Human Teratogens
Update 2011

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Centers for Disease Control and Prevention
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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

The author of this research has no financial or other interests which pose a conflict of interest.
In 1941, Australian ophthalmologist Sir Norman Gregg first recognized and recorded the effects of maternal rubella on the fetus.

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

*MMWR Morb Mortal Wkly Rep 54:279-82, 2005*
WG McBride: “In recent months, I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide during pregnancy . . . to be almost 20%. Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?”

W Lenz: “I have seen 52 malformed infants whose mothers had taken contergan in early pregnancy. . . . Since I discussed the possible aetiological role of contergan in human malformations at a conference on Nov. 18, 1961, I have received letters from many places . . . reporting 115 additional cases in which this drug was thought to be the cause. . . . I venture the estimate that at least 2000, possibly more than 3000, “contergan” babies have been born in Western Germany since 1959.”
**Figure 1**

- **Sales of thalidomide (kg)**
- **Cases of thalidomide embryopathy**

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**Običan and Scialli, Seminars in Medical Genetics – in press**
*(August 15, 2011)*

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**THE NEW ENGLAND JOURNAL OF MEDICINE**

*April 22, 1971*

**ADENOCARCINOMA OF THE VAGINA**

*Association of Maternal Diethylstilbestrol Therapy with Tumor Appearance in Young Women*

**Arthur L. Herbst, M.D.**
**Howard Yousem, M.D.,** and **David C. Parshall, M.D.**

**Abstract.** Adenocarcinoma of the vagina in young women had been recorded rarely before the report of several cases treated at the Vincent Memorial Hospital between 1956 and 1969. The unusual occurrence of this tumor in eight patients born in New England hospitals between 1946 and 1951 led us to conduct a retrospective investigation in search of factors that might be associated with tumor appearance. Four matched controls were established for each patient; data were obtained by personal interview. Results show maternal bleeding during the current pregnancy and previous pregnancy loss were more common in the study group. Most significantly, seven of the eight mothers of patients with carcinoma had been treated with diethylstilbestrol started during the first trimester. None in the control group were so treated (p less than 0.00001). Maternal ingestion of stilbestrol during early pregnancy appears to have enhanced the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

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**The Long-Term Effects of In Utero Exposures — The DES Story**

Annekathryn Goodman, M.D., John Schorge, M.D., and Michael F. Greene, M.D.
Issues to Consider

- What data are needed to say a medication or vaccine is “safe” for use during pregnancy?
- How can we best weigh the benefits of medications or vaccines with potential, but often unknown, risks to the embryo or fetus?
- How can we communicate these complicated issues to health care providers and the public?

Pasternak and Hviid, JAMA 304:859-66, 2010
Association between Prenatal Oral Acyclovir, Valacyclovir and Famciclovir Use and Birth Defects, Denmark

<table>
<thead>
<tr>
<th>Medication</th>
<th># of Women Exposed</th>
<th>Birth Defects N (%)</th>
<th>Adjusted Prevalence Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antiviral</td>
<td>1804</td>
<td>40 (2.2)</td>
<td>0.89 (0.65-1.22)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>1561</td>
<td>32 (2.0)</td>
<td>0.82 (0.57-1.17)</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>229</td>
<td>7 (3.1)</td>
<td>1.21 (0.56-2.62)</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>26</td>
<td>1 (3.8)</td>
<td>1.63 (0.20-13.05)</td>
</tr>
</tbody>
</table>

Pasternak and Hviid, JAMA 304:859-66, 2010

"From a public health perspective, this study provides fairly strong reassurance that acyclovir is not a major cause of birth defects. However, this study leaves a key question unanswered – is acyclovir a teratogen?"

