Human Teratogens Update 2011

Sonja A Rasmussen, MD, MS

Centers for Disease Control and Prevention

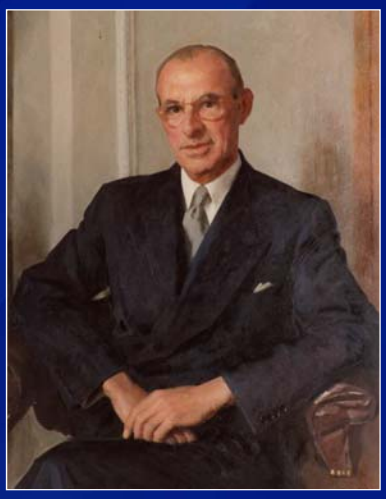
June 26, 2011

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.

U.S Department of Health and Human Services
Centers for Disease Control and Prevention

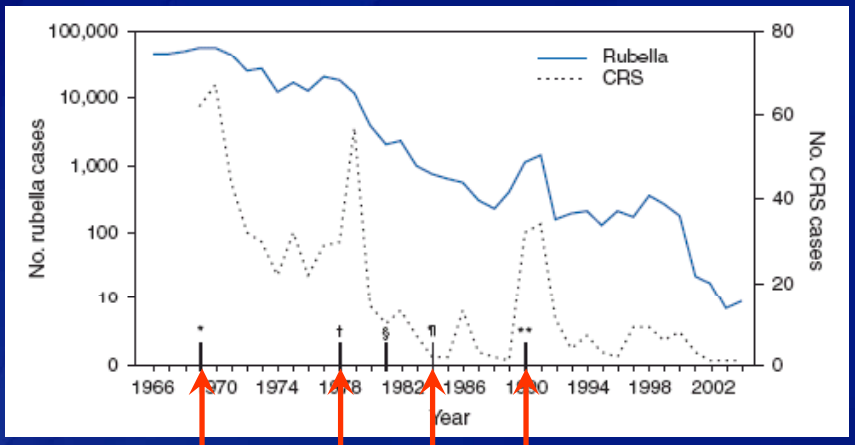
Disclosure

The author of this research has no financial or other interests which pose a conflict of interest.



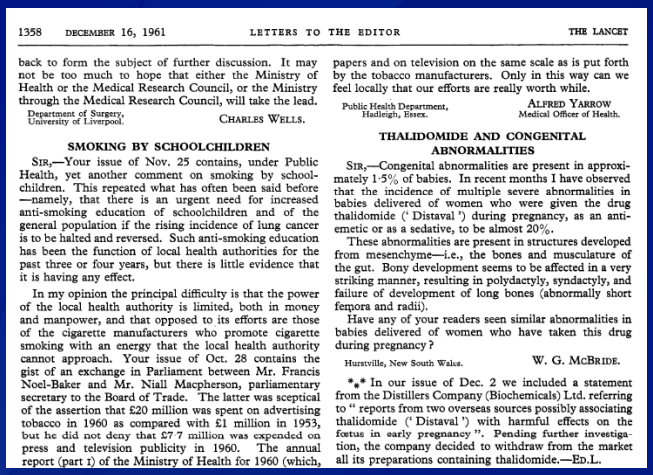
In 1941, Australian ophthalmologist Sir Norman Gregg first recognized and recorded the effects of maternal rubella on the fetus

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



1969 1978 1984 1990

MMWR Morb Mortal Wkly Rep 54:279-82, 2005



1358 DECEMBER 16, 1961 LETTERS TO THE EDITOR THE LANCET

back to form the subject of further discussion. It may not be too much to hope that either the Ministry of Health or the Medical Research Council, or the Ministry through the Medical Research Council, will take the lead.

Department of Surgery, University of Liverpool. CHARLES WELLS.

SMOKING BY SCHOOLCHILDREN

SIR,—Your issue of Nov. 25 contains, under Public Health, yet another comment on smoking by schoolchildren. This repeated what has often been said before—namely, that there is an urgent need for increased anti-smoking education of schoolchildren and of the general population if the rising incidence of lung cancer is to be halted and reversed. Such anti-smoking education has been the function of local health authorities for the past three or four years, but there is little evidence that it is having any effect.

