Sorting Through the Data: Where do Patients and Providers Go for Information?

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Jennifer: Pregnant with a History of Depression and Anxiety

- 35 y.o. married woman
- Unplanned pregnancy, no previous pregnancies
- Now 9 weeks since LMP
- GAD, remote history of MDD
- Stable for past 3 years, residual anxiety related to health issues.
  - Fluoxetine 30 mg
  - Clonazepam 0.5 mg bid/qhs
- History of severe Crohn's Disease. Multiple medication trials, now stabilized on certolizumab (Cimzia) for past year

Medication Usage During Pregnancy

- About 90% of women take a prescription or OTC medication during pregnancy
- Half of pregnancies are unplanned
- For 98% of those medications, there is inadequate data on reproductive safety

Mitchell AA, et al. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

The OB: Hmmm, I know you can't take clonazepam. That one is a category D medication.

The GI: There isn't a lot of safety data on Cimzia, but I've had a couple of patients take it during pregnancy, and their kids turned out fine.

The PCP: I think maybe you should stop allof your psych meds. You probably don't really need them anyway.

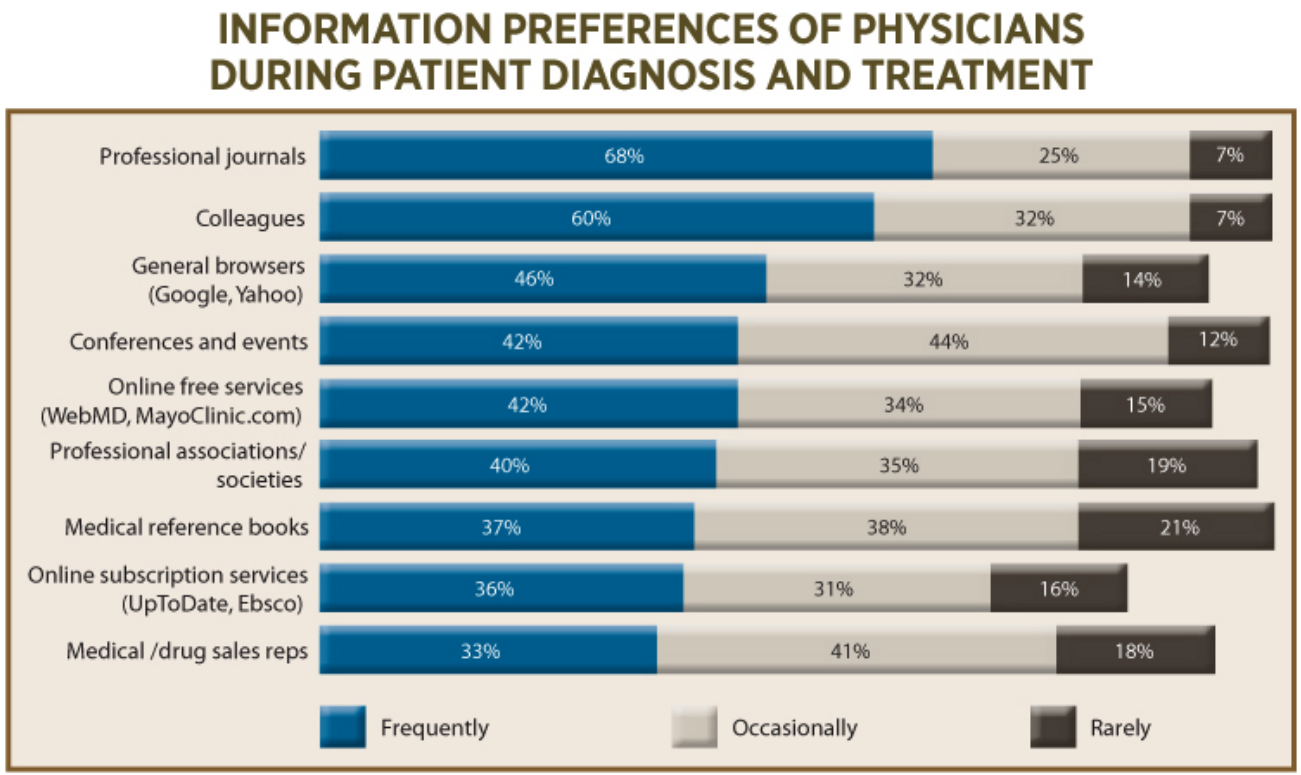
Meds and Pregnancy: How Do Patients Make Decisions?