Mills and Carter, JAMA 304:905-6, 2010
### Association between Use of Proton-Pump Inhibitors during 1st Trimester of Pregnancy and Birth Defects, Denmark

<table>
<thead>
<tr>
<th>Medication</th>
<th># Live Births</th>
<th>Birth Defects N (%)</th>
<th>Adjusted Prevalence Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to any PPI</td>
<td>3651</td>
<td>118 (3.2)</td>
<td>1.10 (0.91-1.34)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>1800</td>
<td>52 (2.9)</td>
<td>1.05 (0.79-1.40)</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>549</td>
<td>21 (3.8)</td>
<td>1.33 (0.85-2.08)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>794</td>
<td>28 (3.5)</td>
<td>1.13 (0.77-1.67)</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>42</td>
<td>3 (7.1)</td>
<td>2.14 (0.60-7.68)</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>668</td>
<td>23 (3.4)</td>
<td>1.19 (0.77-1.84)</td>
</tr>
</tbody>
</table>
“The report on proton-pump inhibitors . . . is therefore both timely and important. . . however, these data provide only a broad – and incomplete – overview.”


Newer-Generation Antiepileptic Drugs and the Risk of Major Birth Defects

### Associations between Newer-Generation Antiepileptic Drug Use in Pregnancy and Birth Defects, Denmark

**Medication** | **# of Women** | **Birth Defects N (%)** | **Adjusted Prevalence Odds Ratio (95% CI)**
--- | --- | --- | ---
Newer-generation antiepileptic drugs | 1532 | 49 (3.2) | 0.99 (0.72-1.36)
Lamotrigine | 1019 | 38 (3.7) | 1.18 (0.83-1.68)
Oxcarbazepine | 393 | 11 (2.8) | 0.86 (0.46-1.59)
Topiramate | 108 | 5 (4.6) | 1.44 (0.58-3.58)
Gabapentin | 59 | 1 (1.7) | 0.53 (0.07-3.85)
Levetiracetam | 58 | 0 | Not estimable


### Medication Exposed

| Medication | Exposed N (%) | Unexposed N (%) | Adjusted Prevalence Odds Ratio (95% CI) |
--- | --- | --- | ---
Newer-generation antiepileptic drugs | | | |
Orofacial clefts | 2 (0.1) | 1421 (0.2) | 0.58 (0.13-2.58)

“Among live-born infants in Denmark, first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam compared with no exposure was not associated with an increased risk of major birth defects.”

“Topiramate, gabapentin, and levetiracetam do not appear to be major teratogens, but our study cannot exclude minor to moderate risks of major birth defects.”
Topiramate and Pregnancy

- FDA changed drug’s pregnancy category to D
- “Health care professionals should carefully consider the benefits and risks of topiramate when prescribing it to women of child-bearing age” – Russell Katz, director of FDA’s division of neurology products

Treatment of Obesity

- Obesity is associated with a wide range of adverse outcomes
- Diet and exercise have been ineffective in most individuals
- New treatments for obesity that work and are safe are urgently needed
- Combination treatment – phentermine and topiramate (Qnexa®) – well tolerated and associated with significant weight loss

Kennett and Clifton, Pharmacol Biochem Behavior 97:63-83, 2010

Flegal et al., JAMA 288:1723-1727, 2002; Ogden et al., JAMA 295:1549-1555, 2006; Ogden et al., NCHS data brief, 2007; Flegal et al., JAMA 303:235-241, 2010

Adverse Infant Outcomes Associated with Prepregnancy Obesity

- Miscarriage
- Perinatal death
- Neonatal death
- Macrosomia
- Shoulder dystocia/birth trauma
- Meconium aspiration
- Birth defects
- Juvenile obesity

FDA and Qnexa® (continued)

• Data reviewed by FDA
  – Topiramate is a teratogen in several animal species
  – UK Epilepsy and Pregnancy Register – 70 exposed pregnancies, 4.8% (95% CI 1.7-3.3%) with major malformations, 2 with oral cleft abnormalities (Hunt et al., Neurology, 2008)
  – North American AED Pregnancy Registry – Prevalence of major malformation 3.8%, Relative Risk for major malformations was 2.8 (95% CI 1.0-8.1) when compared to controls. 4 babies with cleft lip, 2 isolated cleft lip (0.69%, compared to expected of 0.07%) (Hernandez-Diaz et al., presented at Teratology Society meeting, June 2010)
  – FDA AERS database review – 64 topiramate-exposed pregnancies with malformations – 11 with cleft lip and/or palate


