The Impact of Birth Defects and Current Understanding of their Causes

Marcia L. Feldkamp, PhD, PA
Associate Professor
Division of Medical Genetics
Department of Pediatrics
University of Utah
Data were provided by the Utah Birth Defect Network (UBDN), a project of the Utah Department of Health (UDOH). This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services for the amount of $3,046,261.

This content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, the U.S. Government or the Utah Department of Health.
What Are Birth Defects?

- An abnormality affecting body structure or function that is present at birth
  - May be obvious at birth
  - May not be obvious at birth and diagnosed later in life

- Functional defects include developmental disabilities (e.g., cerebral palsy or deafness)

- Structural defects include two types
  - Major malformation
    - Surgical, medical or cosmetic importance
  - Minor malformation
    - Example of minor – single palmar crease
Major Birth Defects Are Common

- 1 in 33 or 3% of children born are identified at birth
  - 120,000 babies each year in the US
- Prevalence increases to 1 in 20 or 5% by 5 years of age

Heart Defects

Normal Heart

Hypoplastic Left Heart Syndrome

Transposition of the Great Arteries

These types of defects will require surgical repair
Neural Tube Defects

Spina bifida

Anencephaly
Abdominal Wall Defects

Gastroschisis

Omphalocele
Birth Defects Are Costly

Average daily hospital charges per newborn

- Uncomplicated birth: $878
- Gastrochisis: $3,795
- Esophageal atresia: $4,337
- Omphalocele: $4,360
- Bladder extrophy: $4,598
- Pulmonary valve atresia: $6,453
- Diaphragmatic hernia: $6,508
- Coarctation of the aorta: $6,562
- Truncus arteriosus: $6,670
- Hypoplastic left heart: $6,954
- Transposition of the great arteries: $7,523

Birth Defects Are Costly

- In 2004, hospitalizations and medical charges cost $2.6 billion per year for all ages.
- Medical care and advances in technology have improved long-term survival among children with birth defects.

Birth Defects Are Critical

- **Infant mortality**
  - 6.7 deaths per 1,000 infants
  - 21% of deaths in the first year of life are due to birth defects
  - Congenital heart defects represent the largest group

**Leading Causes of Infant Mortality, 2011**

- 37% Other
- 21% Birth Defects
- 17% LBW, Prematurity
- 12% Maternal factors
- 8% SIDs
- 5% Accidents
- 5% Other

**LBW**: Low birth weight
2011 US National Vital Statistics Data, National Center for Health Statistics
Most Major Birth Defects Occur Early in Pregnancy
Pregnancy Planning is Primary Prevention of Birth Defects

- The critical time period for all women to reduce their risk is before they become pregnant.
- To reduce the risk of a neural tube defect, a woman must consume folic acid before conception.
- Folic acid fortification of cereals and grains has been very effective because it increases folate levels among women in the US, whether planning a pregnancy or not.
Increasing Prevalence of Gastroschisis Suggests Environmental Influence

Trends in Gastroschisis Prevalence by Maternal Age Group, 1995-2005

Prevalence per 10,000 live births

Year of Birth

Mothers younger than 20 years
Mothers between 20-24 years
Mothers between 25-29 years

Kirby et al. Obstet Gynecol. 2013
The Majority of Birth Defects Do Not Have an Identifiable Cause

Teratogen: an agent or factor that causes a malformation in an embryo

Utah Birth Defect Network, Utah Department of Health
Working to Identify the Unknown Causes

- Major birth defects should be systematically monitored in the population
- Environmental factors that women are exposed to should be investigated
- Major birth defects are common, costly and critical
Advancing Understanding of the Causes of Birth Defects

Jennita Reefhuis, PhD
Epidemiology Team Lead
Birth Defects Branch
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities
How To Study Rare Outcomes Such as Specific Birth Defects

- **Cohort studies**
  - Pro: Prospective exposure information
  - Con: Need a very large study to identify enough cases

- **Data-linkage studies**
  - Pro: Cost-efficient
  - Con: Methods for mother-baby linkage challenging
  - Con: Limited diagnostic and exposure data

- **Pregnancy registries**
  - Pro: Useful to identify major effects
  - Con: Not population based

Case-control studies

- **Pro:** Efficient
- **Pro:** High-quality diagnostic data
- **Pro:** Ability to look at specific birth defects
- **Con:** Needs to be multi-center or many years to have sufficient data
- **Con:** Potential recall bias

