

# Counseling of Female Veterans about Risks of Medication-Induced Birth Defects



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# Disclosures

NONE

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- VA                          -Society of Family Planning
- FDA                         -Hewlett Foundation
- USAID

# Objectives

- Review recent data on Female Veterans' use of medications that can cause birth defects.
- Examine Veterans' reports of the counseling they receive about medication-induced birth defects
- Discuss best practices for safe-prescribing to women of childbearing potential.

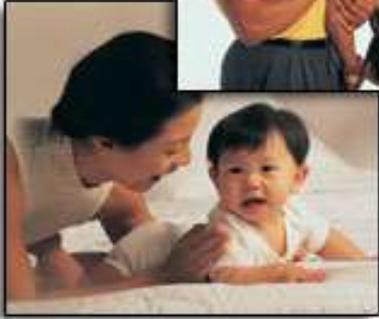
# What is your role within VA?

(choose all that apply)

- Primary care provider
- Women's health specialist
- Nurse
- Social worker
- Behavioral health specialist
- Researcher
- Other

# Vision

1. Healthy moms
2. Healthy babies
3. Comfortable clinicians



Each year in the US...

62 million women of reproductive age

6 million pregnancies



4 million births

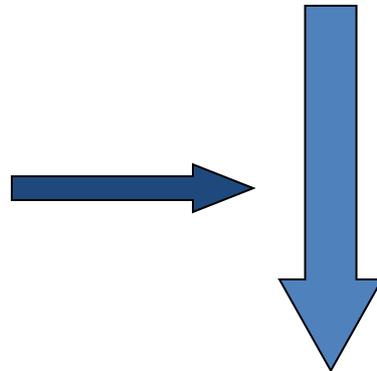
150,000 babies with birth defects

Each year in the US...

62 million women of reproductive age

6 million pregnancies

Maternal  
Illness



4 million births

150,000 babies with birth defects

Each year in the US...

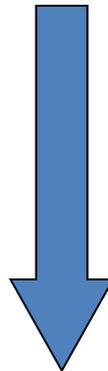
62 million women of reproductive age

6 million pregnancies

Maternal  
Illness



Medication  
Use



4 million births

120,000 babies with birth defects

# Teratogenic Medications

Medicines that can cause birth defects

thalidomide,  
isotretinoin,  
phenytoin,  
warfarin,  
methotrexate,  
lithium...



...more than 100 different drugs!

# FDA Classification System

- Class A: Fetal harm appears remote
- Class B: Animal studies revealed no evidence of fetal harm
- Class C: No adequate studies in women.
- Class D: Evidence of human fetal risk
  - Use in pregnant women may be acceptable for serious disease when no safer drugs exist
- Class X: Contraindicated in women who are or may become pregnant

Are women of reproductive age using class D and X Medications?



# YES!!



# Nationally, how often are potentially teratogenic meds prescribed?

Annually:

11.7 million teratogenic Rx = 1 of every 25 Rx  
283 million prescriptions  
for women age 14-44 years who were not pregnant

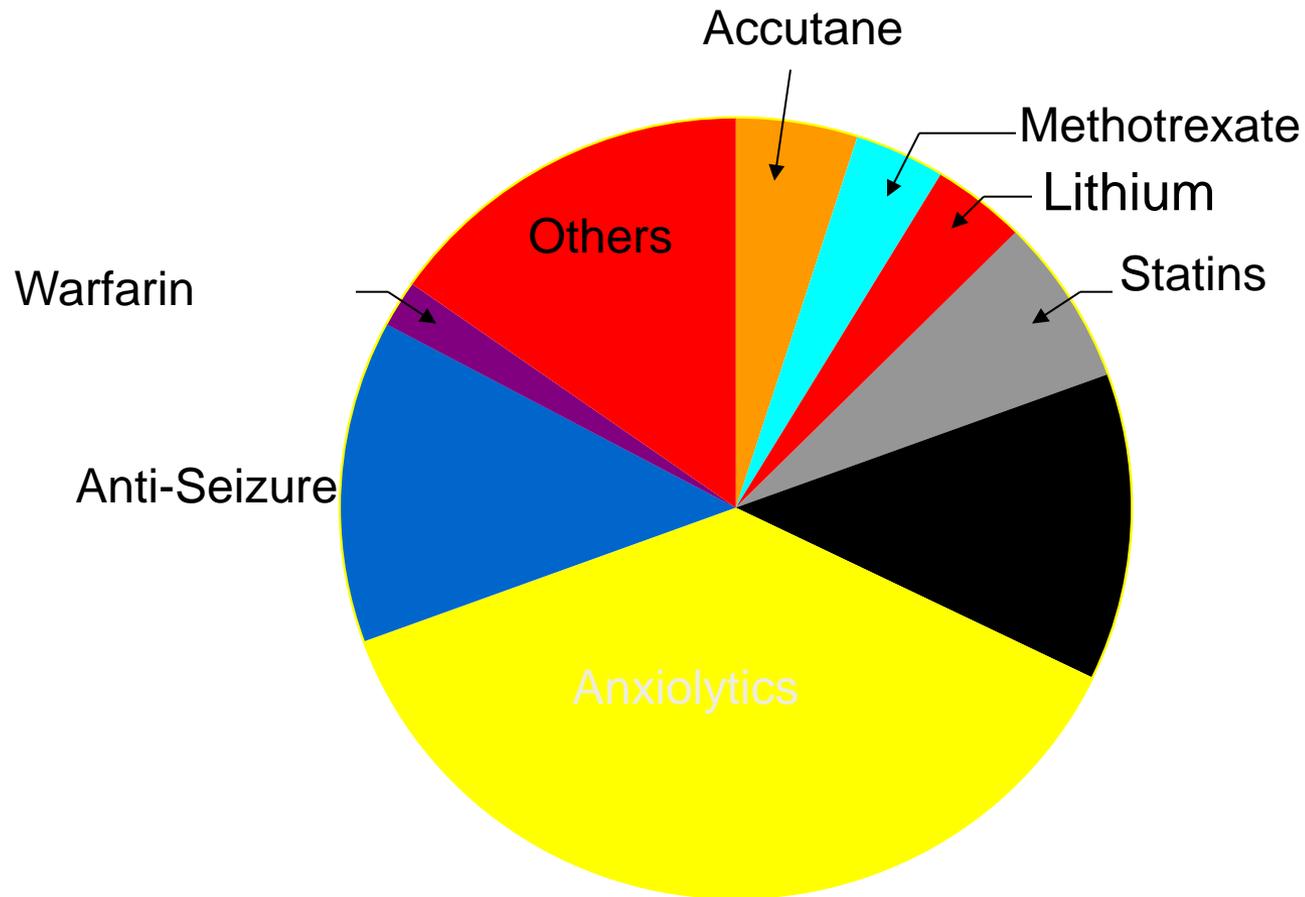
11.7 million teratogenic Rx = 1 of every 13 visits  
147 million outpatient visits  
for women age 14-44 years who were not pregnant