In my opinion the principal difficulty is that the power of the local health authority is limited, both in money and manpower, and that opposed to its efforts are those of the cigarette manufacturers who promote cigarette smoking with an energy that the local health authority cannot approach. Your issue of Oct. 28 contains the gist of an exchange in Parliament between Mr. Francis Noel-Baker and Mr. Niall Macpherson, parliamentary secretary to the Board of Trade. The latter was sceptical of the assertion that £20 million was spent on advertising tobacco in 1960 as compared with £1 million in 1953, but he did not deny that £7·7 million was expended on press and television publicity in 1960. The annual report (part 1) of the Ministry of Health for 1960 (which, papers and on television on the same scale as is put forth by the tobacco manufacturers. Only in this way can we feel locally that our efforts are really worth while.

Public Health Department, Hadleigh, Essex. ALFRED YARROW Medical Officer of Health.

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the foetus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

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?"

JANUARY 6, 1962 IN ENGLAND NOW—LETTERS TO THE EDITOR THE LANCET 45

In England Now

A Running Commentary by Peripatetic Correspondents

One of my long-term analytic patients, who is going through a very active phase of his analysis, had a bad anxiety attack on his way home after a session. His wife called in the family doctor who, to be on the safe side, sent the patient into hospital with the comment ? coronary thrombosis ? perforated ulcer. He was first seen by the surgeon, who found nothing to justify operative interference. When the wife explained that her husband was undergoing analysis " for his nerves " he took one glance at the patient and said: " I see nothing nervous about him," but transferred him to the physician.

The physician ruled out coronary thrombosis on ordinary physical examination, but arranged for an E.C.G. none the less and threw in a barium meal as an extra. When, as expected, all results were negative, he sat down at—or should I say on—the bedside to " reassure " the patient. The patient related some of the analytic findings of the past two years, and received a reassuring pat on the back from the physician. Later, reporting to the wife, the physician said: " Your husband need not have gone all that time to the psychiatrist to find out what happened in his childhood. I got it out of him in five minutes."

* * *

" Hark! the herald angels sing, . . . " came over the radio as we plugged in the electric kettle for tea for breakfast. " This kettle's taking a long time to boil. Has it gone phut again? " " That was a new element and flex and plug that I had put in a week ago. Better look at the plug, it has a fuse in it." And so the investigation began; and the radio continued, " Peace on earth, and mercy mild . . . " The water in the kettle was warm, but wouldn't boil, yet the flex and all parts seemed all right. I unplugged the kettle and plugged in the bed-lamp—no light. The dressing-room light was out too—power failure. The radio continued—transistorised. Our house is near-all-electric. True, the central-heating is gas-operated, but the cooker that was to have been on gas is an electric model. You can't boil a kettle on a central-heating gas-boiler, but we remembered the gas-poker at the lounge fire-place. Saved again—but were we? Try holding a kettle

Letters to the Editor

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Dr. McBride (Dec. 16) describes congenital abnormalities in babies delivered of women who have taken thalidomide. I have seen 52 malformed infants whose mothers had taken ' Contergan ' in early pregnancy, and I understand that contergan is a synonym of thalidomide, others being ' Distaval,' ' Softenon ', ' Neurosedyn ', ' Isomin ', ' Kedavon ', ' Telargan ', and ' Sedalis '.

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 in the German Federal Republic, as well as from Belgium, England, and Sweden, reporting 115 additional cases in which this drug was thought to be the cause.

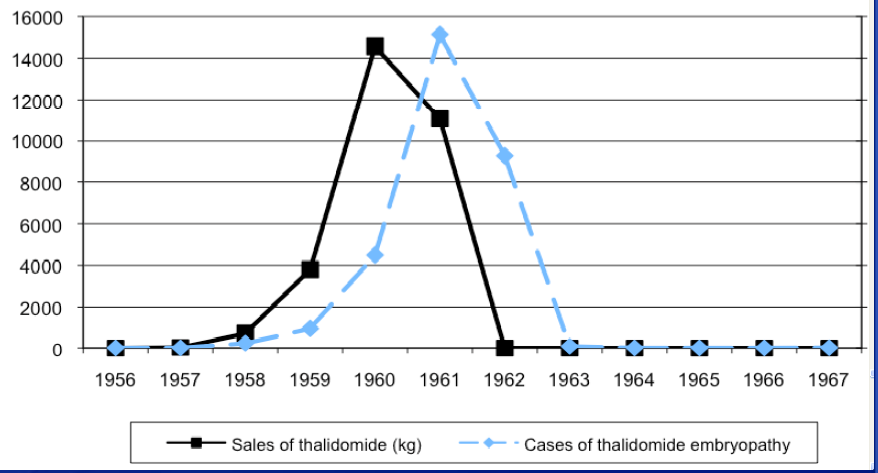
Though these malformations are variable, they are of a rather specific nature. It is usually possible to infer from the type of the abnormalities alone whether contergan has been taken. Typical of a contergan history are defects of the arms (amelia, atypical phocomelia with absence of the thumbs and sometimes of other fingers as well, aplasia of the radius, defects of the long bones of the legs, especially the femora and tibiae, absence of the auricles, haemangiomata of the nose and the upper lip [wine-spot variety], atresia of the oesophagus, the duodenum, or the anus, cardiac anomalies, and aplasia of the gallbladder and of the appendix).

