embryo or fetus are unknown
• Viremia infrequent and placental transmission rare; however, adverse effects may still occur (e.g., hyperthermia)
• Increased risk of pregnancy loss and possibly preterm birth observed in previous pandemics
• Increased risk of certain birth defects seen

Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008

Effects of Influenza on the Infant

• Immune system of a newborn is immature – most of its serum immunoglobulins are from maternal IgG transfer across the placenta
• Infants have increased susceptibility to viral infections, including influenza
• Influenza vaccines are not approved for use in children aged <6 months
• Chemoprophylaxis and treatment options are limited

**Prophylaxis and Treatment of Influenza in Pregnant Women**

- Effects of anti-influenza medications (oseltamivir and zanamivir) on the embryo or fetus unknown
  - Oseltamivir (Tamiflu®) – human data limited to 61 reports of exposed pregnancies in post-marketing period
  - Zanamivir – human data limited to 3 zanamivir-exposed pregnancies during clinical trials

*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*

**Influenza Vaccination of Pregnant Women**

- Influenza vaccine protects pregnant women and their infants up to 6 months of age from influenza
- Influenza vaccine has been used during pregnancy since the 1960s and no maternal or fetal problems have been seen in association with influenza vaccination
- Advisory Committee on Immunization Practices and American College of Obstetricians and Gynecologists have recommended inactivated influenza vaccine for women who will be pregnant during influenza season for many years, regardless of pregnancy trimester, but adherence has been low (<30%)

*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*
Influenza Vaccine during Pregnancy Protects Infants < 6 Months of Age from Laboratory-Proven Influenza

![Influenza Vaccine during Pregnancy](Zaman et al., N Engl J Med 359:1555-64, 2008)

Decisions about Influenza and Pregnancy

- Should pregnant women with pandemic influenza be treated with an antiviral medication? Should treatment vary by pregnancy trimester? Which medication?
- Should pregnant women receive a pandemic influenza vaccine? Should vaccination recommendations vary by pregnancy trimester? Which vaccine?

Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008
Pandemic influenza: Special Considerations for Pregnant Women

April 3-4, 2009, Rayboi Campus, Atlanta, Georgia

Pandemic Influenza and Pregnant Women: Summary of a Meeting of Experts

Sorja A. Rasmussen, MD, MS, Denise J. Jarrieson, MD, MPH, Kitty MacFarlane, DTM, MPH, Janet D. Craig, MD, MPH, Jennifer Williams, MSN, MPH, and Tsakeba Henderson, MD, for the Pandemic Influenza and Pregnancy Working Group

Swine Influenza A (H1N1) Infection in Two Children --- Southern California, March--April 2009
2009-2010 Treatment Recommendations

- Treatment recommended for pregnant women and women up to 2 weeks postpartum with suspected or confirmed influenza, regardless of trimester of pregnancy
  - Oseltamivir (Tamiflu®) - BEST if started as soon as possible (i.e., <48 hours of symptom onset), but later treatment also of benefit
  - Considering severity of disease, treatment benefit outweighs potential risk
  - Acetaminophen for fever

- Do not delay treatment because of a negative rapid influenza diagnostic test or inability to test or while awaiting test results

2009-2010 Vaccine Recommendations

- Pregnant women should receive both 2009 H1N1 and seasonal inactivated vaccines

- Live attenuated vaccine not licensed for use in pregnant women, but can be used postpartum
2009 H1N1 Influenza and Pregnancy

- Illness and deaths seen in all three trimesters
- Pregnant women 4 times more likely to be hospitalized
- 5% of deaths in US from 2009 H1N1 influenza were among pregnant women, even though pregnant women account for ~1% of the US population
- Most women who died were previously healthy
- Early treatment was associated with fewer ICU admissions and fewer deaths

Jamieson et al., Lancet 374:451-8, 2009
Siston et al., JAMA 303:1517-1525, 2010

Maternal Influenza and Newborn Outcomes - 1

- Study of women with 2009 H1N1 admitted to ICU/died in US
  - Delivery during flu hospitalization - infants at increased risk for preterm birth, low 5-minute Apgar scores, and NICU admission
  - Delivery after discharge from flu hospitalization – infants at increased risk for small for gestational age (SGA) and NICU admission

CDC, MMWR Morb Mortal Wkly Rep 60:1193, 2011
Maternal Influenza and Newborn Outcomes - 2