- Consultation with prescriber
  - Do I need to continue this medication? Is it safe?
- Consultation with obstetrician
  - Focus on pregnancy outcomes vs. risks of illness
- Friends and family
  - My friend took Prozac. Her doctor said it was safe.
  - My husband doesn't want me to take any meds.
- Emotional factors
  - No coffee. No alcohol. No medication.
- Assumption
  - My doctor prescribed it to me, so I assumed it was safe.

Medications and Pregnancy: What Does the Internet Say?

- What is the reliability of sources?
  - Many “Safe During Pregnancy” lists contain incorrect information
  - Many sites created by lawyers
  - Few sites from medical professional organizations
- Negative findings get more coverage, rise to the top of the list
- Out of date but popular articles persist, convey outdated, often incorrect information

Physician Preferences for Information Resources



Meds During Pregnancy: What Are the Risks?

- Pregnancy loss - miscarriage, stillbirth
- Worse pregnancy outcomes - Gestational diabetes, HTN, preterm labor/delivery, low birth weight, delivery complications
- Major malformations – Most observed during pregnancy or at time of delivery
- Long-term neurodevelopmental outcomes – autism, increased risk of psychiatric illness

FDA Labeling of Reproductive Safety

- 1975 - Pregnancy Categories: A, B, C, D, X
- Lettered categories incomplete or misleading
- 1998 - FDA acknowledges need for revision
- 2015- Pregnancy and Lactation Labeling Rule (PLLR)
- No letters, more detailed narrative summary
- Source of information in package insert

Pregnancy & Lactation Labeling Rule

- Section 8.1: Pregnancy
- Section 8.2: Lactation
- Section 8.3: Females and Males of Reproductive Potential (new)

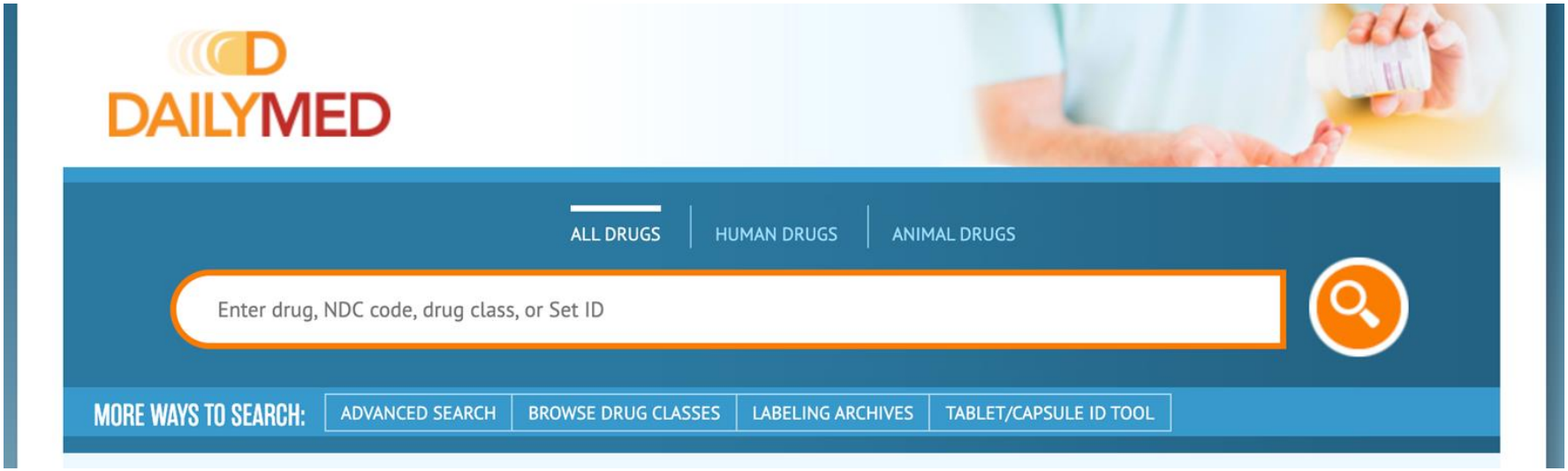
- OTC medications not covered by PLLR

Acceptance of the PLLR

- PLLR introduced in 2015
- Most websites still refer to letter categories
- American Academy of Allergy, Asthma & Immunology surveyed in 2018
- 46% were not aware of new PLLR
- 68% said summaries were too long
- Most (95%) stated they will continue to use pregnancy letter category system to make prescribing decisions