Case-control studies are used to identify factors that may contribute to a medical condition by comparing subjects who have that condition (the "cases") with similar patients who do not have the condition (the "controls").
Population-based case control study
Births October 1997-December 2011
Cases from state-based birth defects surveillance systems
Study cohort
- ~ 6 million total live births
- 48,196 affected pregnancies
NBDPS Data Collection Methods

- Over 30 defects studied
- Live-born control infants
- Telephone interview with mothers of cases and controls
  - 32,209 case mothers interviewed (67.4%)
  - 11,805 control mothers interviewed (64.8%)
- Buccal cell (cheek swab) requested from mother, father, and infant
Selected NBDPS Results

- Over 200 peer-reviewed manuscripts
- Diabetes diagnosed before pregnancy
  - Heart defects: odds ratio 4.6 (2.9 - 7.5)
  - Non-heart defects: odds ratio 2.3 (1.4 - 3.8)
- Stress and neural tube defects
  - 4 or more stressful life events in early pregnancy
    - Such as relative’s death, financial or legal problems, violence
    - Odds ratio 1.5 (1.1 - 2.0)
  - Perception of social support
    - Emotional, financial, daily tasks
    - Odds ratio 0.8 (0.5 - 1.1)

Correa et al. AJOG 2008
Carmichael et al. Paediatr Perinat Epidemiol 2014
NBDPS: National Birth Defects Prevention Study
NBDPS Results: Exposure to Opioid Medications

- **Hypoplastic left heart syndrome**
  - 17 exposed cases
  - Odds ratio 2.4 (1.4 - 4.1)

- **Spina bifida**
  - 26 exposed cases
  - Odds ratio 2.0 (1.3 - 3.2)

- **Gastroschisis**
  - 26 exposed cases
  - Odds ratio 1.8 (1.1 - 2.9)

Broussard et al. AJOG 2011
NBDPS: National Birth Defects Prevention Study
Better Data to Help Inform Treatment Choices

- **Maternal disease in pregnancy may need treatment**
  - Disease can harm mother and baby (e.g., fever or diabetes)

- **Comparing risk-benefit of treatment compared with no treatment**

- **Comparing birth defect risk of different treatments—some options may be safer**
  - Choice of SSRIs for depression
  - Antibacterials in early pregnancy

**SSRIs**: selective serotonin reuptake inhibitors

Antibacterial Medication in Early Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Penicillin OR (95% CI)</th>
<th>Nitrofurantoins OR (95% CI)</th>
<th>Sulfonamides OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular outflow</td>
<td>1.0 (0.8 - 1.4)</td>
<td>1.6 (0.8 - 3.2)</td>
<td>2.9 (1.6 - 5.1)</td>
</tr>
<tr>
<td>tract obstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft lip with or without</td>
<td>0.8 (0.6 - 1.1)</td>
<td>1.9 (1.1 - 3.3)</td>
<td>1.0 (0.5 - 1.9)</td>
</tr>
<tr>
<td>cleft palate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>0.9 (0.6 - 1.2)</td>
<td>1.4 (0.7 - 3.0)</td>
<td>1.4 (0.7 - 2.9)</td>
</tr>
</tbody>
</table>

Crider et al. JAMA Pediatrics 2009
Treating for Two Initiative

- **Expand research to fill knowledge gaps**
  - Accelerate epidemiologic research into medication use and pregnancy outcomes

- **Evaluate evidence to develop reliable guidance**
  - Establish ongoing systematic review of evidence and expert body to translate into summary guidance

- **Deliver information to support decision-making**
  - Disseminate up-to-date, clinically relevant information to prescribers, pharmacists, patients, and consumers

www.cdc.gov/pregnancy/meds/treatingfortwo/index.html
Exploring Modifiable Risk Factors – Medications with New and Expanded Uses

- Pregnant women not included in clinical trials
  - Excluded because of safety concerns
  - Often use medications after licensure

- New medications constantly introduced

- Existing medications with new indications
  - Antiepileptic topiramate used as weight-loss product
  - Antiepileptics used to treat migraines

- Want to include questions about why person is taking medicine, and at what dosage
Birth Defects Study To Evaluate Pregnancy Exposures