Judging from case histories of more than 300 women who have borne normal infants, and of whom none had taken contergan between the 4th and the 8th week after conception, the risk to a foetus of a mother taking contergan during this period may be definitely higher than 20%. I venture the estimate that at least 2000, possibly more than 3000, " contergan " babies have been born in Western Germany since 1959.

Universitäts-Kinderklinik, Hamburg-Eppendorf, Germany. W. LENZ.

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



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

878 THE NEW ENGLAND JOURNAL OF MEDICINE Apr. 22, 1971

ADENOCARCINOMA OF THE VAGINA*

Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women

ARTHUR L. HERBST, M.D., HOWARD ULFELDER, M.D., AND DAVID C. POSKANZER, M.D.

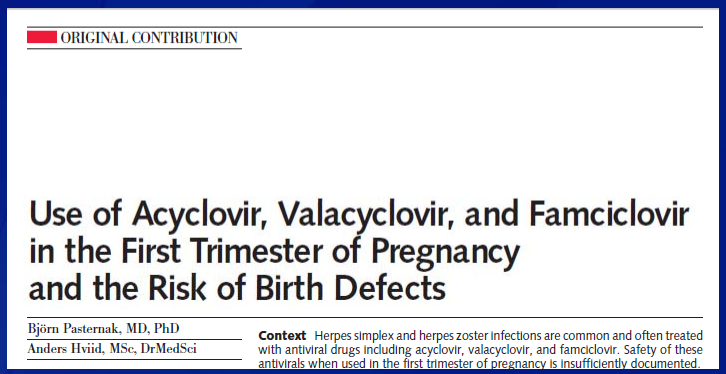
Abstract Adenocarcinoma of the vagina in young women had been recorded rarely before the report of several cases treated at the Vincent Memorial Hospital between 1966 and 1969. The unusual occurrence of this tumor in eight patients born in New England hospitals between 1946 and 1951 led us to conduct 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.

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?



ORIGINAL CONTRIBUTION

Use of Acyclovir, Valacyclovir, and Famciclovir in the First Trimester of Pregnancy and the Risk of Birth Defects

Björn Pasternak, MD, PhD
Anders Hviid, MSc, DrMedSci

Context Herpes simplex and herpes zoster infections are common and often treated with antiviral drugs including acyclovir, valacyclovir, and famciclovir. Safety of these antivirals when used in the first trimester of pregnancy is insufficiently documented.

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

Association between Prenatal Oral Acyclovir, Valacyclovir and Famciclovir Use and Birth Defects, Denmark