# In a large HMO in 2001...

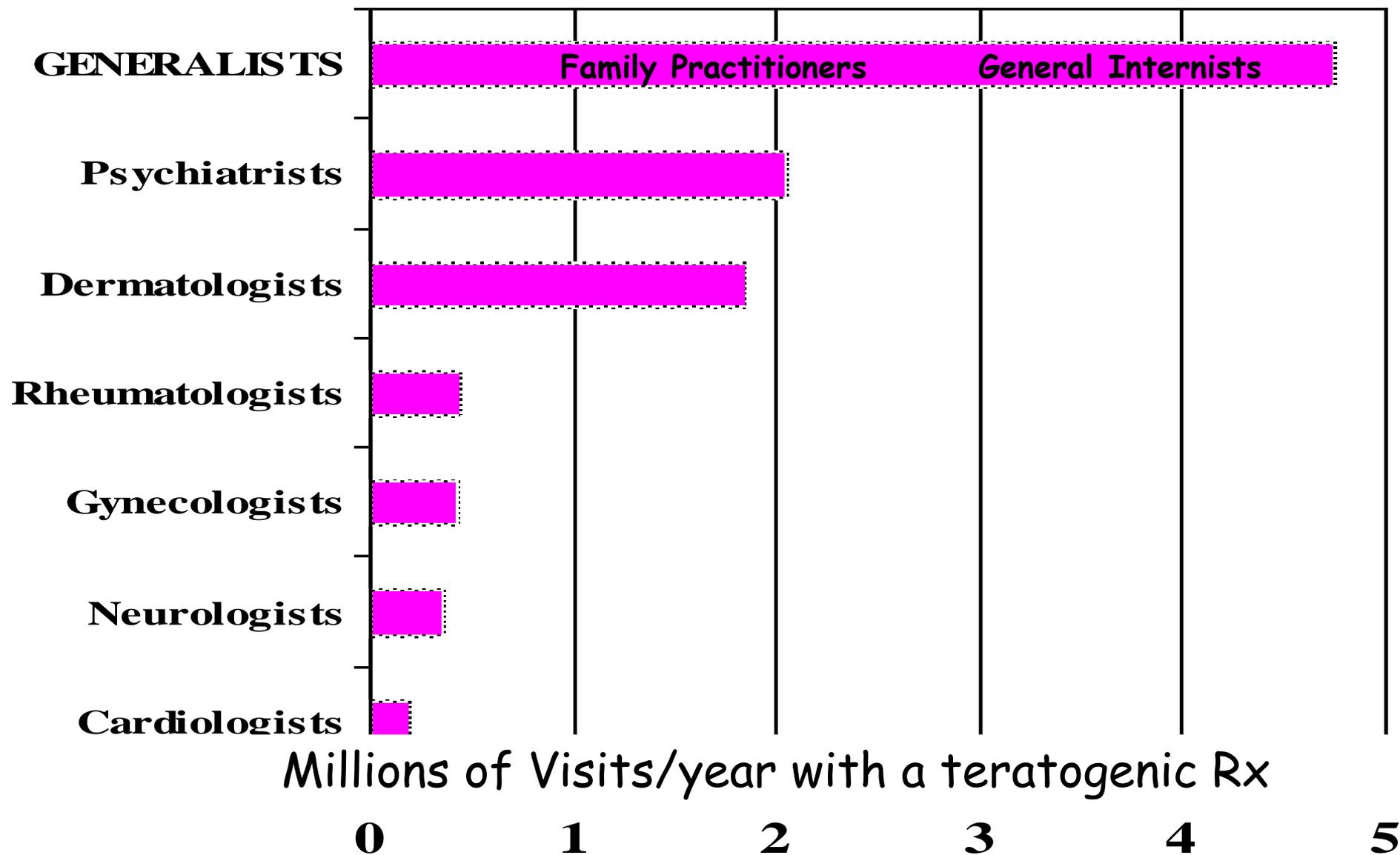
1/6 women filled  
a class D or X Rx



# What are these 11.7 million prescriptions for ?



# Who's writing these prescriptions?



# Our Female Vets...

49% of female Vets  
who received an Rx from a  
VA pharmacy received a  
potentially teratogenic Rx



# Are these chronic meds?

	Women Veterans who filled ≥1 Rx N=38,205		Rx per woman per year  Average #	Days supply per woman Veteran per year Average
	N	%		
<b>Psychiatric</b>	<b>20155</b>	<b>52.8</b>	<b>4.2</b>	<b>133.5</b>
Antidepressant	5162	13.5	2.8	116.0
Benzodiazepine	16430	43.0	3.9	112.5
<b>Antihypertensive</b>	8115	21.2	2.7	195.5
<b>Statin</b>	8790	23.0	2.1	153.5
<b>Neurologic</b>	<b>4687</b>	<b>12.3</b>	<b>3.4</b>	<b>134.0</b>
<b>Tetracycline</b>	6235	16.3	1.0	28.0
<b>Warfarin</b>	547	1.4	4.9	164.5
<b>Retinoid</b>	75	0.2	2.2	65.5
<b>Other</b>	7562	19.8	1.3	34.5

# Participating Female Vets

(OEF/OIF Vets, N=245)	Total
Sexually active	86%
Prior pregnancy	63%
Unintended pregnancy	72%
Prior abortion	29%
Prior birth	66%
Prior birth defect	6%
Infertility <sup>†</sup>	11%
Used contraception	
Condom with last sex	22%
Hormonal method in last 12 months	48%

# Teratogenic Risk Counseling of Female Vets

	Received counseling
Sexually active	25%
Prior pregnancy	25%
Unintended pregnancy	25%
Prior abortion	24%
Prior birth	26%
Prior birth defect	30%
Infertility <sup>†</sup>	35%
Used contraception	
Condom with last sex	15%
Hormonal method in last 12 months	28%

# Female Vets rarely report counseling about teratogenic risks

- 90% were confident that they would be told by their clinician if an Rx might cause a birth defect
  - 81% of women prescribed benzodiazepines
- But, only 24% of women with Rx had been warned of teratogenic risks
  - 22% of women prescribed benzodiazepines