FDA and Qnexa®

• “FDA Nixes Diet Drug Qnexa” – US News and World Report, October 29, 2010
  – FDA has rejected the diet drug Qnexa® out of concern for its potential to cause birth defects and heart problems.
  – Though FDA officials have said they are committed to working to approve drugs that can help fight obesity, the medications must be “safe and effective,” John Jenkins, director of the FDA's office of new drugs, told reporters this month.
  – Many view the latest rejection as a setback not only in the fight against obesity, but also against diabetes.
After the 2009 H1N1 Pandemic: Issues Related to Pregnancy

- Medications used to treat influenza
  - Antiviral medications
  - Antipyretic medications
- Influenza vaccine

Why are Pregnant Women a “Vulnerable Population”? 

- Influenza’s effects on pregnant women differ from effects on general population
  - 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*
Why are Pregnant Women a “Vulnerable Population”? (continued)

- Effects of influenza on the fetus are unknown and difficult to predict
  - Viremia is believed to occur infrequently and placental transmission appears to be rare
  - Even without placental transmission, effects may occur (e.g., hyperthermia as a risk factor)

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

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**Maternal Hyperthermia and Neural Tube Defects: Meta-Analysis**

<table>
<thead>
<tr>
<th>Type of Studies</th>
<th># of Studies</th>
<th>Summary Odds Ratio/Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-Control</td>
<td>9</td>
<td>1.93 (1.53-2.42)</td>
</tr>
<tr>
<td>Prospective Cohort</td>
<td>6</td>
<td>1.95 (1.30-2.92)</td>
</tr>
</tbody>
</table>

Treatment with antipyretic medications appeared to attenuate the risk

*Moretti et al., Epidemiology 16:216-9, 2005*
Oseltamivir (Tamiflu®)

• Effects on fetus
  – Animal (rat, rabbit) – pregnancy loss at high doses, no malformations noted
  – Human data – 61 reports of oseltamivir-exposed pregnancies in post-marketing period
    ✓ 4 spontaneous abortions, 6 elective terminations
    ✓ Single cases of trisomy 21 and anencephaly reported
    ✓ Majority reported normal outcome

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Zanamivir (Relenza®)

• Effects on fetus
  – Animal data (rat, rabbit) – no evidence of embryotoxicity or increased risk of malformations
  – Human data – 3 zanamivir-exposed pregnancies during clinical trials
    ✓ 1 spontaneous abortion
    ✓ 1 elective termination
    ✓ 1 normal outcome

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Freund et al., Drug Saf 21:267-81, 1999

Influenza Vaccine and Pregnancy

• ACIP and ACOG recommend trivalent inactivated vaccine for women who will be pregnant during influenza season, regardless of pregnancy trimester, but compliance has been low
Influenza Vaccine during Pregnancy Protects Infants < 6 Months of Age


Safety of influenza vaccination during pregnancy

- 11 studies published between 1964 and 2008 about safety of seasonal influenza vaccination during pregnancy
- None identified maternal or fetal problems with influenza vaccination

Tamma et al., Am J Obstet Gynecol 201:547-52, 2009
Pandemic Influenza and Pregnant Women: Summary of a Meeting of Experts

Swine Influenza A (H1N1) Infection in Two Children --- Southern California, March--April 2009
• Treatment is recommended for pregnant women and women up to 2 weeks postpartum with suspected or confirmed influenza, regardless of trimester of pregnancy
• Do not delay treatment because of a negative rapid influenza diagnostic test or inability to test or while awaiting test results

Oseltamivir (Tamiflu®)
– BEST if started as soon as possible (i.e., within 48 hours of symptom onset), but later treatment also of benefit
• Considering severity of disease, treatment benefit outweighs potential risk
• Acetaminophen for fever
2009-2010 Vaccine Recommendations

- Pregnant women should receive both 2009 H1N1 and seasonal vaccines
- Pregnant women can receive:
  - multidose inactivated vaccine
  - prefilled single dose inactivated vaccine (preservative-free)
- Live attenuated vaccine not licensed for use in pregnant women, but can be used postpartum