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

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

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

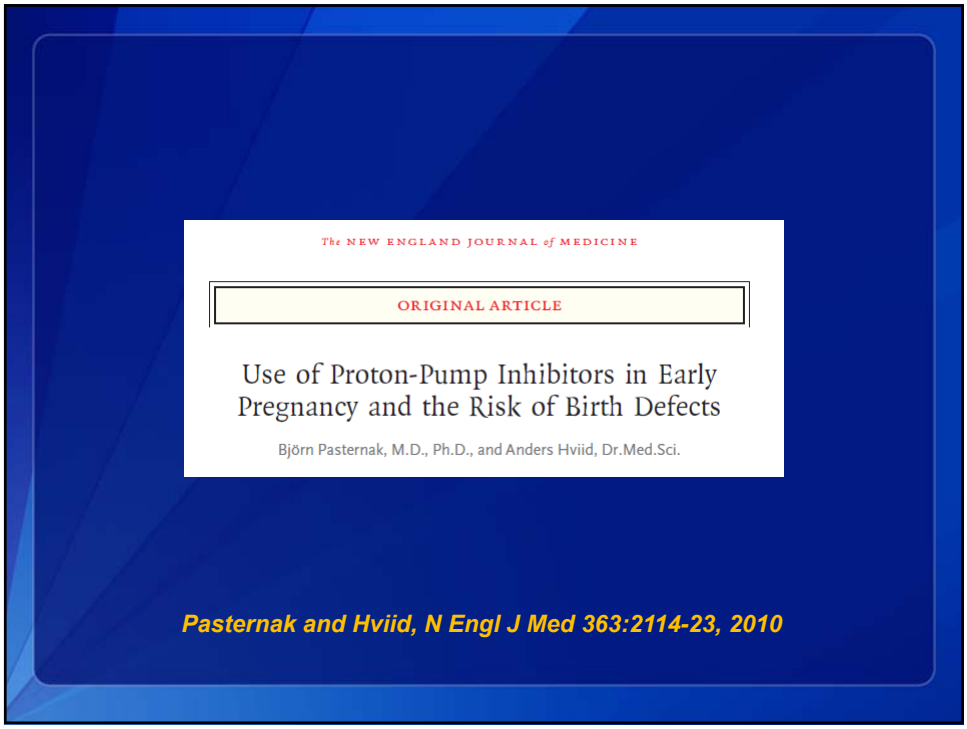
Acyclovir Exposure and Birth Defects
An Important Advance, But More Are Needed

James L. Mills, MD, MS
Tonia C. Carter, PhD

1.17) and in 3.1% of infants exposed to valacyclovir (adjusted POR, 1.21; 95% CI, 0.56-2.62). Few infants were exposed to famciclovir.

"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

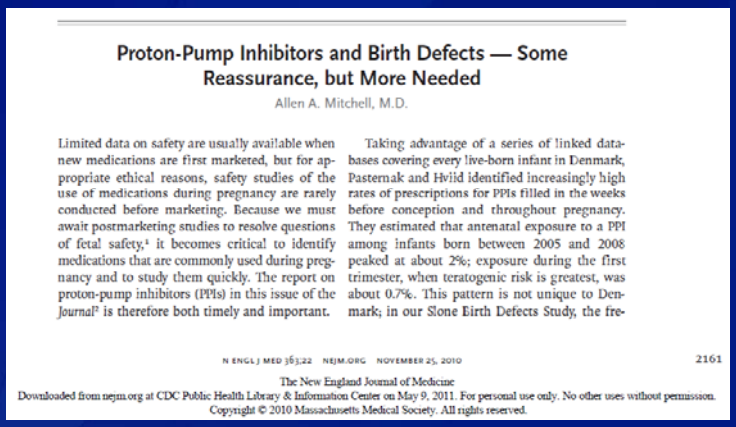


Pasternak and Hviid, N Engl J Med 363:2114-23, 2010

Association between Use of Proton-Pump Inhibitors during 1st Trimester of Pregnancy and Birth Defects, Denmark

Medication	# Live Births	Birth Defects N (%)	Adjusted Prevalence Odds Ratio (95% CI)
Exposed to any PPI	3651	118 (3.2)	1.10 (0.91-1.34)
Omeprazole	1800	52 (2.9)	1.05 (0.79-1.40)
Pantoprazole	549	21 (3.8)	1.33 (0.85-2.08)
Lansoprazole	794	28 (3.5)	1.13 (0.77-1.67)
Rabeprazole	42	3 (7.1)	2.14 (0.60-7.68)
Esomeprazole	668	23 (3.4)	1.19 (0.77-1.84)

Pasternak and Hviid, N Engl J Med 363:2114-23, 2010



Proton-Pump Inhibitors and Birth Defects — Some Reassurance, but More Needed

Allen A. Mitchell, M.D.

Limited data on safety are usually available when new medications are first marketed, but for appropriate ethical reasons, safety studies of the use of medications during pregnancy are rarely conducted before marketing. Because we must await postmarketing studies to resolve questions of fetal safety,[1] it becomes critical to identify medications that are commonly used during pregnancy and to study them quickly. The report on proton-pump inhibitors (PPIs) in this issue of the *Journal*[2] is therefore both timely and important.