- 17 defects selected
  - Severity
  - Prevalence
  - Consistent ascertainment

- 7 centers
  - Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina

- Births starting January 1, 2014

- Focus on first trimester exposures

www.cdc.gov/ncbddd/birthdefects/bd-steps.html
Exploring Modifiable Risk Factors
Maternal Disease and Treatment with Medications

- Increased survival among women with
  - Cancer
  - Organ and tissue transplants

- Increased prevalence
  - Asthma
  - Attention-deficit hyperactivity disorder

- Assess diagnostic and treatment details
  - Diabetes
  - Mental health disorders
Going Beyond Case-Control Studies

- To establish causation, confirmation of epidemiologic findings needed
  - Surgeon General’s 2014 report included a finding that smoking is causally related to orofacial clefts (such as cleft lip, cleft palate)
  - Isotretinoin and severe birth defects
  - Thalidomide and limb and other defects

- Statistical modeling studies
  - Assess the prevention impact of substituting “safer” medications

Important to remember that 1 in 33 pregnancies are affected by birth defects
- Relatively common at the population level, but individual defects are rarer

CDC’s Birth Defects Branch and its collaborators continue to contribute to:
- Identifying risk factors for birth defects among medicines, diseases, and environmental factors
- Assessing risk-benefit of medications
- Determining whether there are safer treatment options for certain diseases
Birth Defects Research and Emergency Preparedness: The Vaccines and Medications in Pregnancy Surveillance System

Allen A. Mitchell, MD

Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics,
Boston University Schools of Public Health and Medicine
Trends in Medication Use During Pregnancy

Pregnancy Health Interview Study (Birth Defects Study), Slone Epidemiology Center, Boston University
Medications whose exposure prevalence in pregnancy has increased in recent years include:

- Selective serotonin reuptake inhibitors (SSRIs)
- Attention deficit hyperactivity disorder medications, primarily amphetamine mixed salts (e.g., Adderall®)

What Are the Implications of Greater Medication Use During Pregnancy?

- For the purposes of birth defects prevention, we need to focus on medications and vaccines for which:
  - Trends document increasing use in pregnant women
  - Pregnancy exposure is common but data on pregnancy risk and safety are insufficient
Proportion of Women Receiving Any Influenza Vaccine during Pregnancy

H1N1 influenza pandemic

Unpublished data; Birth Defects Study, Slone Epidemiology Center, Boston University

* Incomplete year
Proportion of Women Receiving Influenza Antiviral Drugs during Pregnancy

Unpublished data; Birth Defects Study, Slone Epidemiology Center, Boston University

* Incomplete year
Proportion of Women Receiving Tdap Vaccine During Pregnancy

Unpublished data; Birth Defects Study, Slone Epidemiology Center, Boston University
Tdap: Tetanus Toxoid, Diphtheria Toxoid, and Acellular Pertussis Vaccine
* Incomplete year
How Do We Learn About Risks and Relative Safety for “New” Exposures in Pregnancy?

- Need to identify risks and relative safety of drugs, vaccines, and biologics (e.g., immune globulins) used by pregnant women
- Particularly important to have a system that is agile in its ability to identify and study new products
Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

- Specifically designed to assess the risks and safety of vaccines and medications used in pregnancy.
- Funding model is public-private partnership.
- Identifies wide range of relatively common adverse pregnancy outcomes, including birth defects overall.
- Has statistical power to evaluate specific birth defects and their possible causal relation to drugs or vaccines.
Objectives of VAMPSS

- Targets new (and old) drugs and vaccines recommended for use or have come into use during pregnancy
  - Current examples
    - Annual influenza, acellular pertussis vaccines
  - Future examples
    - Respiratory syncytial virus vaccines
    - Group B streptococcus vaccines
  - Emergent examples
    - Ebola vaccines, drugs, or biologics that might be licensed or approved for emergency use

- Prospective cohort and case-control study arms can direct focus on new exposures within a few months’ time
Structure of VAMPSS

American Academy of Allergy Asthma and Immunology
Michael Schatz, MD, MS

Prospective Cohort
Organization of Teratology Information Specialists Research Center at the University of California San Diego
Tina Chambers, PhD, MPH
Kenneth Lyons Jones, MD

Case-Control Study
Slone Epidemiology Center at Boston University
Allen A. Mitchell, MD
Carol Louik, ScD