2009 H1N1 Influenza and Pregnancy

- 34 confirmed or probable cases in US pregnant women (4/15-5/18/09)
- Infections and deaths in all three trimesters
- Pregnant women more likely to be hospitalized (risk ratio 4.3, 95% CI 2.3-7.8)
- Pregnant women more likely to die
- Most women who died were previously healthy
- Initiation of antiviral treatment was often delayed

Jamieson et al., Lancet 374:451-8, 2009
2009 H1N1 among Pregnant Women in the US, 2009

- ~ 5% of deaths in US from 2009 H1N1 influenza were among pregnant women (based on data from April-August 2009) -- pregnant women account for ~1% of the general population
- Early treatment was associated with fewer ICU admissions and fewer deaths
- Limited data on infant outcomes – 30% of infants on whom data were available were delivered preterm

Siston et al., JAMA 303:1517-1525, 2010

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
Oseltamivir (Tamiflu®)

- Among 90 pregnant women exposed in first trimester to oseltamivir (data from two Japanese teratogen information services):
  - 1 infant with birth defect (VSD)
  - 3 spontaneous abortions
  - 4 preterm births
- No evidence of increased risk, but numbers are small

Tanaka et al., CMAJ 181:55-8, 2009

Oseltamivir (Tamiflu®)

- Retrospective cohort study at Parkland Hospital from October 2003 to March 2008
- Compared women exposed to oseltamivir (n=135) to controls (n=82,097) (18 exposed in 1st trimester)
- Found no increased risk for preterm birth, premature rupture of membranes, gestational diabetes, preeclampsia, low birth weight, major or minor malformations among infants born to oseltamivir-exposed women

Greer et al., Obstet Gynecol 115:711-6, 2010
Influenza Vaccine: Data from Vaccine Adverse Event Reporting System

- Searched VAERS data for reports of adverse events in pregnant women following influenza vaccine -- trivalent inactivated influenza vaccine (TIV) from 7/1/90-6/30/09 or live attenuated influenza vaccine (LAIV) from 7/1/03-6/30/09
  - 148 reports after TIV
  - 27 reports after LAIV
- Most common pregnancy-specific adverse event was spontaneous abortion: 17 after TIV (11.5%) and 3 after LAIV (11%) – rate of reporting of SAB was 1.9 per million pregnant women vaccinated
- No unusual patterns of pregnancy complications or fetal outcomes observed


Vaccine Adverse Event Reporting System (VAERS): Spontaneous Reporting System Co-administered by the FDA and CDC

**Strengths**
- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis
- Encourages reports from healthcare providers and accepts reports from patients and others
- Data available to the public

**Limitations**
- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an adverse event (AE)
- Lack of unvaccinated comparison group
Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

- Prospective cohort identified through Organization of Teratology Information Specialists (OTIS)
  - Pregnant women who contact a TIS after receiving an influenza vaccine or antiviral medication, regardless of illness status
  - Outcomes: birth weight, spontaneous abortion, stillbirth, neonatal death, preterm birth, small for gestational age, preeclampsia, total malformations
- Case-control study through Slone Epidemiology Center
  - Focus on specific major malformations
  - Maternal interviews about influenza vaccine (seasonal and/or H1N1) and antiviral meds, regardless of illness status, potential confounders


VAMPSS Proposal to Address Safety

- Odds ratio that approximates <1.0 with an upper 95% confidence bound of <4.0 may be defined as “no evidence of risk”
- Odds ratio that approximates <1.0 with an upper 95% confidence bound of <2.0 may be defined as “evidence of relative safety”

**Acetaminophen and Birth Defects**

- Birth defects overall: No increased risk identified
- Specific defects: No increased risks for most specific defects, but inconsistent associations with some
  - 2010 report from National Birth Defects Prevention Study found no increased risks for each of over 50 specific defects


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**Acetaminophen (APAP) during Pregnancy and Childhood Asthma**