Namazy J, et al. J Allergy Clin Immunol Pract. 2020 Jun;8(6):1947-1952.

Where to Find Up-to-Date Labeling Information

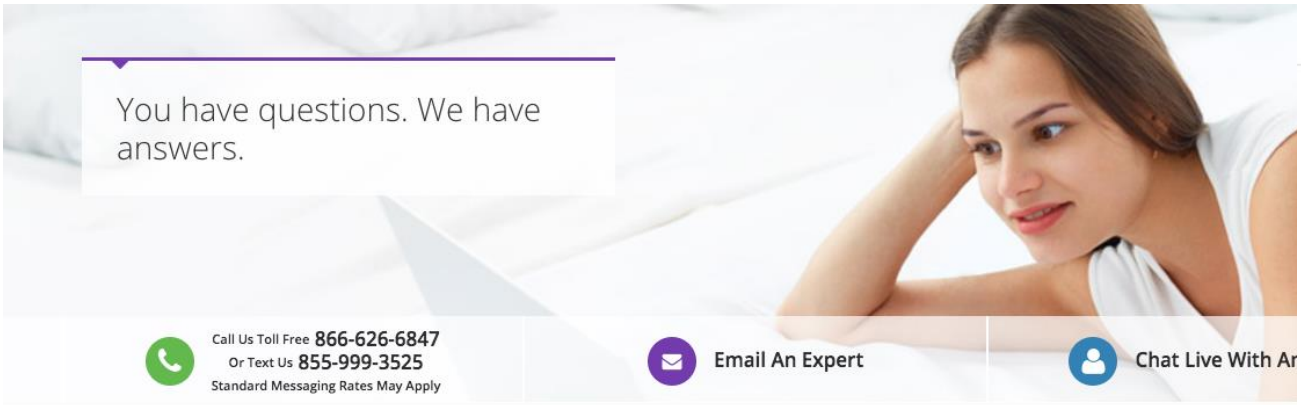


- https://dailymed.nlm.nih.gov
- Updated drug label information (PLLR)
- Site maintained by the FDA