Independent Advisory Committee
Includes:
CDC
NICHD
NIAID
ACOG
AAP
Biostatistician
Consumer Representative

VAMPSS: Vaccines and Medications in Pregnancy Surveillance System
NICHD: National Institute of Child Health and Human Development
NIAID: National Institute of Allergy and Infectious Diseases
ACOG: American Congress of Obstetricians and Gynecologists
AAP: American Academy of Pediatrics
Prospective Cohort – Organization of Teratology Information Specialists

- OTIS is a North American network of university or hospital-based services in existence since 1979
- Specialists provide risk counseling to 80 - 100,000 pregnant women and health care providers per year
- Network can screen callers from a geographically diverse area to identify those who received a vaccine or medication of interest, along with an unexposed comparison group
Participants of Prospective Cohort–OTIS

- **OTIS sites refer potential participants to coordinating center**
  - An exposed cohort, a disease-matched cohort and a healthy unexposed cohort are concurrently recruited
  - Each cohort followed for birth defects overall, preterm birth, growth and spontaneous abortion

- **All groups receive**
  - A series of structured telephone interviews at standard time points during and after pregnancy, and an outcome interview
  - Medical records review
Data Collected from Prospective Cohort – OTIS

- Maternal interviews and medical records review provide detailed information
  - Dose, timing, duration of medication and vaccine exposure
  - Maternal disease or indication for medication
  - Pregnancy history, health history, demographics
  - Wide range of potential confounders including
    - Other prescription or over-the-counter medications
    - Body mass index
    - Tobacco, alcohol and vitamin and mineral use
Case-Control–Birth Defects Study

BDS began in 1976 at Slone Epidemiology Center, Boston University

Objectives

- Identify risks and safety of a wide range of medications and vaccines with respect to the wide range of specific birth defects
- Establish ranges of risk for specific medications
- Identify rates of exposure to specific agents
Case-Control Study Participants–BDS

- **Study participants**
  - Infants with specific major congenital malformations (cases)
  - Infants without congenital malformations (controls)

- **Multi center design**
  - Hospital and clinic surveillance
    - Greater metropolitan Boston, Philadelphia, San Diego, Nashville
  - Birth defects registries
    - Massachusetts, New York
Data Collected from Case-Control Study–BDS

- Data obtained from mothers by computer-assisted telephone interview
  - Interviewed by study nurses within six months of delivery

- Interview data include
  - Demographic and reproductive factors (e.g., age, education, number of previous pregnancies and births)
  - Medical history
  - Indications for use and use of prescription and OTC medications; including vaccines, vitamins and minerals, supplements
  - Wide range of potential confounders (e.g., smoking, alcohol, diet)
VAMPSS and Pandemic H1N1 Influenza

- Anticipating a pandemic caused by H1N1 influenza and the widespread use of the pH1N1 vaccine among pregnant women in 2009 - 2010
- BARDA requested VAMPSS to monitor the risks and relative safety of the pandemic H1N1 vaccine and influenza antiviral drugs

BARDA: Biomedical Advanced Research and Development Authority
VAMPSS: Vaccines and medications in pregnancy surveillance system
pH1N1: pandemic H1N1 influenza virus
VAMPSS was able to quickly modify data collection to meet the objectives of safety monitoring for pH1N1 vaccines and influenza antivirals in pregnant women.
Findings from VAMPSS pH1N1 Studies: No Increased Risk of Birth Defects

Prospective Cohort (OTIS)

Women exposed to a pH1N1 vaccine did NOT have an increased risk of having a baby born with a birth defect

Relative risk = 0.79
95% CI: 0.26 - 2.42

Case-Control Study (BDS-Slone)

For 41 specific defects, most adjusted odds ratios were close to 1.0, and most of those had relatively narrow confidence intervals

VAMPSS: Vaccines and medications in pregnancy surveillance system
pH1N1: pandemic H1N1 influenza virus
Importance of VAMPSS for Public Health Emergency Response

- Pregnant women may be at high risk for complications that endanger their pregnancies.
- Drugs, vaccines, or other medical products might be used in pregnant women with little or no study.
- VAMPSS is proven to work in monitoring safety of emergency countermeasures in pregnant women, on short notice.
- VAMPSS represents a key tool to maintain confidence among providers and the public that preventive measures are being actively monitored for safety.