- Study of hospitalized women in Nova Scotia
  - Infants born to hospitalized women more likely to be born SGA and to have lower mean birth weight than infants born to women who were not hospitalized
- Study of women with lab-confirmed 2009 H1N1 in US
  - No difference in outcomes among all women with H1N1 compared to matched controls
  - Hospitalized women had higher incidence of SGA infants


Maternal Influenza and Birth Defects

- Systematic review and meta-analysis of the association between 1st trimester influenza exposure and birth defects

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any birth defect</td>
<td>2.00 (1.62-2.48)</td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>3.33 (2.05-5.40)</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>5.74 (1.10-30.00)</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>1.56 (1.13-2.14)</td>
</tr>
<tr>
<td>Cleft lip +/- cleft palate</td>
<td>3.12 (2.20-4.42)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>1.71 (1.09-2.69)</td>
</tr>
<tr>
<td>Limb deficiencies</td>
<td>2.03 (1.27-3.27)</td>
</tr>
</tbody>
</table>

Luteijn et al., Human Reprod 29:809-23, 2014
Safety of Neuraminidase Inhibitors

- Safety of neuraminidase inhibitors evaluated in several studies
  (Greer et al., 2010; Svensson et al., 2011; Saito et al., 2013; Xie et al., 2013; Dunstan et al., 2014; Beau et al., 2014)
- None have shown evidence of harm, except for one study which showed an association with late transient hypoglycemia

Safety of Influenza Vaccine

- Safety of influenza vaccine (seasonal and pH1N1) evaluated in several studies
  (Moro et al., 2011a; Moro et al., 2011b; Moro et al., 2013; Chambers et al., 2013; Louik et al., 2013; Nordin et al., 2014)
- None have shown evidence of harm, except for two studies that showed an association with preterm birth with pH1N1-containing vaccines (<3 days decrease in gestational age)
- Several studies have shown benefits of influenza vaccine on birth outcomes (lower risk of preterm birth, low birth weight, SGA)
  (Steinhoff et al., 2012; Omer et al., 2011; Fell et al., 2012; Richards et al., 2013; Legge et al., 2014)
Provider recommendation is one of the strongest predictors of influenza vaccination among pregnant women


Patient Barriers to Influenza Vaccination during Pregnancy

- Safety concerns
- Lack of knowledge about influenza (unfamiliar with recommendations)
- Fear of needles
- Vaccination history (no previous flu vaccination)
- General mistrust of the medical establishment
- Lacking an established relationship with an ob/gyn as a vaccine provider
- Access to care

Update on Vaccine Recommendations

- All people ≥ 6 months of age are recommended to receive influenza vaccination - priority groups include:
  - Pregnant women
  - Household contacts and caregivers of children <5 years, with particular emphasis on contacts of infants <6 months of age

Grohskopf et al., MMWR Rec Reports, 62(RR07);1-43, 2013.

Estimated Influenza Vaccination (trivalent) Coverage, Pregnant Women*

* Behavioral Risk Factor Surveillance (BRFSS) data from December-February interviews only, for women 18-44 years pregnant or not pregnant when interviewed. Differences in influenza vaccination coverage between pregnant and not pregnant women were statistically significant (p<0.05) only for the 2009-10, 2010-11, and 2011-12 seasons. Other estimates for pregnant women from PRAMS (MMWR December 3, 2010;59(47):1541-1545); NHFS (Chung et al. Am J Obstet Gynecol June 2011 Supplement); and internet panel survey (MMWR August 19, 2011;60(32):1078-1082; MMWR September 28, 2012;61(8);758-63).
Update on Treatment Recommendations

- Treatment with oseltamivir recommended for pregnant women and women up to 2 weeks postpartum with suspected/confirmed influenza
  - Regardless of trimester of pregnancy
  - Regardless of whether woman received influenza vaccine
  - Early treatment (<48 hours) best, but later treatment also of benefit
  - Do not delay treatment because of negative rapid influenza diagnostic test or inability to test or while awaiting test results

http://www.cdc.gov/flu/protect/vaccine/pregnant.htm

Pregnant Women in the 2013-2014 Flu Season
Conclusions

• Public health recommendations require weighing the risks and benefits of planned intervention
  – Often data on risks and benefits are incomplete
• Based on experience from these 3 examples:
  – Engage experts and partners
  – Be transparent about what you know and don’t know
  – Collect data on outcomes to guide future interventions
  – Alter course based on data collected

