Teratogen Update

Teratology Society

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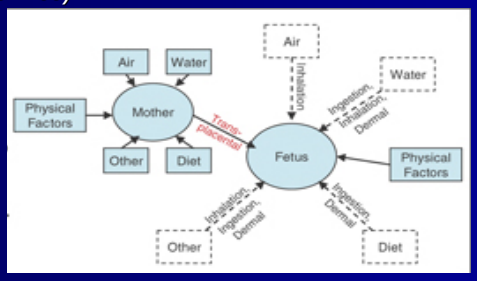
Overview

- Review and Update
- What is new [and what to watch]
- Delivery of the message

Disclaimer: The views expressed in this presentation are those of the speaker and do not reflect any official statements of the FDA

A Teratogen

- Definition
  - Any agent (a drug) or factor that induces or increases incidence of abnormal prenatal development (Stedman's Medical Dictionary)
  - An exposure in pregnancy that has a harmful fetal effect (L. Holmes)



Hubal E, Moya J and Selevan S. A lifestage approach to assessing children's exposure. Birth Defects Research Part B. 2008 Vol 83, Issue 6, Page 524

CHARACTERISTICS OF A HUMAN TERATOGEN*

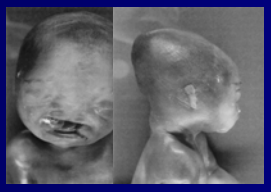
- An increase in the frequency of an abnormal fetal effect – consistent epidemiological studies
- A dose-response relationship
  - a threshold below which the exposure is not teratogenic;
- Period of greatest sensitivity
- Genetically susceptible population.
- Established mechanism of action – animal models
- Biologic plausibility – the proposed teratogenicity must make sense

* L. Holmes – Annual Update 2008

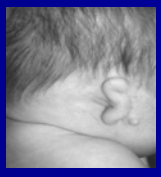
Update: Mycophenolate Mofetil (MMF) A new Human Teratogen?

- Immunosuppressant drug for use in transplant patients
- Wide use in combination with cyclosporine and corticosteroids
- Off label use in autoimmune disorders
- Teratogenic in both rats and rabbits
- Category C → Category D based on growing number of clinical case reports

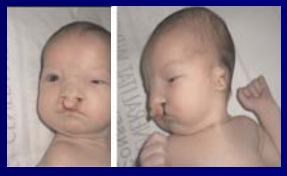
MMF-Exposed Case Reports



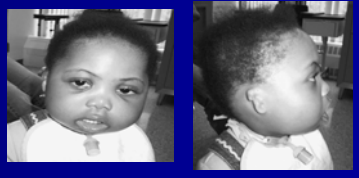
Le Ray et al., 2004



Tjeertes et al., 2007



Perez-Aytes et al. 2008



Velinov and Zellers, 2008.

Anderka et al., Am J Med Genet Part A 149A:1241-48, 2009

SSRIs

- Retrospective cohort study* suggesting prolongation of QT interval in newborns exposed in 3d trimester
- Clinically present
  - long term consequence?
- Need for prospective study to confirm findings

* Dubnov-Raz et al., Pediatrics 122;e710-15 2008

Metoclopramide Use in Pregnancy

- Wide use with little or no data on its safety during pregnancy
- Retrospective cohort study* to examine the safety of use in first trimester using a health services database and a large medical center database
- Typical dose 30 mg/day, prescribed for 7 days
- Dispensed tablets not actual consumption
- No association with increased risks for adverse pregnancy outcome

*Matok et al., NEJM 360;24:2528-35, 2009

Metoclopromide

- Labeled indication in US
  - Symptomatic gastroesophageal reflux and diabetic gastric stasis
- February 2009, FDA added boxed warning for all metoclopramide-containing products
  - High dose or Chronic use (> 3 mo.) linked to risk for Tardive dyskinesia

Public Health and Maternal Disease

- The Environment
  - Baby bottles [Bisphenol A]
  - Formulations [Diethylene glycol -still!]
  - Peanut butter [salmonella and food safety]
- Obesity
- Folate levels and NTDs
- Malaria
- Infection and Influenza
  - H1N1
  - CMV
- Valproate and developmental delay
- Autism