Taking advantage of a series of linked databases covering every live-born infant in Denmark, Pasternak and Hviid identified increasingly high rates of prescriptions for PPIs filled in the weeks before conception and throughout pregnancy. They estimated that antenatal exposure to a PPI among infants born between 2005 and 2008 peaked at about 2%; exposure during the first trimester, when teratogenic risk is greatest, was about 0.7%. This pattern is not unique to Denmark; in our Slone Birth Defects Study, the fre-

"The report on proton-pump inhibitors. . .is therefore both timely and important. . .however, these data provide only a broad – and incomplete – overview."

Mitchell, N Engl J Med 363:2161-3, 2010

ORIGINAL CONTRIBUTION

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

Ditte Mølgaard-Nielsen, MSc
Anders Hviid, MSc, DrMedSci

Context Epilepsy during pregnancy is a therapeutic challenge. Since the 1990s, the number of licensed antiepileptic drugs has substantially increased, but safety data on first-trimester use of newer-generation antiepileptic drugs and birth defects are limited.

THE PREVALENCE OF ANTIEPILEP-

Molgaard-Nielsen and Hviid, JAMA 305:1996-2002, 2011

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

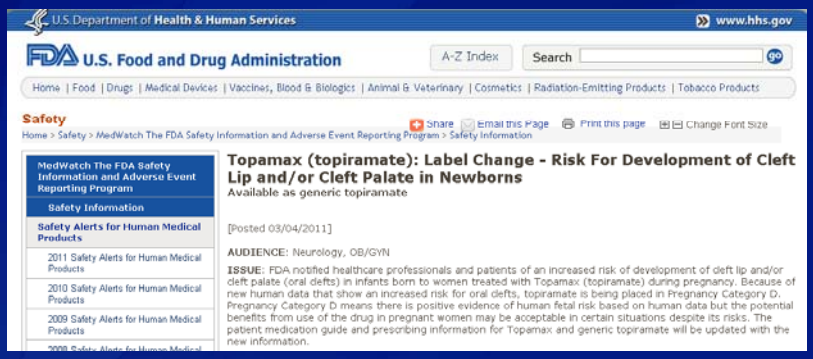
Molgaard-Nielsen and Hviid, JAMA 305:1996-2002, 2011

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



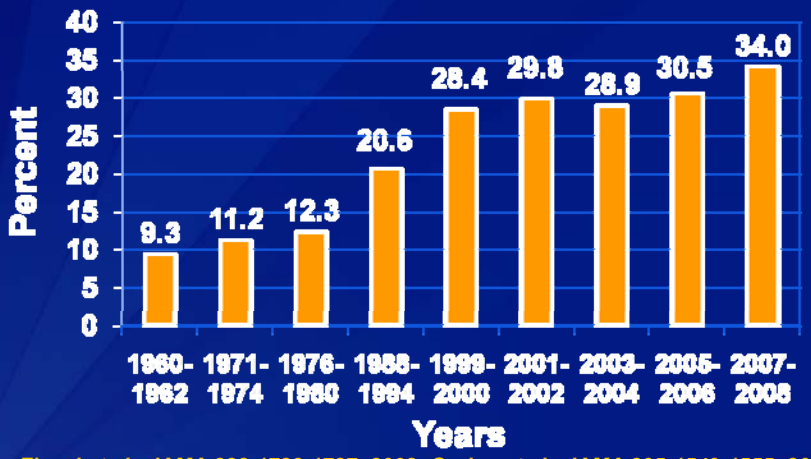
- FDA changed drug's pregnancy category to D
- "Health care professionals should carefully consider the benefits and risks of topiramate when prescribing it to women of child-bearing age" – Russell Katz, director of FDA's division of neurology products

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

Trends in Obesity among Women Ages 20-39, United States, 1960-2008



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

Teratology Society Public Affairs Committee, Birth Defects Research Part A, 76:73-77, 2006

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

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm227050.pdf

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)