Acknowledgments

Margaret (Peggy) Honein, PhD, MPH
Questions

Contact information:
skr9@cdc.gov
Effectiveness of Neuraminidase Inhibitors

- Meta-analysis of NAI effectiveness in reducing mortality of hospitalized patients (published online March 19, 2014)
  - Pregnant women (n=2166) – Treatment any time vs. none - AOR 0.46, 0.23-0.89
  - Pregnant women (n=917) – Early vs late treatment - AOR 0.27, 0.11-0.63
  - Pregnant women (n=1303) – Early treatment vs none - AOR 0.16, 0.04-0.67

- Cochrane review – reviewed data from 20 oseltamivir and 26 zanamivir randomized controlled trials (released April 10, 2014)
  - Pregnant women excluded from RCTs

  Muthuri et al., Lancet Resp Dis, online
  Jefferson et al., Cochrane Database Systematic Reviews 2014

Maternal Outcomes (ICU Admissions and Deaths) by Timing of Antiviral Treatment, US, April--August 21, 2009

<table>
<thead>
<tr>
<th>Timing of treatment after symptom onset</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU Admissions</td>
</tr>
<tr>
<td>&gt;4 days vs. ≤2 days</td>
<td>6.0 (3.5-10.6)</td>
</tr>
<tr>
<td>3-4 days vs. ≤2 days</td>
<td>2.4 (1.2-4.8)</td>
</tr>
</tbody>
</table>

Siston et al., JAMA 303:1517-1525, 2010
Timeline of 2009 H1N1 Influenza Outbreak - 1

- April 15, 17, 2009 – CDC identifies novel influenza A (H1N1) virus from 2 patients, US government notifies WHO
- April 25, 2009 – WHO declares public health emergency of international concern
- April 26, 2009 – US declares public health emergency

Timeline of 2009 H1N1 Influenza Outbreak - 2

- April 27, 29, 2009 – WHO raises global pandemic alert to phases 4/5
- May 4, 2009 – 2nd documented death in the US from 2009 H1N1 was a healthy pregnant woman
- June 11, 2009 – WHO raises global pandemic alert to phase 6
- August 10, 2010 – WHO declares end to 2009 H1N1 influenza pandemic
What We Knew before 2009 H1N1

Pandemic Influenza and Pregnant Women
Sonja A. Rasmussen,* Denise J. Jamieson,* and Joseph S. Bresee*

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 14, No. 1, January 2008

Infant Outcomes among Severely Ill Pregnant Women with 2009 H1N1 Influenza

Live singleton births n=143*

• Delivered during maternal influenza hospitalization n=85
  – 23 mothers died
• Delivered after maternal influenza hospitalization n=54
  – Median days from discharge to delivery = 85
  – Range = 5-187 days

*Missing delivery timing information n=4

CDC, MMWR Morb Mortal Wkly Rep 60:1193, 2011
### Infant Outcomes among Severely Ill Pregnant Women with 2009 H1N1 Influenza

<table>
<thead>
<tr>
<th>Infant Outcomes</th>
<th>Delivery during maternal hospitalization for influenza illness</th>
<th>Delivery after discharge from influenza illness hospitalization</th>
<th>US Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%; 95% CI)*</td>
<td>N (%; 95% CI)*</td>
<td></td>
</tr>
<tr>
<td>Preterm Birth</td>
<td>49 (64%; 52–74%)</td>
<td>10 (21%; 11–35%)</td>
<td>12%</td>
</tr>
<tr>
<td>SGA</td>
<td>3 (4%; 0–2%)</td>
<td>13 (25%; 14–39%)</td>
<td>10%</td>
</tr>
<tr>
<td>Low Birthweight</td>
<td>32 (44%; 32–56%)</td>
<td>10 (19%; 10–33%)</td>
<td>8%</td>
</tr>
<tr>
<td>Low 5-Minute Apgar Score</td>
<td>21 (29%; 19–41%)</td>
<td>1 (2%; 0–11%)</td>
<td>2%</td>
</tr>
<tr>
<td>NICU Admission</td>
<td>50 (69%; 58–80%)</td>
<td>11 (22%; 12–36%)</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Exact 95% Confidence Interval

**CDC, MMWR Morb Mortal Wkly Rep 60:1193, 2011**

### Influenza Vaccine during Pregnancy Protects Infants < 6 Months of Age from Laboratory-Proven Influenza

**Zaman et al., N Engl J Med 359:1555-64, 2008**
Prevalence of Neural Tube Defects, 24 Surveillance Programs, National Birth Defects Prevention Network

What We Know Now

Novel Influenza A (H1N1) Virus Infections in Three Pregnant Women --- United States, April–May 2009