<table>
<thead>
<tr>
<th>Source</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avon Longitudinal Study of Parent and Children (Shaheen et al., 2002)</td>
<td>APAP exposure from wks 20-32 gestation (but not wks 0-19) associated with increased risk of asthma (aOR 2.10; 95% CI 1.30-3.41)</td>
</tr>
<tr>
<td>Singapore Children’s Asthma and Allergy Network (Koniman et al., 2007)</td>
<td>More children with asthma than controls had mothers who took APAP during pregnancy (35% vs. 0%, p=0.03)</td>
</tr>
<tr>
<td>Danish National Birth Cohort (Rebordosa et al., 2008)</td>
<td>Prenatal APAP use associated with increased risk of MD-diagnosed asthma/bronchitis at 18 months (RR 1.18, 95% CI 1.13-1.23)</td>
</tr>
<tr>
<td>Peer Education in Pregnancy Study (Persky et al., 2008)</td>
<td>APAP use in middle-late (but not early) pregnancy was related to wheezing in the 1st year of life (OR 1.8, 95% CI 1.1-3.0)</td>
</tr>
</tbody>
</table>

Reviewed by Scialli et al., Repro Toxicol 30:508-19, 2010
### Acetaminophen (APAP) during Pregnancy and Childhood Asthma (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murcia (Spain) study (Garcia-Marcos et al., 2009)</td>
<td>Among non-asthmatic mothers, prenatal APAP use (at least once monthly) associated with wheezing at preschool age (OR 1.94; 95% CI 1.34-2.79)</td>
</tr>
<tr>
<td>The Yale Study (Kang et al., 2009)</td>
<td>Prenatal APAP use did not increase the risk of asthma (aOR 0.76, 95% CI 0.53-1.10)</td>
</tr>
<tr>
<td>Columbia Center for Children’s Environmental Health Study (Perzanowski et al., 2010)</td>
<td>Prenatal APAP use predicted current wheeze (multivariate RR, 1.71; 95% CI 1.20-2.42); Risk increased with increasing number of days of prenatal APAP</td>
</tr>
<tr>
<td>Oslo Environment and Asthma Study (Bakkeheim et al., 2010)</td>
<td>No association between prenatal APA use and diagnosis of childhood asthma at age 10</td>
</tr>
</tbody>
</table>

Reviewed by Scialli et al., Repro Toxicol 30:508-19, 2010

### Pertussis Outbreak in California

- 9,120 cases with onset in 2010 (23.3 cases per 100,000) – highest number in 63 years (1947) and highest rate in 52 years (1958)
  - 9% of cases were hospitalized (55% <3 months of age, 72% <6 months of age)
  - 10 deaths (9 in infants <2 months of age)
  - Case-fatality rate among infants < 3 months of age is 1.3%
- As of 6/15/11, 1,428 cases with onset in 2011 reported
  - 8% of cases were hospitalized (67% <2 months of age)
  - No deaths

Pertussis

• Respiratory illness (commonly known as whooping cough)
• Caused by bacteria *Bordetella pertussis*
• Very contagious – spread person to person by coughing or sneezing while in close contact
• Symptoms typically within 7-10 days of exposure
• Control of pertussis - vaccination
Pertussis Vaccination

- Different formulations of diphtheria, tetanus, and pertussis vaccines - DTaP, Tdap, and Td vaccines
  - DTaP is given to children <7 years of age
  - Tdap and Td are given to older children and adults
- Children should get 5 doses of DTaP at ages: 2, 4, 6, and 15-18 months and 4-6 years

Pertussis Vaccination (continued)

- Adults
  - Td – given as a booster shot every 10 years or after an exposure to tetanus under some circumstances.
  - Tdap – also contains protection against pertussis - adolescents 11-18 years of age (preferably at age 11-12 years) and adults 19 through 64 years of age should receive a single dose of Tdap. For adults 65 and older who have close contact with an infant and have not previously received Tdap, one dose should be received
REPORTED PERTUSSIS INCIDENCE BY AGE GROUP, 1990-2009