VAMPSS: Vaccines and medications in pregnancy surveillance system
Identifying What Else We Can Do To Prevent Birth Defects

Suzanne Gilboa, PhD, MHS
Partnerships and Applied Epidemiology Team Lead
Birth Defects Branch
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities
Folic Acid Fortification Prevents Neural Tube Defects

- In 1992, the U.S. Public Health Service recommended all women of childbearing potential consume 400μg folic acid daily.
- In 1998, enriched cereal grain products were required to be fortified at 140μg per 100g serving.
- Ready-to-eat cereals were allowed to be fortified up to 400μg per serving.

CDC. MMWR 1992;41(No RR-14)
μg: Micrograms
g: Grams
Impact of U.S. Folic Acid Fortification on NTD

- Prevented 15,000 cases of NTD since 1999

NTD: Neural tube defects
MMWR January 16, 2015 / 64(01);1-5
What Else Might Have An Impact on Birth Defects?

- Use mathematical modeling of other risk factors to see how we might have a further impact
  - Obesity
  - Pregestational diabetes
  - Smoking
Basic Modeling Approach

- Use data inputs from the published literature to estimate
  - Prevalence of the risk factor
  - Prevalence of the birth defect
  - Magnitude of association between risk factor and birth defects
    - If data not available from published literature, conduct a meta-analysis to obtain a summary measure of association

- Estimate the population attributable fraction for the risk factor

- Estimate the number of preventable birth defects
  - Modeling incorporates uncertainty (e.g., Monte Carlo simulation)
Overall Obesity Trends in the United States

By 2010, every state had 20% or greater prevalence of obesity
Accounting for Uncertainty in the Prevalence of Prepregnancy Obesity

- For pregnant women, prepregnancy prevalence-18.7%
  - PRAMS has self-reported height and weight data

- For U.S. women 20 years or older, obesity prevalence-33%
  - NHANES has measured height and weight data

- For U.S. women 20 years or older, obesity prevalence-20%
  - BRFSS has self-reported height and weight data

- Model used 18.7% estimate, plus bias factor based on NHANES measured data and BRFSS self-reported data
  - Bias factor accounts for differences in these estimates

PRAMS: Pregnancy Risk Assessment Monitoring System
NHANES: National Health and Nutrition Examination Survey
BRFSS: Behavioral Risk Factor Surveillance System
Chu et al. Matern Child Health J 2009
## Input Data to Model the Impact of Prepregnancy Obesity on Birth Defects

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Strength of Association (Odds Ratio)</th>
<th>Estimated Prevalence of Birth Defect in US*</th>
<th>Estimated Annual Number of Children Born with Birth Defect in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart defects</td>
<td>1.30</td>
<td>81.4</td>
<td>33,960</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>2.24</td>
<td>3.5</td>
<td>1,460</td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>1.20</td>
<td>10.63</td>
<td>4,437</td>
</tr>
</tbody>
</table>

* per 10,000 births
### Estimates of the Impact of Reducing Prepregnancy Obesity on Birth Defects

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Population Attributable Fraction* (95% Uncertainty Interval)</th>
<th>Annual Preventable Number (95% Uncertainty Interval)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If 100% Elimination of Prepregnancy Obesity</td>
<td>If 10% Reduction in Prepregnancy Obesity</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>8% (3%–14%)</td>
<td>2,850 (1,035–5,065)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>28% (21%–34%)</td>
<td>405 (305–505)</td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>6% (1%–11%)</td>
<td>260 (35–500)</td>
</tr>
</tbody>
</table>

* Population Attributable Fraction: The percent of cases estimated to be caused by prepregnancy obesity
** Rounded to the nearest 5

Honein, et al. *Obesity* 2013
Prevalence of Prepregnancy Diabetes

- Among women of reproductive age, diabetes prevalence estimates vary between 1.9% and 4.0%
- Additional 0.5% to 1% have undiagnosed diabetes
- Model used NHANES race-ethnicity specific prevalence estimates for women aged 20 - 44

## Input Data to Model the Impact of Diabetes Control on Congenital Heart Defects

<table>
<thead>
<tr>
<th>Congenital Heart Defect</th>
<th>Odds Ratio (Strength of Association)</th>
<th>Estimated Prevalence of Birth Defect in US*</th>
<th>Estimated Annual Number of Children Born with Birth Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>All congenital heart defects</td>
<td>3.8</td>
<td>81.4</td>
<td>32,182</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>3.7</td>
<td>4.5</td>
<td>1,767</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>3.7</td>
<td>2.3</td>
<td>909</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>6.5</td>
<td>4.0</td>
<td>1,570</td>
</tr>
</tbody>
</table>