# Associated with Teratogenic Risk Counseling?

	p-value
Sexually active	0.15
Prior pregnancy	0.27
Unintended pregnancy	0.61
Prior abortion	0.58
Prior birth	0.96
Prior birth defect	0.79
Infertility <sup>†</sup>	0.12
Used contraception	
Condom with last sex	0.06
Hormonal method in last 12 months	0.16

# Counseling by medication class

	Received counseling	Confident they'd receive counseling
Any medication ( <i>n</i> =286)	24 %	90 %
ACE-inhibitor or ARB blocker ( <i>n</i> =4)	0 %	50 %
Benzodiazepine ( <i>n</i> =37)	22 %	81 %
Statin ( <i>n</i> =16)	19 %	81 %

# Confidence Vet'd receive teratogenic risk counseling

- NOT associated with sociodemographics
- Confidence *decreased* with:
  - Difficulty obtaining contraception in military  
78% vs. 91%,  $p=0.04$
  - Pregnancy after MST, 67% vs. 91%,  $p=0.05$
  - History of drug use
- Confidence *increased* with prior pregnancy affected by birth defects

# Does confidence matter?

Confidence associated with more likely to:

- Agree that “VA provides good quality healthcare,”  $p=0.04$
- Plan to use VA as a primary source of healthcare in the future (85% vs 94%,  $p=0.04$ )

# Does FDA label affect contraceptive counseling?

<i>Apparently not</i>	Safe Rx Class A or B (95% CI)	Risky Rx Class D or X (95% CI)	p-value
Nationally, visits with contraceptive counseling or Rx	<b>5.4%</b>	<b>4.1%</b>	p=0.24
In Northern CA, Rx with contraceptive counseling or use	<b>39.4%</b>	<b>37.0%</b>	p<0.001

Schwarz EB, et al. Am J Med 2005

Schwarz EB, et al. Ann Intern Med. 2007

# Nationally...

- <20% of US women receiving potentially teratogenic medications had documented receipt of family planning services

# Among Female Vets

Receipt of family planning services  
(e.g. contraception, contraceptive counseling  
or pregnancy testing) was documented for

- 36% of women filling only class A or B meds
- 52% of women who filled class C meds
- 56% of those who filled class D or X meds



Does contraceptive method affect rates of positive pregnancy tests after filling a potentially teratogenic medication?

**YES**

Women 15-44 yo with + pregnancy test <3 months after filling a potentially teratogenic Rx	%
Overall	1.0
Women with any contraceptive documentation	0.8
Women with a most effective contraceptive	0.2

# What affects rates of safe prescribing to women of reproductive age?

- **Patient characteristics?**

- Age=

- at KP: 25-34 yrs > 15-24 yrs > 35+ yrs
    - at VA: 18-25 yrs > 26-34 yrs > 35+ yrs
    - at UPMC: 18-29 yrs > 30+ yrs