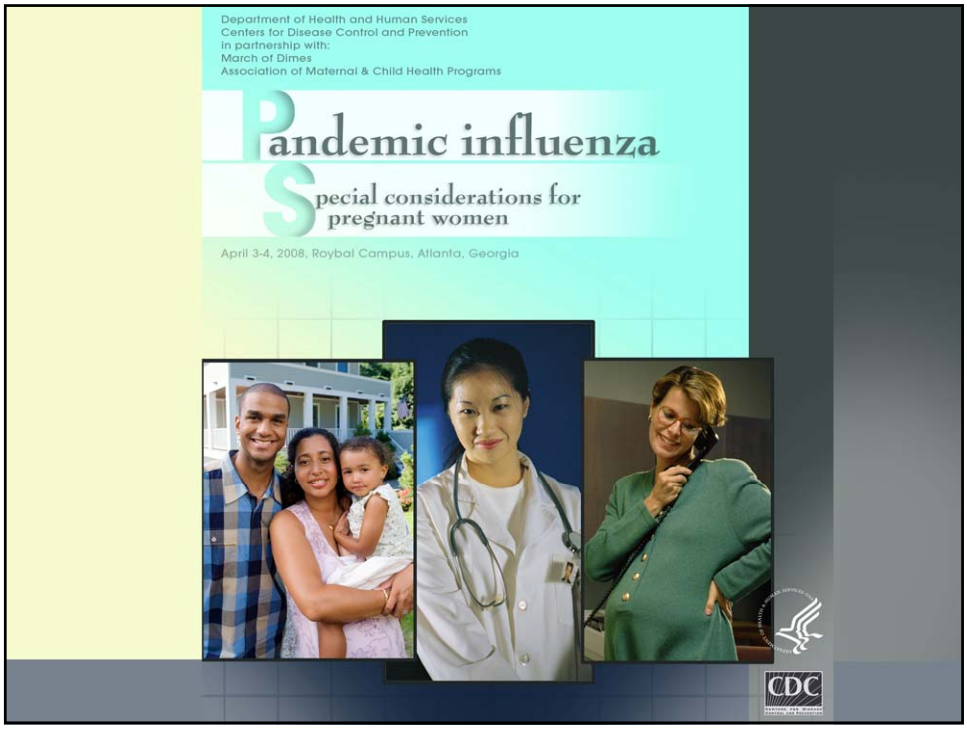
Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008

Maternal Hyperthermia and Neural Tube Defects: Meta-Analysis

Type of Studies	# of Studies	Summary Odds Ratio/Relative Risk (95% CI)
Case-Control	9	1.93 (1.53-2.42)
Prospective Cohort	6	1.95 (1.30-2.92)

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/
Ward et al., J Antimicrob Chemother 55(Suppl1):15-21, 2005

Zanamivir (Relenza®)

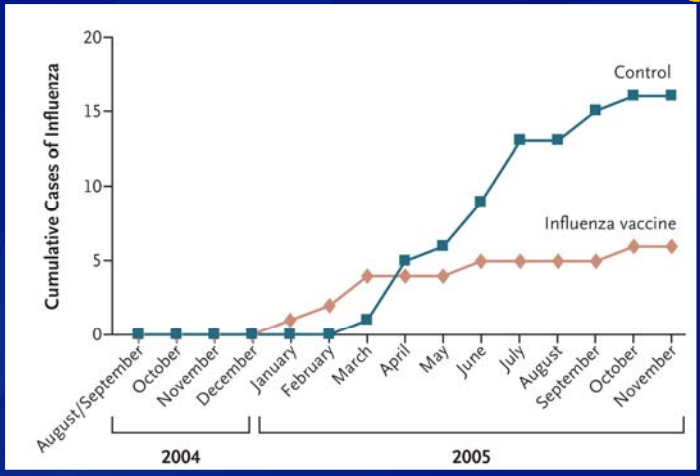
- Effects on fetus
  - Animal data (rat, rabbit) – no evidence of embryotoxicity or increased risk of malformations
  - Human data – 3 zanamivir-exposed pregnancies during clinical trials
    - ✓ 1 spontaneous abortion
    - ✓ 1 elective termination
    - ✓ 1 normal outcome

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



Zaman et al., N Engl J Med 359:1555-64, 2008

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

Pandemic Influenza: Special Considerations for Pregnant Women was a meeting convened by the Centers for

Sonja A. Rasmussen, MD, MS, Denise J. Jamieson, MD, MPH, Kitty MacFarlane, CNM, MPH, Janet D. Cragan, MD, MPH, Jennifer Williams, MSN, MPH, and Zsakeba Henderson, MD; for the Pandemic Influenza and Pregnancy Working Group

