

## How to Design a Pregnancy Registry for a Suspected Human Teratogen

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Sonja A Rasmussen, MD, MS  
National Center on Birth Defects  
and Developmental Disabilities, CDC



*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.*



## Sources of Information on Potential Teratogens

- Case reports/case series
- Birth defects surveillance systems
- Cohort studies
- Case-control studies
- Pregnancy registries

*Rasmussen et al., Am J Med Genet A 143A:2896-2903, 2007*

## Pregnancy Registries

- Pros
  - Provides ongoing collection of data on outcomes of exposed pregnancies
  - Ascertains exposure before outcome is known (prospective)
  - Provides resource for identifying exposed women for further study
  - Could provide indication of worsening or improving public health problem

*Rasmussen et al., Am J Med Genet A 143A:2896-2903, 2007*

## Pregnancy Registries

- Cons
  - Difficult to determine causal relationships between exposure and adverse outcomes without a comparison population
  - Complete ascertainment of exposed mothers and adverse outcomes is difficult
  - Follow-up for outcomes not identified at birth is often limited
  - Sample size usually too small to allow for identification of moderate increases in risk in rare outcomes (e.g., birth defects)

*Rasmussen et al., Am J Med Genet A 143A:2896-2903, 2007*

## Before Deciding on Design of Pregnancy Registry

- Need to define registry goals and determine if pregnancy registry is the best way to reach these goals

## Major Study Design Issues

- Should registry focus on maternal condition or medication?
- Should data collection be prospective or retrospective?
- What is an appropriate comparison group?
- What outcomes are to be assessed?  
What is duration of follow-up?
- Will sufficient numbers of exposed women be able to be collected to reach registry goals?

## Two Examples

- Mycophenolate mofetil (MMF)
- Pandemic H1N1 2009 influenza virus, anti-influenza medications (oseltamivir and zanamivir), and flu vaccine



## Mycophenolate Mofetil

- Used for:
  - Prophylaxis of organ rejection in patients who have received solid-organ transplants
  - Immunosuppressant for treatment of several autoimmune diseases (e.g., systemic lupus erythematosus, psoriasis, dermatomyositis)
- Reports to National Transplantation Pregnancy Registry and individual case reports demonstrate a phenotype (e.g., microtia/anotia and orofacial clefts) associated with MMF exposure, suggesting that it may be a teratogen

## Pandemic H1N1 2009 Virus

- Illness resulted from quadruple reassortant virus of human, avian and swine influenza virus genes
- Viruses susceptible to oseltamivir and zanamivir, resistant to amantadine and rimantadine
- Median age – 20 years, range 3 months to 81 years; 60% were 18 years or younger (based on 642 confirmed cases reported 4/15-5/5/2009)



Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, N Engl J Med 361, 2009  
CDC, MMWR Morb Mortal Wkly Rep 58:536-41, 2009 and 58:497-500, 2009

## Pandemic H1N1 2009 Virus (continued)

- In the US, most confirmed cases characterized by self-limited, uncomplicated febrile respiratory illness: similar to seasonal influenza (cough, sore throat, rhinorrhea, headache, and myalgia) – 38% with vomiting or diarrhea (based on 642 confirmed cases reported 4/15-5/5/2009)
- Consistent with seasonal influenza and previous pandemics, data thus far suggest that pregnant women are more severely affected
- H1N1 vaccine not yet available, but expected to be available by fall; uptake of seasonal flu vaccine among pregnant women has been poor
- Effects on fetus of H1N1 virus, anti-influenza meds, and H1N1 vaccine are unknown

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, N Engl J Med 361, 2009  
CDC, MMWR Morb Mortal Wkly Rep 58:536-41, 2009 and 58:497-500, 2009

## Use of Anti-Influenza Medications during Pregnancy

- Treatment (“should be initiated ASAP”)
  - Confirmed, probable, or suspected cases
  - Start ASAP, ideally within 48 hours of onset of symptoms, 5-day course used for treatment
  - First choice - oseltamivir (Tamiflu™) (oral) (preferred due to systemic absorption); second choice - zanamivir (Relenza™) (inhaled)
- Chemoprophylaxis (“should be considered”)
  - Close contact with confirmed, probable, or suspected case
  - Begin within 7 days of exposure, 10 day course after last known exposure
  - Zanamivir may be preferable due to limited systemic absorption, however, respiratory complications need to be considered

## Should registry focus on maternal condition or medication?

- Maternal illness
  - If illness might affect pregnancy outcomes, registry focusing on maternal illness might provide better comparison – between women with same illness treated with different medications or untreated
  - Data collected likely to be similar for different medications to treat same disease, potentially less expensive