Articles
Acetaminophen Use during Pregnancy - 1

Scialli et al., Reprod Toxicol 30:508-19, 2010

At present, the evidence is inconclusive that any such association is causal.
### Acetaminophen Use during Pregnancy - 2

**Original Investigation**

**Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders**

Liew et al., JAMA Pediatr 168:313-20, 2014

Cooper et al., JAMA Pediatr 168:306-7, 2014

### Information on Safety of Neuraminidase Inhibitors during Pregnancy - 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Numbers exposed/unexposed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greer et al., 2010</td>
<td>Retrospective cohort, Parkland Hospital, 2003-2008</td>
<td>Oseltamivir - 135 Unexposed - 82,097</td>
<td>No increased risk for preterm birth, premature rupture of membranes, gestational diabetes, preeclampsia, low birth weight, major or minor malformations</td>
</tr>
<tr>
<td>Svensson et al., 2011</td>
<td>Retrospective cohort, national registers, Sweden, 2005-2007</td>
<td>Oseltamivir - 81 Zanamivir – 2 Both – 3 Unexposed - 860</td>
<td>Increased risk of late transient hypoglycemia (crude OR 4.0, 1.3-12.8). No increased risk of low Apgars, congenital malformations, SGA, low birth weight, preterm birth or birth-related death</td>
</tr>
<tr>
<td>Saito et al., 2013</td>
<td>Case series study, Japan, 2009-2010</td>
<td>Oseltamivir – 619 Zanamivir – 50</td>
<td>No increased risk of malformations, miscarriage, preterm birth, neonatal death, low birthweight, SGA, NEC, IVH, seizures</td>
</tr>
</tbody>
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Information on Safety of Neuraminidase Inhibitors during Pregnancy

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<tr>
<td>Xie et al., 2013</td>
<td>Retrospective cohort, maternal newborn database, Ontario, 2009-2010</td>
<td>Oseltamivir – 1,237</td>
<td>Infants exposed to oseltamivir were less likely to be SGA (10th centile) – ARR 0.77 (0.70-0.98). No increased risk of SGA (3rd centile), preterm birth, very preterm birth, low Apgar scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unexposed – 54,118</td>
<td></td>
</tr>
<tr>
<td>Dunstan et al., 2014</td>
<td>Prospective cohort, UK teratology information service during 2009 H1N1 pandemic</td>
<td>Zanamivir – 180</td>
<td>No increased risk of major malformations, preterm delivery, low birth weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oseltamivir - 27</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unexposed – 575</td>
<td></td>
</tr>
<tr>
<td>Beau et al., 2014</td>
<td>French prescription database 2004-2010</td>
<td>Oseltamivir - 337</td>
<td>No increased risk for pregnancy loss, preterm birth, neonatal pathology, congenital defects</td>
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<tr>
<td></td>
<td></td>
<td>Unexposed - 674</td>
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<td></td>
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<td>(matched by age, month, delivery year)</td>
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Maternal Influenza Vaccine’s Effects on Fetus/Newborn

- Randomized controlled trial in Bangladesh -- pregnant women received inactivated influenza vaccine vs. pneumococcal
- Higher birth weights (p=0.02) and lower risk of small for gestational age (SGA) (p=0.03) among infants whose mothers received influenza vaccine

Steinhoff et al., CMAJ 184:645-53, 2012
Maternal Influenza Vaccine’s Effects on Fetus/Newborn - 2

- Observational study from Georgia PRAMS
  - Infants born during the putative influenza season (1 October-31 May) to mothers who received influenza vaccine prenatally were less likely to be preterm (aOR=0.60, 95% CI 0.38-0.94) and SGA (aOR= 0.31, 95% CI 0.13-0.75) compared to unvaccinated women.

- Observational study from Ontario
  - Infants born to mothers who received H1N1 vaccine prenatally were less likely to be SGA (aRR=0.90; 95% CI 0.85, 0.96) or preterm (<32 weeks) (aRR = 0.73; 95% CI = 0.58, 0.91). Fetal death was also less likely (aRR = 0.66; 95% CI = 0.47, 0.91).

  Omer et al., PLoS Med 8:e1000441, 2011

Maternal Influenza Vaccine’s Effects on Fetus/Newborn - 3

- Observational study from Kaiser Permanente GA and Mid-Atlantic
  - Infants born to mothers who received H1N1 vaccine prenatally had 37% lower odds of being born preterm than infants of unvaccinated mothers. Mean birth weight difference of 45.1 g (1.8-88.3) between infants of H1N1-vaccinated mothers and of unvaccinated mothers. No significant association between H1N1 influenza immunization and LBW or SGA.