Bisphenol A

- Found in a huge variety of plastics
  - Transfer from polycarbonate plastics in food and drink containers are chief source for human exposure
- Conflicting studies created high public concern for its possible toxicity
  - Estrogenic potency
  - True exposure rates
- FDA task force review
- NTP-CERHR expert panel report on the reproductive and developmental toxicity of Bisphenol A [BDR B 83;3, 2008]

Bisphenol A

- FDA review – “an adequate margin of safety exists for BPA at current levels of exposure from food contact uses for infants and adults.”
- More research needed to address concerns raised by expert panel review (pregnant women, infants and children)
  - Possible neural and behavioral effects
  - Estrogenic activity potential to accelerate puberty
  - Improved human exposure assessment

And the Challenges remain Diethylene glycol

- Deaths reported. “Many of them were children being treated for sore throats…All exhibited similar symptoms, characteristic of kidney failure: stoppage of urine, severe abdominal pain, nausea, vomiting, stupor and convulsions”

USA 1937

- “The kidneys fail first. Then the nervous system begins to misfire. Paralysis spreads. Making breathing difficult, then often impossible without assistance. In the end, most victims die.”

Panama 2007

Nigeria, 2009 - “My Pikin Baby Teething Mixture”

Malaria

- WHO: “Pregnant women are particularly vulnerable to malaria as pregnancy reduces a woman's immunity to malaria. In most malaria-endemic areas of Africa, pregnant women are the main adult risk group for malaria. “
- Spontaneous abortion, stillbirth, premature delivery and low birth weight (in Africa 200,000 newborn deaths each year
- Recommended treatment – artemisinin-combination therapies ACT
- Pregnant women receive Sulfadoxine-pyrimethamine

Artemisinins
Can they be used in pregnancy?

- Clinical studies in pregnant women in 2nd and 3d trimester report no adverse outcomes. Few have been treated in first trimester
- Series of articles in BDR B 83;4 2008 and BDR B 86;2 2009
- Further defined the window of susceptibility
  - embryolethality and fetal cardiovascular and skeletal toxicity in rat and monkey
  - first trimester effects

H1N1 Influenza

- Pandemic declaration by WHO - June
  - 35,928 cases; 163 deaths in 76 countries (June 15, 2009)
- Past pandemics and seasonal flu experience
  - Increased morbidity and mortality for pregnant women
  - Increased risk for complications
- Degree of placental transfer? - unknown but rare in seasonal flu
- Hyperthermia risk - neural tube defects
  - Maternal treatment of fever
- Will tax the safety data for anti-viral therapies

H1N1 Influenza

- CDC recommendations
  - Vaccination
  - Start treatment as early as possible (5 days)
    - Neuraminidase inhibitors -oseltamiver or zanamivir
    - Virus is resistant to amantadine and rimantadine
    - Treat fever - acetaminophen
- Getting ready for the upcoming flu season
  - Overcome reluctance to take medications [successful message delivery]
  - Low vaccination rates for pregnant women
    - Will have no data for H1n1 vaccine
- Safety data from labels - www.cdc.gov/h1n1
- *Pregnancy Registry Workshop Part 2 - Wed.*

Cytomegalovirus

- Cytomegalovirus [CMV]
  - 50-80% of US population are CMV-positive by age 40
  - Usually asymptomatic but is a particular risk during pregnancy
- Congenital CMV infection
  - 1/150 births and 1/750 babies will have or will develop permanent disabilities
    - Hearing loss, vision loss, cognitive impairment

Towards a CMV vaccine

- A phase II double -blind, placebo controlled trial *
  - 3 doses of vaccine or placebo given to seronegative women w/in 1 yr after giving birth
  - Recombinant CMV envelope glycoprotein B with M59 adjuvant
  - Vaccine efficacy was 50% based on 100 person-year infection rates
  - More work to be done but for now a public health communication effort to increase awareness of the disease and prevention [a bar of soap]+