**SOURCE:** CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

**REPORTED PERTUSSIS-RELATED DEATHS BY AGE GROUPS, UNITED STATES, 1980-2009**

<table>
<thead>
<tr>
<th>Age-group</th>
<th>1980-1989 (^1)</th>
<th>1990-1999 (^1)</th>
<th>2000-2009 (^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 month</td>
<td>38</td>
<td>68</td>
<td>152</td>
</tr>
<tr>
<td>2-3 months</td>
<td>11</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>4-5 months</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>6-11 months</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>1-4 years</td>
<td>13</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5-10 years</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>11-18 years</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>77(^*)</strong></td>
<td><strong>103</strong></td>
<td><strong>194</strong></td>
</tr>
</tbody>
</table>

\(^*\) Includes one case with unknown age


Advisory Committee on Immunization Practices: Guidance for Vaccination of Pregnant Women

Pregnancy is not a contraindication for use of Tdap

- Data on safety, immunogenicity and pregnancy outcomes not available for pregnant women who receive Tdap
- Transplacental maternal antibodies might protect infants against pertussis in early life
- Pre-existing maternal antibody could interfere with infant's immune response to DTaP, decreasing infant protection against pertussis
Advisory Committee on Immunization Practices: Guidance for Vaccination of Pregnant Women (continued)

Special Situations may warrant Tdap instead of Td
• Second or third trimester is preferred
• Providers who choose to administer Tdap to pregnant women at increased risk (e.g. adolescents, healthcare personnel, child care providers) should discuss lack of data with pregnant women
• Providers encouraged to report Tdap administration, regardless of trimester, to appropriate manufacturer's pregnancy registry

Methods to Protect Infants from Pertussis

• Vaccination of infants
  – Infants not fully protected because of immaturity of immune system
• Cocooning
  – Give Tdap booster vaccines to mothers and family members of newborn infants – protect contacts from getting pertussis and passing it on to young infants
• Vaccination of Pregnant Women
  – Vaccination in the late 2nd or 3rd trimester believed to provide protection to infants in the first 6 months of life (evidence for maternal antibody transfer)
Should Tdap be Recommended for Pregnant Women in late 2\textsuperscript{nd}/3\textsuperscript{rd} Trimester?

- **Advantages**
  - Maternal antibody transmitted to infant – expected that antibody will protect infants during time before they are protected by vaccine in infancy
  - Easier to implement than cocooning, given pregnant women’s frequent visits to health care providers during the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester of pregnancy

- **Disadvantages**
  - Is evidence available to say that vaccine is safe/benefits outweigh potential risks?
  - Will maternal vaccination result in blunting of infant’s immune response to primary DTaP series?

**Draft Recommendation from June 22, 2011 ACIP Meeting**

- Women’s health care providers should implement a maternal Tdap vaccination program for women who have not previously received Tdap. Health care providers should administer Tdap preferably during the third or late second trimester (after 20 weeks gestation). Alternatively, administer Tdap immediately postpartum.
Issues to Consider

• What data are needed to say a medication or vaccine is “safe” for use during pregnancy?
• How can we best weigh the benefits of medications or vaccines with potential, but often unknown, risks to the embryo or fetus?
• How can we communicate these complicated issues to health care providers and the public?

Kaplan-Meier Analysis: Time from FDA Approval to TERIS Risk Rating Assignment other than “Undetermined”

Adam, Polifka and Friedman, Seminars in Medical Genetics – in press (August 15, 2011)
“Although clinical trials address questions regarding drug safety for most segments of the population, pregnant women constitute one special group that is “orphaned” with respect to this issue. The lack of adequate pregnancy safety information for the vast majority of medications, combined with a need to make appropriate treatment decisions and to communicate risk information to a potentially vulnerable population, are some of the most challenging and critical women’s health issues.”
What is Needed:

- Continue research to understand causes of birth defects and other adverse outcomes
- Examine when it is appropriate to include pregnant women in clinical trials (Responsible Inclusion of Pregnant Women in Medical Research)
- Perform studies using different study designs to evaluate risks of medications and vaccines during pregnancy
- Focus on understanding mechanisms of teratogenesis
- Carefully consider benefits of medication or vaccine vs. potential risks
- Perform research on how best to communicate uncertainty to pregnant women and their partners

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