www.womensmentalhealth.org

MotherToBaby

Medications & More During Pregnancy & Breastfeeding
Ask The Experts

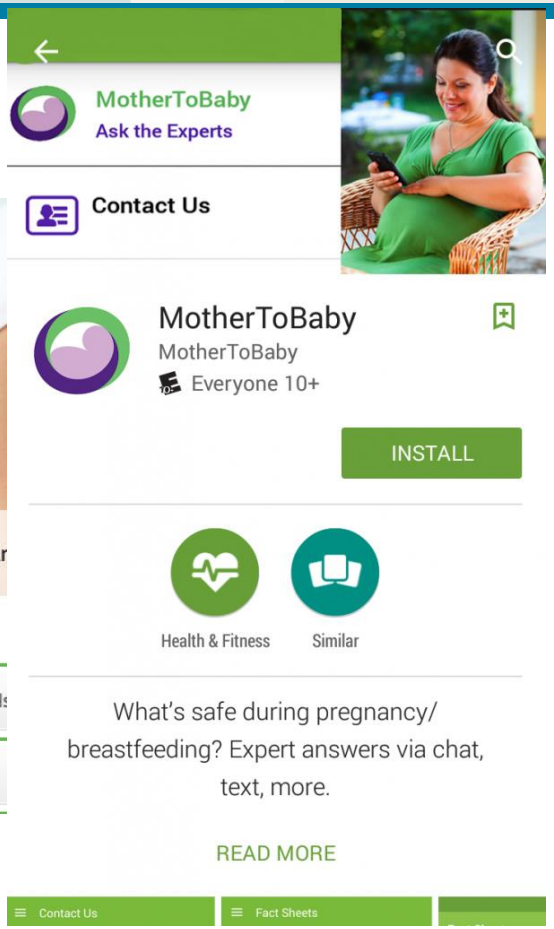


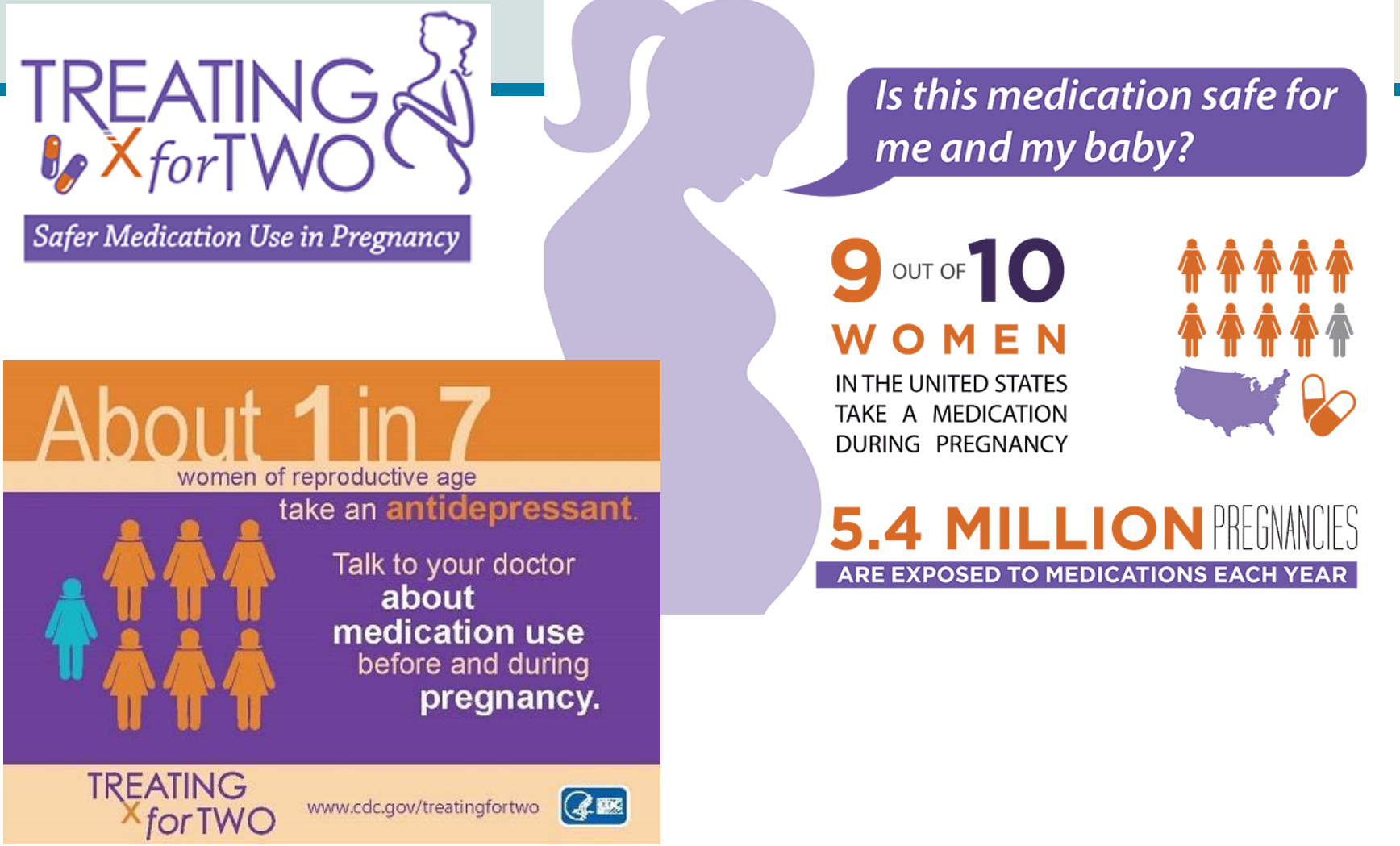
Fact Sheets

The experts behind MotherToBaby have created fact sheets that answer frequently asked questions about exposures during pregnancy and breastfeeding. MotherToBaby Fact Sheets are available in both English and Spanish and can be downloaded for free. Currently available fact sheets are listed below by category of exposure. All medications are listed by generic name. The generic name can be found on your prescription or medication packaging listed as the Active Ingredient, or in parentheses after the medication's brand name.