- **Provider characteristics?**

- Gyn > non-gyn; NPs/PAs/CNMs > MDs

- *Not* gender, age, race, or years in practice

# What affects rates of safe prescribing to women of reproductive age?

## *Clinic characteristics*

- VA Women's clinic OR=1.96\*
- At KP and UPMC some clinics 2x others

## *Provider characteristics*

- Not gender, age, race, or tenure
- Gyn > non-gyn
- NPs/PAs/CNMs > MDs

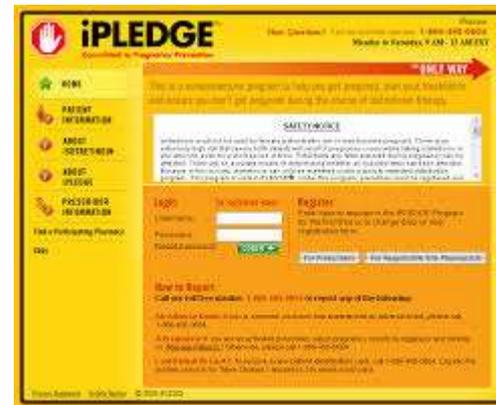
Schwarz EB, et al. QAAal. Am J Med 2005

Schwarz EB, et al. Ann Intern Med 2007

Schwarz EB et al. Med Care 2010 2010

# Clinical Indication?

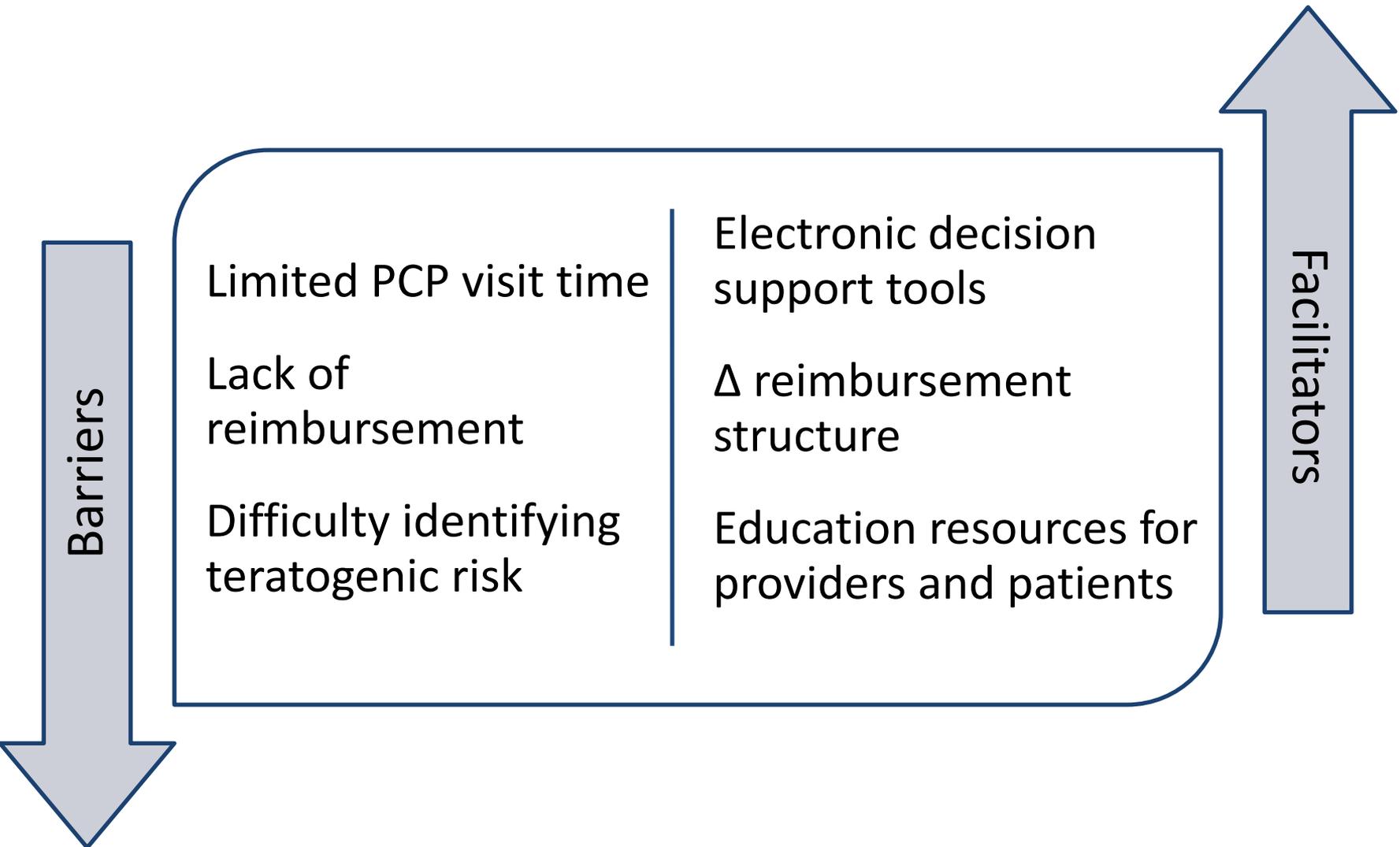
- Isotretinoin better than all others



- Coumadin worse than others

Schwarz EB, et al. Am J Med 2005  
Schwarz EB et al. Med Care 2010

# Barriers & Facilitators



Schwarz EB et al. Birth Defects Res A Clin Mol Teratol. 2009 85(10): 858–863.

Eisenberg DL et al. J Gen Intern Med. 2010;25(4):291-7.

# Electronic Decision Support?

41 primary care physicians  
randomized

## Simple Alerts

“Concern has been raised about  
use of this med during pregnancy.”

## Multifaceted Alerts

“Concern has been raised about  
use of this med in pregnancy.”

*Plus links to:*

- Info on meds
- Order for pregnancy testing
- Orders for contraception
- Refer to specialist