* per 10,000 live births

## Estimates of the Impact of Diabetes Control on Congenital Heart Defects

<table>
<thead>
<tr>
<th>Congenital Heart Defect</th>
<th>Population Attributable Fraction (95% Uncertainty Interval)</th>
<th>Annual Preventable Number (95% Uncertainty Interval)*</th>
<th>If Elimination of Risk Associated with Diabetes (Complete Glycemic Control)</th>
<th>If 50% Reduction in Risk Associated with Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All congenital heart defects</td>
<td>8.3% (5.6%–11.8%)</td>
<td>2,670 (1,795–3,795)</td>
<td>1,335 (900–1,900)</td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>7.9% (2.1%–17.8%)</td>
<td>140 (35–315)</td>
<td>70 (20–160)</td>
<td></td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>8.0% (1.6%–20.4%)</td>
<td>75 (15–185)</td>
<td>40 (10–95)</td>
<td></td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>14.8% (6.6%–26.3%)</td>
<td>230 (105–415)</td>
<td>115 (55–210)</td>
<td></td>
</tr>
</tbody>
</table>

* Rounded to the nearest 5
## Potential Impact of Preconception Care on Costs Associated with Birth Defects

<table>
<thead>
<tr>
<th>Input Parameter</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of pregestational diabetes</td>
<td>Diagnosed: 2.9% (2.7%-3.2%)</td>
</tr>
<tr>
<td></td>
<td>Undiagnosed: 0.5%</td>
</tr>
<tr>
<td>Percent of births affected by birth defects among women with untreated</td>
<td></td>
</tr>
<tr>
<td>pregestational diabetes</td>
<td>7.3%</td>
</tr>
<tr>
<td>Preconception care effectiveness, risk reduction</td>
<td>0.25 (0.15 - 0.42)</td>
</tr>
<tr>
<td>Lifetime costs of birth defects</td>
<td>$411,723</td>
</tr>
</tbody>
</table>

Potential Impact of Preconception Care on Costs Associated with Birth Defects

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth defects averted</td>
<td>4,731 (4,158–5,215)</td>
</tr>
<tr>
<td>Total lifetime costs for birth defects averted</td>
<td>$1.9 billion ($1.7–$2.1 billion)</td>
</tr>
</tbody>
</table>

Smoking and Orofacial Clefts

- **50th Anniversary Surgeon General’s Report**
  - Released in January 2014
  - Marked first confirmation of causal link between smoking in early pregnancy and orofacial clefts

- **Smoking is one of the few known risk factors for orofacial clefts with potential for prevention**

- **Prevalence of smoking just before pregnancy: 23.2%**

---

PRAMS: Pregnancy Risk Assessment Monitoring System
Tong et al. MMWR Surveil Summ, 2013
Input Data to Model the Impact of Smoking Cessation on Orofacial Clefts

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Odds Ratio (Strength of Association)</th>
<th>Estimated Prevalence of Birth Defect in US*</th>
<th>Estimated Annual Number of Children Born with Birth Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orofacial clefts</td>
<td>1.28</td>
<td>17.0</td>
<td>7088</td>
</tr>
</tbody>
</table>

* per 10,000 live births
Estimates of the Impact of Early Pregnancy Smoking Cessation on Orofacial Clefts

<table>
<thead>
<tr>
<th>Birth Defect</th>
<th>Population Attributable Fraction (95% Uncertainty Interval)</th>
<th>If Elimination of Risk Associated with Early Pregnancy Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orofacial clefts</td>
<td>6.1% (4.4%–7.5%)</td>
<td>430 (310–550)</td>
</tr>
</tbody>
</table>

* Rounded to the nearest 10
Advancing Prevention of Birth Defects

- Birth defects are common, costly, and critical

- Majority of birth defects still do not have an identifiable cause
  - The causes are likely to be multi-factorial with an interaction between genetic factors and modifiable (environmental) risk factors

- Based on the modifiable risk factors that have been recognized, we know that we can improve prevention
Understanding the Causes of Major Birth Defects: Steps to Prevention