Health Professionals

Fact Sheets




TREATING X for TWO
Safer Medication Use in Pregnancy
Is this medication safe for me and my baby?
9 OUT OF 10 WOMEN
IN THE UNITED STATES TAKE A MEDICATION DURING PREGNANCY
5.4 MILLION PREGNANCIES
ARE EXPOSED TO MEDICATIONS EACH YEAR
About 1 in 7
women of reproductive age
take an antidepressant.
Talk to your doctor about medication use before and during pregnancy.
TREATING X for TWO
www.cdc.gov/treatingfortwo

Part 2: Diving Deeper into the Data


PLLR

PLLR: Sources of Data

- Animal data, greater focus on human data
- No case reports or adverse event reporting
- Human data from clinical trials, pregnancy exposure registries, epidemiological or surveillance studies, some case series
- Data submitted by manufacturer, approved by FDA committee

Gold Standard: Pregnancy Registry

- Organized by manufacturer or independent research group
- FDA does not require pregnancy registries
- Participants are enrolled prior to knowledge of pregnancy outcomes (first trimester)
- Minimizes, does not eliminate selection bias
- Variability in how outcomes assessed (maternal report, chart review)

Sample Size

- 600-700 exposures to detect a twofold increase in risk of common malformations
- Even larger numbers needed to detect changes in risk of rare malformations
- Larger studies can control for confounding factors, lower quality of data
- Smaller studies may overestimate or underestimate risk

MGH Registry for Psychiatric Medications

The National Pregnancy Registry for Atypical Antipsychotics

Real World Perinatal Psychiatry

- Few registries available
  - North American Antiepileptic Drug Registry
- Many registries - small numbers
- Limited data on newer medications
- Consideration of polypharmacy

Risk of Persistent Pulmonary Hypertension of the Newborn

- Failure of normal circulatory transition at birth, poor oxygenation
- Case-control study: 337 infants with PPHN, 836 healthy controls
- Infants with PPHN: 14 exposed to SSRI after 20 weeks gestation
- Healthy infants: 6 exposed to SSRI
- Adjusted odds ratio of 6.1

Chambers CD, Er al. N Engl J Med. 2006 Feb 9;354(6):579-87.

Study Design: Case-Cohort vs. Case-Control

- Case-Cohort Studies
  - Identify exposed cases (fetal exposure to medication)
  - What is the risk of a particular outcome?
  - If large, can give accurate estimate of risk

- Case-Control Studies
  - Identify cases (children with birth defect)
  - Are cases more likely in exposed cases vs. non-cases?
  - Good at identifying rare events, overestimate risk

Study Design: Retrospective vs. Prospective

- Retrospective Studies
  - Recall bias
  - Timing and duration of drug exposures
  - Difficult to assess other exposures: alcohol, tobacco, infection, other medications
  - Medical databases – larger cohorts
  - Patient recruitment- selection bias?
- Prospective studies preferred
  - Enrolled before outcome is known
  - Higher quality of data regarding exposures
  - Labor-intensive, smaller studies

Study Design: How Are Outcomes Assessed?

Timing of Assessments	• Major malformations identified early • Neurodevelopmental effects identified much later
Highest Quality	• Prospectively gathered data • Standardized assessments using blinded raters
Lower Quality	• ICD-10 diagnostic codes • Parental reporting vs. standardized evaluation, unblinded raters

PPHN and SSRIs: Newer Data

- Case-cohort study
- 2000-2010 Medicaid Analytic eXtract
- 3,789,330 pregnant women
- 102,179 (2.7%) used an SSRI
- Adjusted odds ratio for SSRI exposure was 1.28 (95% CI, 1.01-1.64)

Huybrechts KF, et al. JAMA. 2015 Jun 2;313(21):2142-51.