# Hypotheses

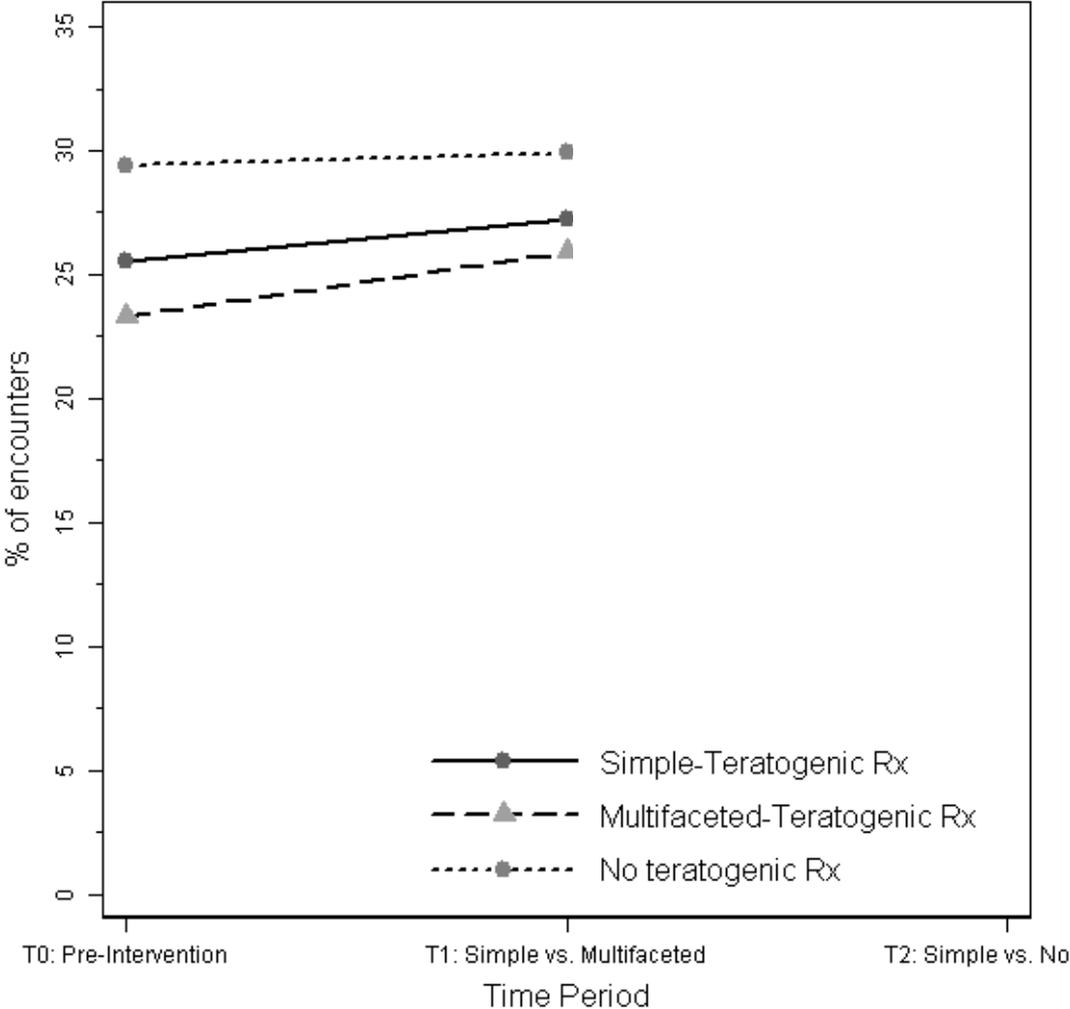


- Simple alert would be good

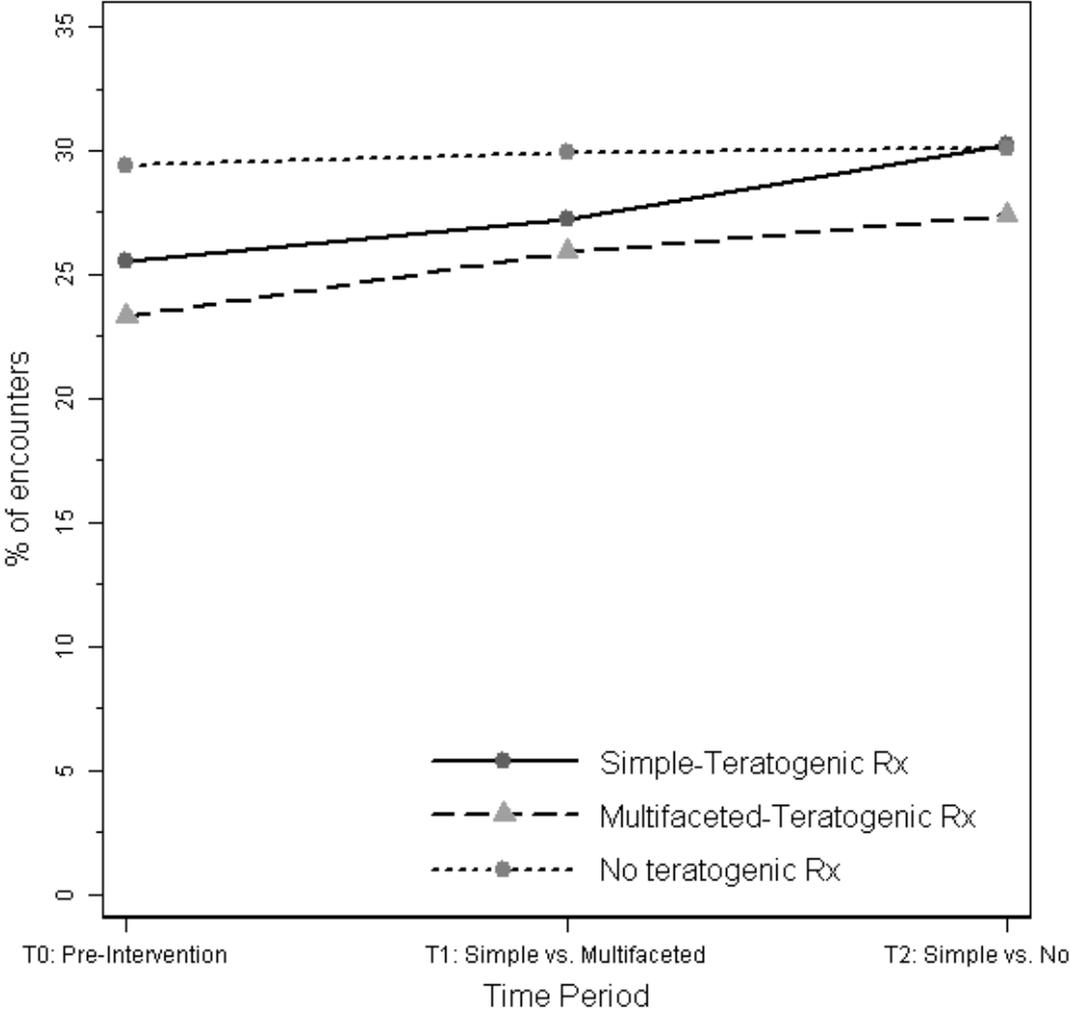


- Multifaceted alert would be better

# Clinical Decision Support

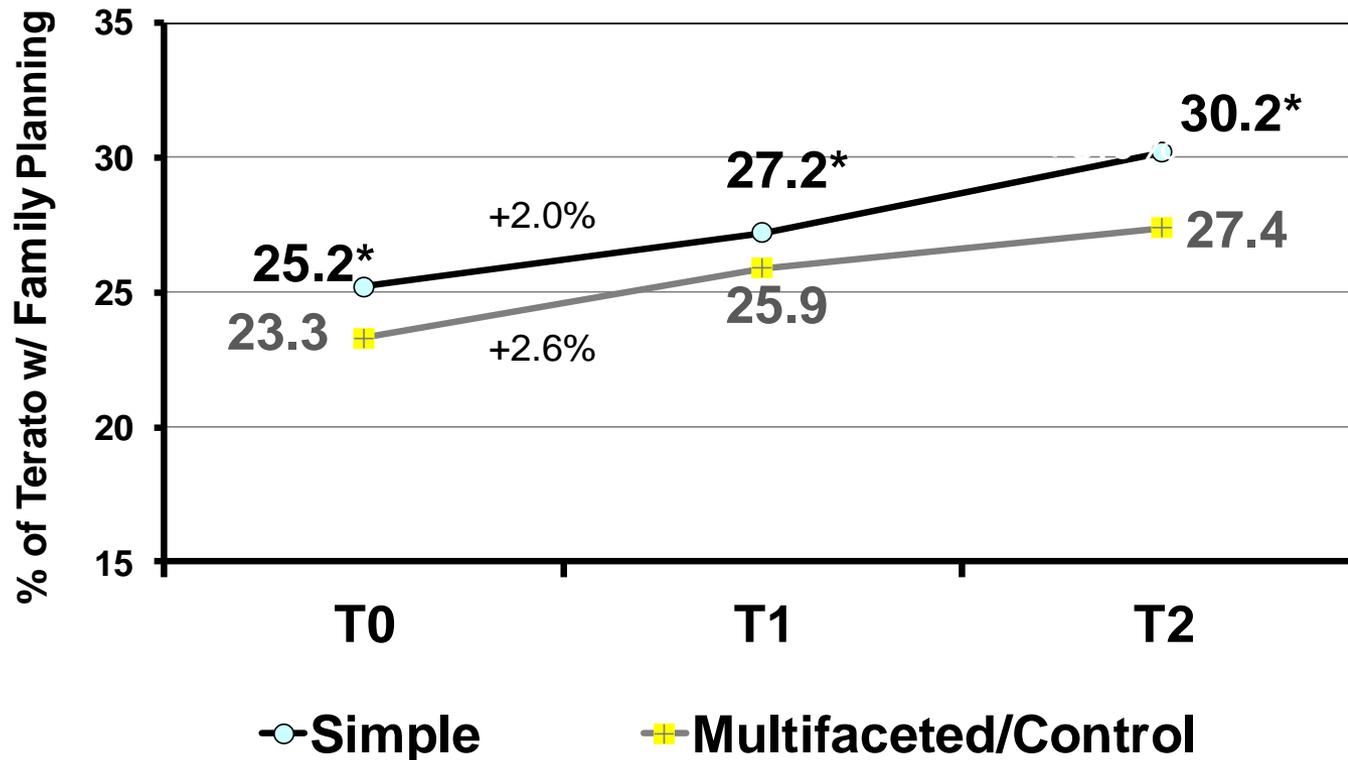


# Clinical Decision Support



# Visits with Teratogenic Rx & Family Planning Services

\*  $p = 0.04$  for improvement over time



# Results

- 3 types of patients:
  - Contraception on all visits = 26%
  - NO contraception on any visits = 69%
  - No contraception before intervention, *with* contraception after alert = 5%

# Challenges

- Doctors who received multifaceted alerts accessed links only 16% of time.
- Alerts fired only once per visit:
  - 14% doctors who received alert cancelled Rx, *AND* unknowingly Rx'd another teratogen!
    - Limited visible effect of intervention.