## Should registry focus on maternal condition or medication? (continued)

- **Specific medication**
  - Examples (for Multiple Sclerosis): Betaseron Pregnancy Registry, Avonex Pregnancy Registry, Rebif Pregnancy Registry, Tysabri Pregnancy Registry
  - When medication is used for treatment of multiple conditions, focus on medication might be better
  - For some agents (e.g., vaccines or medications used for prophylaxis), no maternal condition is present

## Should registry focus on maternal condition or medication?: MMF

- Women treated with this medication often have serious illness – comparison to other women with the same illness makes sense (difficult to separate fetal effects of condition from those of medications)
- Women treated with MMF are often treated with multiple medications – including them in the same registry is appropriate
- Infrastructure is in place to collect information on transplant recipients who become pregnant
- MMF is used to treat a number of illnesses -- if focus is on maternal condition, data will not be collected on non-transplant patients

## Should registry focus on maternal condition or medication?: Flu

- Women with flu often develop fever, which could have adverse effects – thus, collecting data on women with flu and comparing those who take/don't take anti-flu medications is appropriate
- Focusing on “H1N1 flu” may be complicated, given that many women won't have diagnostic testing performed and those who do have testing done may differ in some ways
- Focusing on flu will miss collecting women who have received vaccine or who have received prophylactic anti-flu meds – these exposures would be captured in a registry that focuses on med/vaccine

## Should data collection be prospective or retrospective?

- **Prospective** (enrolled before outcome is known)
  - Important to collect data prospectively to reduce bias
- **Retrospective**
  - Difficult to discard information on exposed patient on whom something about outcome is already known (e.g., prenatal diagnosis of defect)
  - Consider registering retrospective patients separately

## Should data collection be prospective or retrospective?: MMF and flu

- **Prospective data collection ideal** – otherwise unknown whether cases with adverse outcome would have been enrolled had outcome been normal
- However, information on retrospectively collected cases contributes to a better understanding of the phenotype

## What is an appropriate comparison group?

- **Internal controls**
  - Example: women with same illness, but receiving no or different treatment; friends/family of exposed women
- **External controls/Historical cohort**
  - Example: comparing results to data from MACDP

## What is an appropriate comparison group?

- Issues with use of historical cohort/external controls
  - Important to be sure that ascertainment methods are similar (e.g., similar scrutiny of infant, follow-up to similar age, etc.) and that outcome is clearly defined
  - Same information may not be available as is available on exposed women
  - For historical cohort, important to recognize that examining outcomes during different time periods may alter frequency of outcomes (e.g., different diagnostic methodologies, etc.)

## What is an appropriate comparison group?: MMF

- Appropriate comparison group is other women with similar disease not treated with MMF; however, many will be treated with other meds
- Other than transplant recipients, no infrastructure is in place to collect women who use MMF for other reasons; if women using MMF for other reasons are included in National Transplantation Pregnancy Registry, transplant recipients not on MMF are not an appropriate comparison group

## What is an appropriate comparison group?: Flu

- Depends on which exposure – if effects of flu or vaccine are focus, then women without influenza or without vaccine exposure serve as appropriate comparison group
- If focus is anti-flu meds used for treatment, then women who had flu, but didn't receive meds, are appropriate comparison
- If focus is anti-flu meds used for prophylaxis, then women without med exposure would be an appropriate control group

## What outcomes should be assessed?

- Usually birth defects are chosen as an outcome
- Outcomes determine length of follow-up needed
- What about other outcomes? Developmental disabilities, etc.
- Are data available from case reports/case series that suggest phenotype that might be associated with exposure?

## What outcomes should be assessed?: MMF

- Data from NTPR and case reports suggest that focus on birth defects identifiable at birth is reasonable
- However, whether risk for other adverse outcomes is increased will only be identified through further study (such as that gleaned from pregnancy registries)

## What outcomes should be assessed?: Flu

- Maternal influenza has been associated with an increased risk for certain birth defects, but other adverse outcomes have also been proposed
- Very limited information is available on the effects of anti-influenza medications on the fetus; no evidence of adverse outcomes associated with vaccine use

### **Will sufficient numbers of exposed women be able to be collected to reach registry goals?**

- How common is exposure?
- Have concerns about agent's possible teratogenicity decreased its use among pregnant women?

### **Will sufficient numbers of exposed women be able to be collected to reach registry goals?: MMF**

- Medication is widely used for prevention of transplant rejection and other uses have been increasing
- Impact of concerns about teratogenicity on use in pregnant women is unknown

### **Will sufficient numbers of exposed women be able to be collected to reach registry goals?: Flu**

- Sufficient numbers of cases of influenza, including those treated with anti-influenza meds, are expected
- Whether sufficient numbers of women will be available for vaccine will depend on vaccine uptake among pregnant women

### **Conclusions**

- Issues related to study design are critical to quality of data and its interpretation
- There is no "right answer" to these questions – study design depends on goals of registry, type of exposure, funds available, etc.

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