SSRIs and Risk of Autism Spectrum Disorders

- Case-control study
- 298 case children with ASD from Kaiser Permanente Northern California
- 1507 control children without ASD
- Prenatal exposure to antidepressant in 20 case children with ASD (6.7%) vs. 50 controls without ASD (3.3%)
- Adjusted odds ratio = 2.2 (CI 1.2-4.3)

Croen et al. Arch Gen Psychiatry 2011 Nov;68(11):1104-12.

CORRELATION

does NOT necessarily imply

CAUSATION

Confounding by Indication

Is it exposure to the medication that increases risk for a particular outcome?

OR

Is it the underlying illness (the reason for taking the medication) or associated factors driving risk for that outcome?

What is the Impact of the Underlying Illness?

- Genetic vulnerability
- Physiologic changes
  - Dysregulation of HPA axis, increased cortisol
  - Higher levels of inflammatory markers
- Comorbid illness, exposure to other medications
- Associated changes in behavior
  - Diet, exercise
  - Use of alcohol, tobacco, recreational drugs
  - Inadequate prenatal care, use of prenatal vitamins

Study Design: Selection of Comparison Group

- Women taking psychiatric medications
  - Higher rates of tobacco, substance use
  - Higher rates of medical comorbidity
  - Age, marital status, education, SES
- Control Groups
  - Healthy pregnant women
  - Women with histories of psychiatric illness who discontinue medication
  - Sibling controls (one exposed, one not)
  - Paternal controls (father taking medication)

Study Design: Confounding Factors

Can we account for other exposures which may affect outcomes?

- Exposure to other medications
- Overall health - BMI, comorbid medical illness
- Use of tobacco, other substances
- Lifestyle factors - exercise, diet
- Impact of psychiatric illness itself
- Exposure to stress

Risk of Autism After Controlling for Confounding Factors

- Children born in Denmark 1996-2006 (n=668,468)
- SSRI Exposure: Risk of ASD increased 1.62 (95% CI, 1.23 to 2.13) compared to non-exposed children
- Risk of ASD increased in women who received SSRIs before – but not during — pregnancy (aOR = 1.46; 95% CI, 1.17 to 1.81).
- Risk associated with SSRI exposure during pregnancy may be related to genetic and/or environmental factors.

Sørensen MJ, et al. Clin Epidemiol. 2013 Nov 15;5:449-59.

Statistical vs. Clinical Significance

- Meta-analysis
- Comparison of pregnancy outcomes in SSRI-exposed vs. unexposed pregnancies
- SSRI Exposure -statistically significant decreases in:
  - Gestational age – Difference of 0.45 weeks
  - Birth weight – Difference of 74g or 2.5 ounces
  - Apgar scores – Difference of o.5 points

Ross LE, et al. JAMA Psychiatry 2013.

Information on Reproductive Safety of Medications

- Product label (PLLR updated by FDA) - DailyMed website
- Treating for Two (CDC) - patient oriented
- Mother To Baby (Organization of Teratology Information Specialists))
- MGH Center for Women's Mental Health at womensmentalhealth.org
- Original Articles

Interpreting Original Articles?

- Design: Case-Cohort vs. Case-Control
- Quality of the data collected
  - Retrospective vs. prospective
  - ICD-10 codes vs. standardized assessments
  - Biased vs. blinded raters?
- What are possible confounding factors?
- Correlation does not imply CAUSATION
- Are the findings clinically significant?