# Limitations

- Electronic medical record data incomplete
  - Vasectomy, sterilization, condoms
  - Contraceptive counseling ICD-9 codes rarely used because no reimbursement provided
- Should not differ between groups

# Not just poor documentation

Counseling about risk of birth defects and/or contraception was reported by Women

- 41% if no potentially teratogenic Rx
- 45% if pot'ly teratogenic Rx, no CDS
- 57% if pot'ly teratogenic Rx and CDS

# Conclusions

- Computerized alerts can be helpful, but refinement is needed.
- Alerts need to re-fire if Rx *another* teratogen.
- Routine documentation of fertility and contraception is important for safe Rx to women of childbearing age.

# Safe prescribing to women of childbearing potential



- Risks of teratogenic exposure greatest in early pregnancy
- 49% of US pregnancies unintended
- 6% of US pregnancies exposed to potentially teratogenic medication

# Proactive counseling

- Risks are greatest in early pregnancy
  - Before most receive prenatal care
  - Before many know they are pregnant
- Perception (or misperception) of risks impact behavior
  - Discontinue needed medication
  - Abortion



Koren G et al Can J Pub Health 1991 May-Jun;82(3):S11-4, S33-7

Jasper JD, et al Lancet. 2001 Oct 13;358(9289):1237-8

# “Scares” can have long-term effects

Is my child normal?



After a false-positive screen for congenital hypothyroidism...

- 78% reported strong emotional reaction
- After one year, 18% had persistent insecurity about their child's health
- Some without concerns at 1 year, reported insecurity after 4 years
- At 4 years, 80% reported persistent insecurity

# Clinician counseling is important

96 women with a h/o Anxiety requiring meds

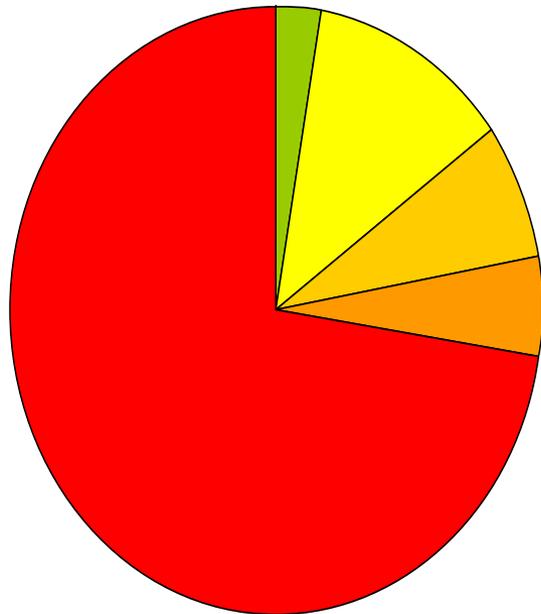
- In pregnancy? 29% “likely” to continue meds
- If FDA warning? 5% “likely” to continue meds
- If clinician counseled med was safe (despite FDA warning)? 41% switched to “likely”

# Know her plans

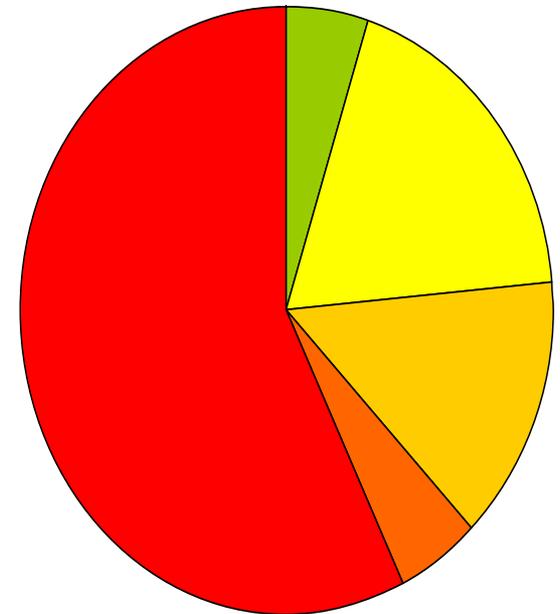
- When, if ever, would you like to have a baby in the future?
- What are you doing to delay or avoid pregnancy?
  - 50% of female Veterans have no documented use of prescription contraception