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MMWR

Dispatch

April 21, 2009 / 58 (Dispatch);1-3

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

www.cdc.gov/H1N1flu/pregnancy
www.cdc.gov/H1N1flu/clinician_pregnant.htm

2009-2010 Treatment Recommendations

- 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

2009-2010 Treatment Recommendations (continued)

- 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

Timing of treatment after symptom onset	Relative Risk (95% CI)	
	ICU Admissions	Deaths
>4 days vs. ≤2 days	6.0 (3.5-10.6)	53.5 (7.3-391.7)
3-4 days vs. ≤2 days	2.4 (1.2-4.8)	9.9 (1.1-87.2)

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

Moro et al., Am J Obstet Gynecol 2011;204:146.e1-7.

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

Schatz et al., Am J Obstet Gynecol 204(6 Suppl 1):S64-8, 2011

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"

Schatz et al., Am J Obstet Gynecol 204(6 Suppl 1):S64-8, 2011

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

Rebordosa et al., Am J Obstet Gynecol 198:178,e1-7, 2008
Feldkamp et al., Obstet Gynecol 115:109-15, 2010

Acetaminophen (APAP) during Pregnancy and Childhood Asthma

Source	Results
Avon Longitudinal Study of Parent and Children (Shaheen et al., 2002)	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)
Singapore Children's Asthma and Allergy Network (Koniman et al., 2007)	More children with asthma than controls had mothers who took APAP during pregnancy (35% vs. 0%, p=0.03)
Danish National Birth Cohort (Rebordosa et al., 2008)	Prenatal APAP use associated with increased risk of MD-diagnosed asthma/bronchitis at 18 months (RR 1.18, 95% CI 1.13-1.23)
Peer Education in Pregnancy Study (Persky et al., 2008)	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)

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

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

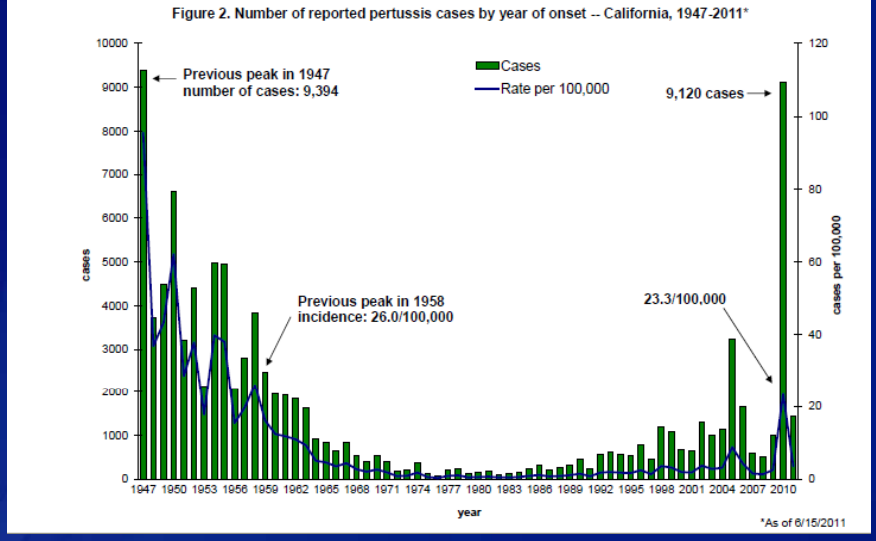
Source	Results
Murcia (Spain) study (Garcia-Marcos et al., 2009)	Among non-asthmatic mothers, prenatal APAP use (at least once monthly) associated with wheezing at preschool age (OR 1.94; 95% CI 1.34-2.79)
The Yale Study (Kang et al., 2009)	Prenatal APAP use did not increase the risk of asthma (aOR 0.76, 95% CI 0.53-1.10)
Columbia Center for Children's Environmental Health Study (Perzanowski et al., 2010)	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
Oslo Environment and Asthma Study (Bakkeheim et al., 2010)	No association between prenatal APA use and diagnosis of childhood asthma at age 10