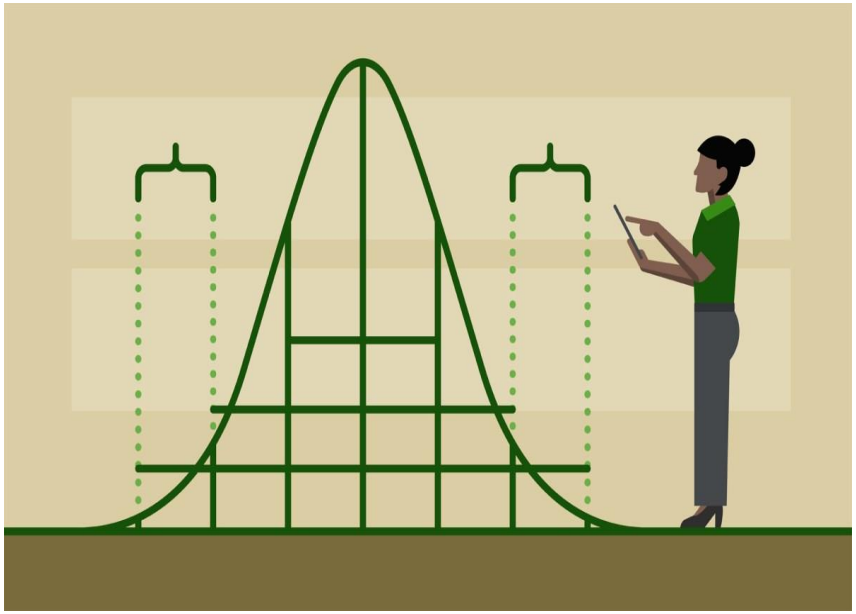
Emphasis on Preconception Planning

- Emphasis on PLANNING and PREPARATION
- 50% of pregnancies are unplanned
- Obstetricians first see patients AFTER they conceive
- US Preventive Services Task Force (USPSTF) recommends that ALL WOMEN with childbearing potential should take supplemental FOLIC ACID
- Women with chronic or recurrent illness
  - Discuss contraception
  - Review plans for pregnancy
  - What are the risks associated with illness?
  - What are the risks associated with medication?

Part 3

Self-Study:
Basic Statistical Principles

A Quick Stroll Through Statistics



- Risk Ratios, Odds Ratios
- P-Values
- Confidence Intervals
- Relative vs. Absolute Risk
- Statistical vs. Clinical Significance

Risk Ratios and Odds Ratios

- Risk ratio (RR) or relative risk: Compares risk in exposed group vs. comparison group
- RR=1: Both groups have same risk of outcome
- Odds ratio (OR): Compares the odds or probability of a particular outcome in 2 groups
- OR used in case-control studies

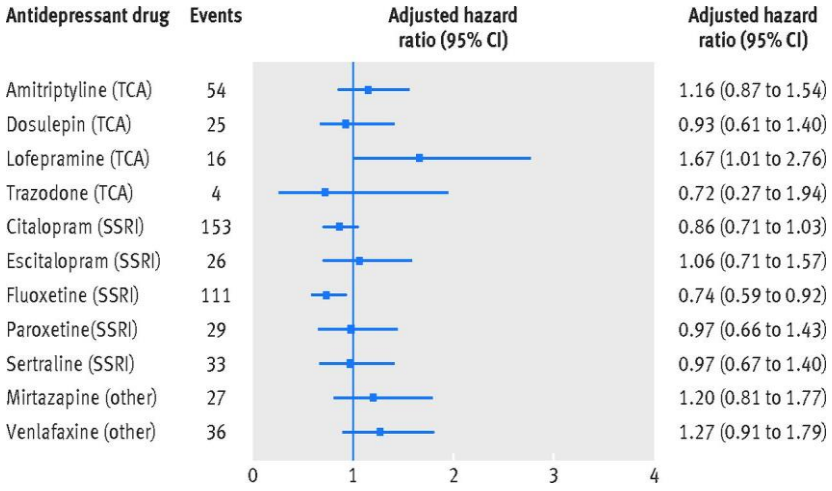
P-Values

- Measures statistical significance, the difference between two numbers or groups
- Smaller P-values are better
- Typical cut-off is 0.05= statistically significant

Confidence Intervals

- Are two sets of numbers (populations) different?
- Null value is 1: Two groups are the same
- If 95% confidence interval does not include the null value (RR=1), the finding is statistically significant
- Wide confidence intervals indicate increased variability in the population

Risk of Cardiovascular Malformations in Infants Exposed to Antidepressants



Relative Risk vs. Absolute Risk

- Relative Risk compares risk between two populations (risk of oral clefts in children exposed to topiramate vs. unexposed)
- Absolute risk – Overall risk of particular outcome
- Example – First trimester exposure to topiramate; relative risk or RR =10.1, absolute risk 1.5%

Margulis AV, et al. Am J Obstet Gynecol 2012.

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