*Pass et al., NEJM 360:1191-9, 2009, + R. Miler, OTIS, 2009

Valproates - Association with developmental delay

- A well studied teratogen -neural tube defects
- Prospective observational study in anti-epileptic drugs - Cognitive Function at 3 yrs of age after prenatal exposure*
  - Dose dependent reduction in IQ unrelated to maternal IQ
- BPCA safety review - Divalproex Sodium (June FDA Pediatric AC)
  - 2 cases of developmental delay
  - 2 with autism [siblings]
  - 1 learning disability
  - 1 mental retardation [concomitant exposure to carbamazapine]
- A raised concern – need for further review

*Meador et al NEJM 360:1597-1605 2009

Benefit-Risk Delivering the message

- Pregnancy and Lactation Labeling Rule
  - A process with a very long gestation
  - The final piece of the significant overhaul of the entire label [Physician Labeling Rule - PLR]
  - The Proposed Rule was published for comment in May 2008 - 90 day period
  - All comments are now being addressed
  - Once done the final draft will begin the clearance process.

Benefit-Risk:Delivering the message Overview of the Proposed Rule

- **Will remove the letter pregnancy categories from all drugs**
- For drugs falling under the PLR, the section will follow the new format outlined in the Rule
- Pregnancy and lactation labeling will be required even if there is no systemic absorption of the drug
- Old sections called “pregnancy” and “labor and delivery” are merged.
- “nursing mothers” is replaced by the lactation section.

Benefit-Risk:Delivering the message Section 8.1 Pregnancy, required elements

- Pregnancy Registry contact information [if available]
- Standard statement of background population risk of fetal abnormalities
- Fetal risk summary
  - Describe the likelihood that the drug increases the risk for developmental abnormalities
- Clinical considerations
  - Known or predicted risk from inadvertent exposure
  - Known risk to the pregnant woman or fetus from the disease or condition
  - Information on dosing or maternal AEs due to pregnancy
  - Potential neonatal complications
- Data - to support the fetal risk section

Pregnancy Registries

- A need - now more than ever
  - Safety assessment once a drug has been approved
  - But do all drugs need this type of post marketing surveillance?
- How should they be done?
  - Disease versus product
- What are the desired endpoints?
  - What is the balance between wanting all possible information and a feasible study?
- How are the results communicated and used?
- ***Pregnancy Registry Workshop***
  - ***This afternoon and Wednesday am***

Benefit-Risk
Delivering the message

- Post market drug safety information
  - Ongoing information to patients and HCPs about any new safety information
  - FDA Drug Safety Information
    - Safety alerts; early communications, public advisories
  - REMS – Risk Evaluation and Mitigation Strategy
    - more than just a package insert or a Medication Guide
    - Plan must outline not only the issue but also the strategies for communication to HCPs
    - Outline of plans to implement and assess effectiveness of the program.

When these tools may not be enough
Testosterone Gels

- Indication: Replacement therapy in men with conditions associated with endogenous testosterone deficiency [Androgel 1%, Testim 1%]
- Pregnancy category X with warnings to avoid secondary transfer
- Not approved for use under age 18
  - Cautions against improper use leading to acceleration of bone age and premature closure of epiphyses
- BPCA safety review* - serious Adverse events due to secondary exposure in children under 5 yrs of age
  - Elevated testosterone levels, enlargement of genitalia, premature development of pubic hair, advanced bone age, hypersexualized behavior.

* FDA Pediatric Advisory Committee meeting June 23 2009

When these tools may not be enough Testosterone Gels

- How should this risk be communicated?
  - Set options for the regulated products
    - May 2009 FDA safety announcement
    - Addition of a boxed warning to label
    - Medication guide as part of a REMS
- What about exposure from non regulated compounded formulations used for off label purposes?
  - How does this message get to the broader public?

Looking Ahead

- Down Syndrome testing - noninvasive genetic testing from maternal blood samples
- Disease management in pregnancy
- Infections and teratogenicity - Ljungan Virus
- Is an economic downturn teratogenic?
  - Stress
  - Postponement of pre-conception and prenatal care?
- Animal models – when rats and rabbits won't do
  - NHP (D.Rice, State of the Art lecture & MTA/MARTA Symposium; Wed. am)
  - Guinea pig (BDR B 86;no2, 2009)
  - Zebra fish
  - Sea Urchin (M.Collins - Wiley Blackwell Symposium; Thursday)

Thanks to friends and colleagues

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Lew Holmes

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