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

www.cdph.ca.gov/programs/immunize/Documents/PertussisReport2011-06-15.pdf



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

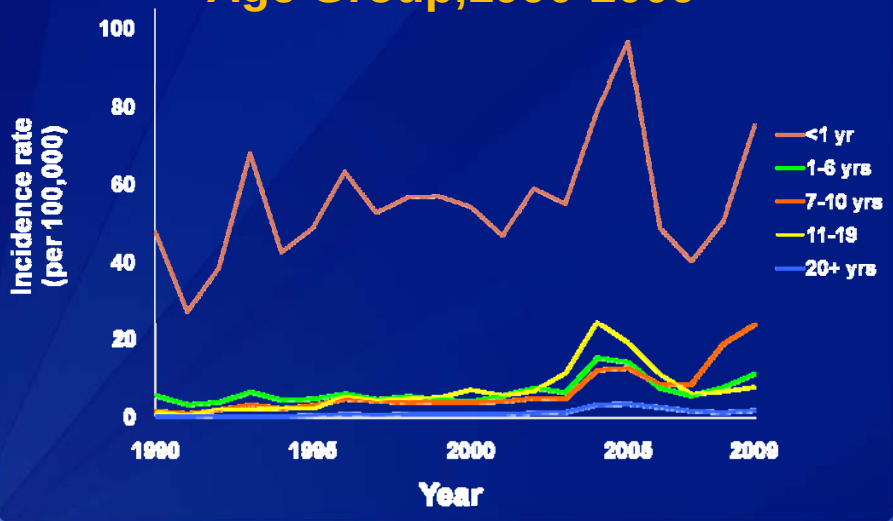
Pertussis Vaccination

- 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

Age-group	1980-1989[1]	1990-1999[1]	2000-2009[2]
0-1 month	38	68	152
2-3 months	11	16	23
4-5 months	5	5	2
6-11 months	7	4	1
1-4 years	13	2	2
5-10 years	1	6	3
11-18 years	0	0	3
>18 years	1	2	8
Total	77*	103	194

* Includes one case with unknown age

[1] Vitek CR, *et al.* Pediatr Infect Dis J 2003; 22(7): 628-34.

[2] National Notifiable Diseases Surveillance System, CDC, 2009.

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

	Vaccine	Should be considered if otherwise indicated	Contraindicated during pregnancy	Special/Conditional Recommendation (see text)
Routine	Hepatitis A			See Hepatitis A text
	Hepatitis B	X		
	Human Papillomavirus (HPV)			See HPV text
	Influenza (Inact.)	Recommended		
	Influenza (LAIV) *		X	
	Measles*		X	
	Meningococcal (MCV4)			See Meningococcal text
	Mumps*		X	
	Pneumococcal			See Pneumococcal text
	Polio (IPV)			See Polio text
	Rubella*		X	
	Tetanus - Diphtheria	X		
	Tetanus - Diphtheria - Pertussis (Tdap)			See Tdap text
	Varicella*		X	

http://www.cdc.gov/vaccines/pubs/preg-guide.htm

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

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 2nd/3rd 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 2nd and 3rd 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?

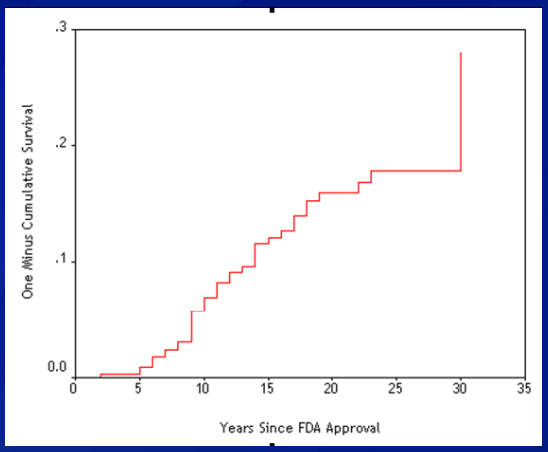
Draft Recommendation from June 22, 2011 ACIP Meeting

- 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)

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Review

Risks and benefits of immunizing pregnant women: The risk of doing nothing☆

Robert L. Brent*
Laboratory of Clinical and Environmental Teratology, Room 308, R/A, Alfred I. duPont Hospital for Children, Thomas Jefferson University, Box 269, Wilmington, DE 19899, USA

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ETHICS

See COMMENTARY page 22

Drug Safety in Pregnant Women and Their Babies: Ignorance Not Bliss

CD Chambers[1,2], JE Polifka[3] and JM Friedman[4]

"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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