- Observational study from Nova Scotia
  - Odds of preterm delivery among infants of vaccinated women were lower than those of nonvaccinated women (aOR=0.75, 0.60-0.94). Rate of low birthweight infants was also lower among vaccinated women (aOR=0.73, 0.56-0.95).

  Richards et al., Clin Infect Dis 56, 1216-22, 2013
  Legge et al., CMAJ 186:E1577-164, 2014
### Information on Safety of Influenza Vaccines during Pregnancy - 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Numbers exposed/unexposed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro et al., 2011</td>
<td>Review or reports of adverse events to VAERS, US, 1990-2009</td>
<td>148 reports of adverse events after TIV and 16 after LAIV</td>
<td>No unusual patterns of pregnancy complications or fetal outcomes</td>
</tr>
<tr>
<td>Moro et al., 2011</td>
<td>Review of reports of adverse events to VAERS, US, 2009-2010</td>
<td>294 reports of adverse events after 2009 H1N1 inactivated vaccine</td>
<td>No concerning patterns of maternal or fetal outcomes</td>
</tr>
<tr>
<td>Moro et al., 2013</td>
<td>Review of reports of adverse events to VAERS, US, 2009-2010</td>
<td>113 reports of adverse events after 2009 H1N1 LAIV</td>
<td>No concerning patterns of medical conditions in infants</td>
</tr>
</tbody>
</table>

### Information on Safety of Influenza Vaccines during Pregnancy - 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Numbers exposed/unexposed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers et al., 2013</td>
<td>Prospective cohort</td>
<td>- 841 exposed to pH1N1-containing vaccine - 191 unexposed to any influenza vaccine</td>
<td>No meaningful evidence of increased risk for major birth defects, spontaneous abortion or SGA. Increased risk of PTD – AHR=3.28, 1.25-8.63 (decrease in gestational age ~3 days)</td>
</tr>
<tr>
<td>Louik et al., 2013</td>
<td>Birth defects – case-control Preterm delivery – cohort</td>
<td>Birth defects - 3104 cases - 1098 controls PTD - 370 exposed to pH1N1-containing vaccines - 573 unexposed</td>
<td>41 specific birth defects – most AORs ~1.0, 3 defects - AORs &gt;2.0 and 4 defects - AORs &lt;0.5, wide 95% CIs PTD - 2009-2010 season – AHR=2.82, 1.16-6.86 (decrease in gestational age &lt;2 days) - 2010-2011 season – AHR=0.22, 0.06-0.83</td>
</tr>
<tr>
<td>Nordin et al., 2014</td>
<td>Retrospective matched cohort, 7 US sites, 2004-2009</td>
<td>57,749 vaccinated 92,440 unvaccinated</td>
<td>No increased or decreased risk for PTD or SGA</td>
</tr>
</tbody>
</table>
Prepating for influenza after 2009 H1N1: special considerations for pregnant women and newborns

Sonia A. Rasmussen, MD, MS; Dmitry M. Kislin, MD, MPH; Lorraine F. Yeung, MD, MPH; Kitty MacFarlane, MN, MPH; Susan I. Cho, PhD, MSPH; Retna M. Turnier-Rutja, MD; Elizabeth W. Mitchell, PhD; Jennifer Williams, MSN, MPH; Alicia M. Fry, MD, MPH; Jeffrey Hageman, MHS; Timothy M. Uyeki, MD, MPH, MPP; Denise J. Jamieson, MD, MPH; and the Pandemic Influenza and Pregnancy Working Group

Current Treatment Recommendations - 1

• All pregnant women with suspected influenza should receive prompt empiric treatment with appropriate influenza antiviral medications

• Pregnant women with suspected influenza should be treated, regardless of influenza vaccination status

• Currently available diagnostic tests should not be used to guide initial treatment decisions

Current Treatment Recommendations - 2

• Prophylaxis recommendations should be the same as those for other groups at high risk for influenza-associated complications (can be considered)

• Recommendations for treatment /prophylaxis should apply to women for at least 2 weeks following the end of pregnancy

• Acetaminophen for fever
Strategies to Improve Immunization Coverage

- Use reminder/recall systems
- Enter information regarding vaccine administration into immunization information systems
- Use standing orders
- Review immunization status at each patient visit
- Educate health care providers who administer vaccines
- Regularly assess provider coverage rates
- Improve public and provider awareness to increase demand

*Shavell et al., Am J Obstet Gynecol 207:S67-74, 2012*