# What are your plans for pregnancy?

High SES clinic



Low SES clinic



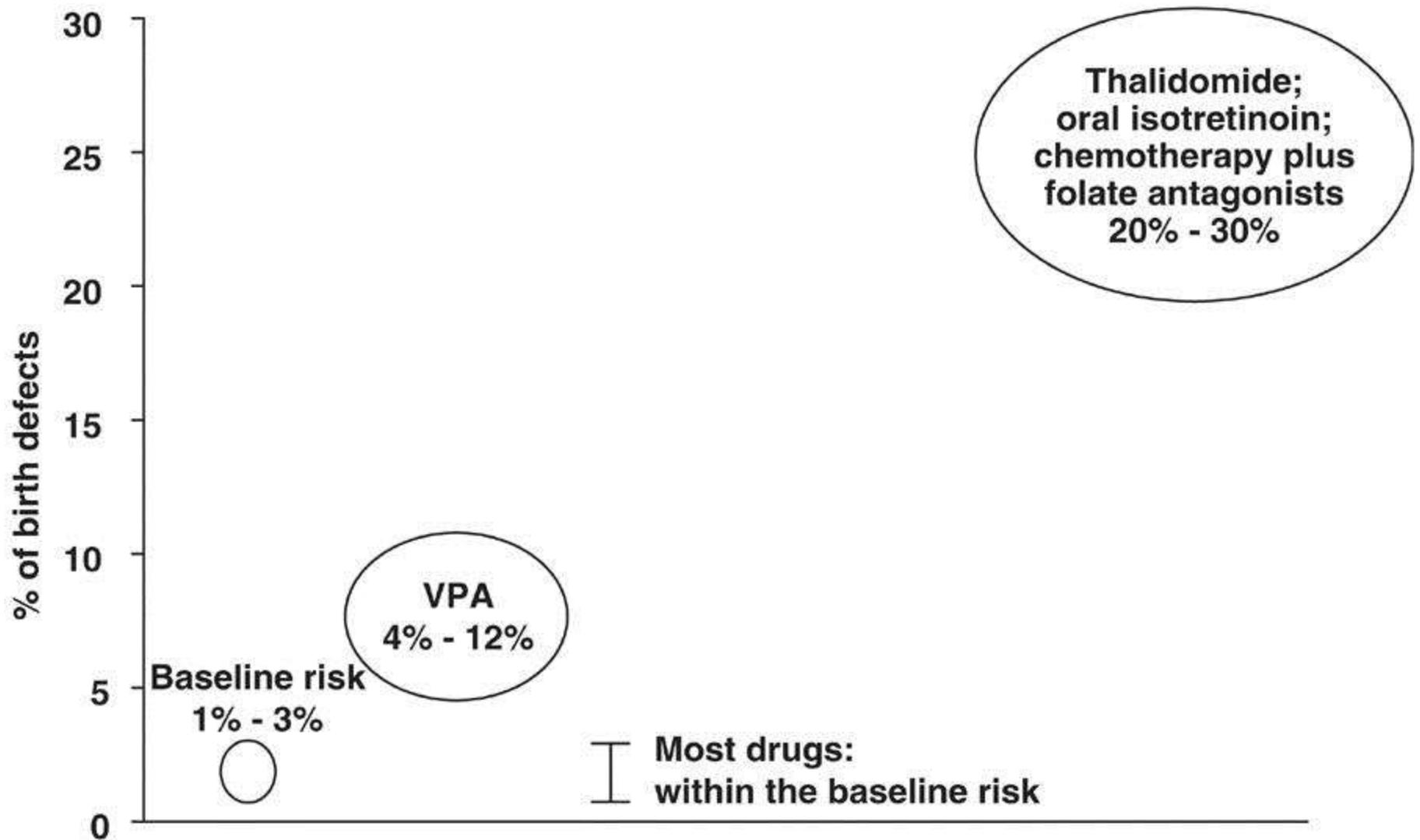
- trying to conceive
- wouldn't mind conceiving
- don't know
- wouldn't mind avoiding
- trying to avoid

# Discuss Absolute Risks

Twice a very, very, small risk  
is still a very small risk

Relative Risk	Baseline risk	Absolute risk
2	1/100	2/100
2	1/million	2/million





**FIGURE 1.** Graphical representation of risks in pregnancy. The risk of major congenital malformations of most of the drugs is at base line risk level (1% to 3%). Only few drugs are documented teratogens with a risk between 20% and 30%. VPA indicates valproic acid.

From:

# *OTIS Mother to Baby*

Benzodiazepines

<http://www.mothertobaby.org/files/benzodiazepines.pdf>

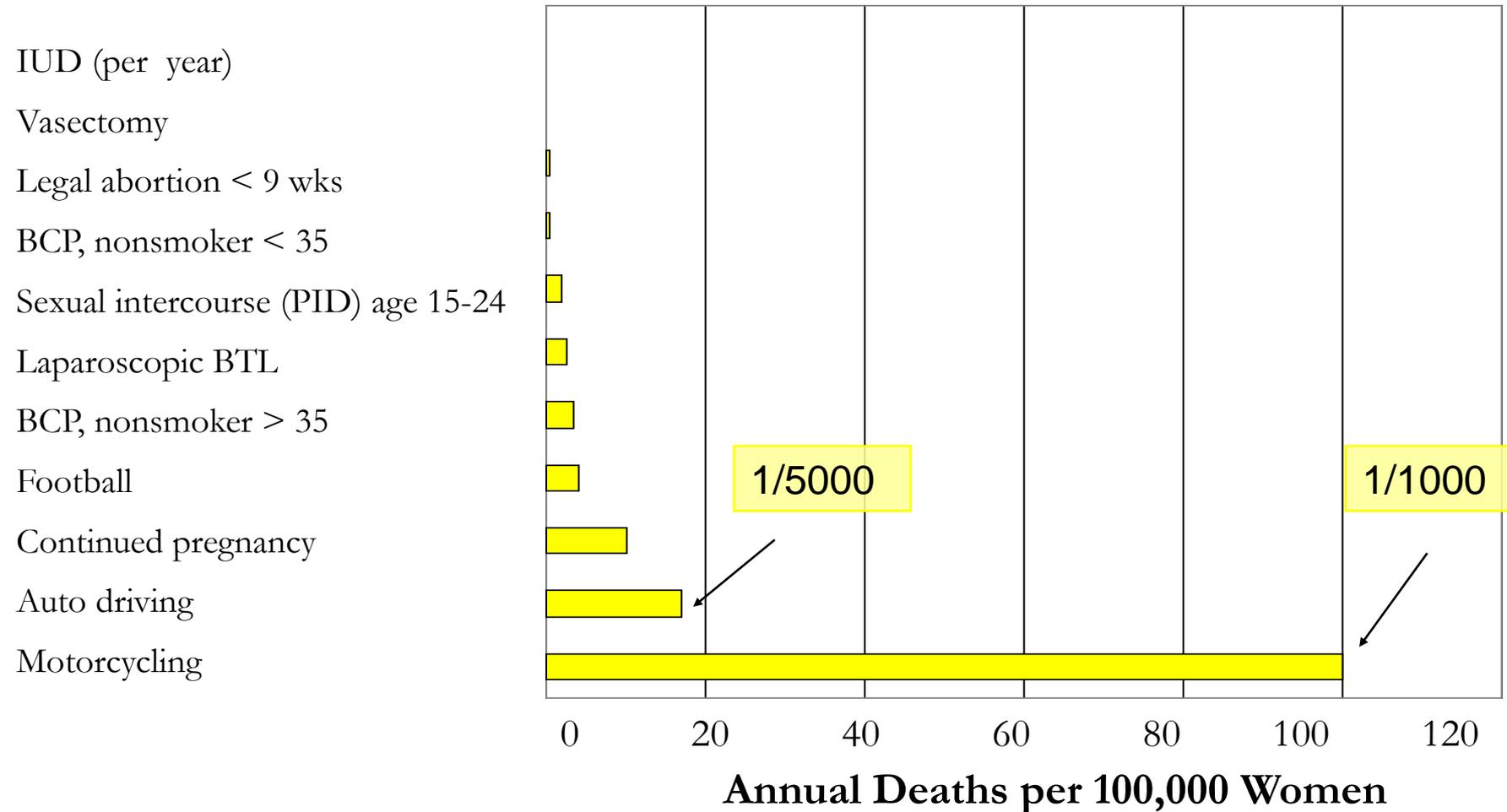
- Paroxetine

<http://www.mothertobaby.org/files/paroxetine.pdf>

- Fluoxetine

<http://www.mothertobaby.org/files/fluoxetine.pdf>

# Voluntary Risks in Perspective



# Unfortunately

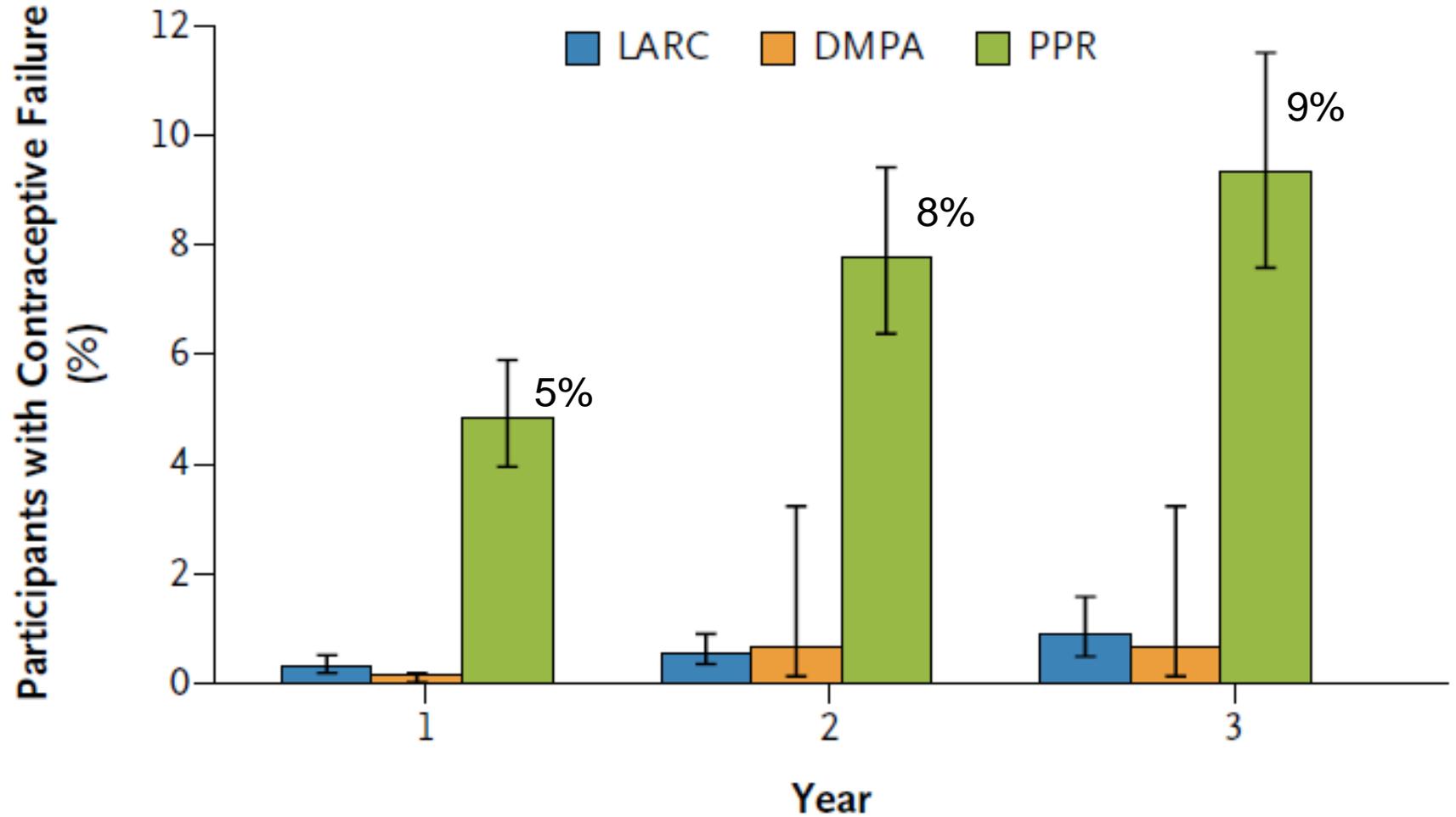
- Unintended pregnancy is common
  - 49% of US pregnancies
  - 5% of US women each year
- Even more common among military women

# 3 Simple Ways to Prevent Medication-induced Birth Defects

- **Nexplanon**<sup>®</sup> etonogestrel (2006)
  - Labeled use for 3 years
  - Lighter menses
- **Mirena**<sup>®</sup> levonorgestrel (2001)
  - Labeled for 5 years, Studied to 7 yrs
  - Lighter menses/Amenorrhea
- **ParaGard**<sup>®</sup> “copper T” (1988)
  - Labeled use for 10 years
  - Effective in studies for 12-20 yrs
  - May have heavier cramping/menses



# Real world effectiveness



# Complicated patient?

Guidance is available!

- the CDC “US Medical Eligibility Criteria”
  - <http://www.cdc.gov/mmwr/pdf/rr/rr59e0528.pdf>
- the WHO Medical Eligibility Criteria for Contraceptive Use, 4<sup>th</sup> edition
  - [http://whqlibdoc.who.int/publications/2010/9789241563888\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf)

# Medical Eligibility Criteria

Category	Interpretation
1	<b>No restriction for use</b> Use method for any circumstance
2	<b>Advantages outweigh theoretical/proven risks</b> Generally use the method
3	<b>Theoretical/proven risks outweigh advantage</b> Generally not recommended unless no other method available or acceptable
4	<b>Unacceptable health risk</b> Do not use

# Do YOU know?

If 100 fertile women are sexually active, how many would you expect to become pregnant within one year if they use no form of contraception?

- 5%
- 25%
- 50%
- 85%



# Do YOU know?

If 100 fertile women are sexually active, how many would you expect to become pregnant within one year if they use no form of contraception?

- 5%
- 25%
- 50%
- **85%**



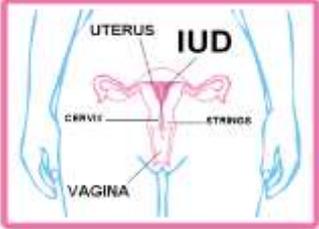
# Cumulative failure rates



“During a lifetime of use of reversible methods, the typical woman will experience 1.8 contraceptive failures”

# POLL: Have you been trained to place nexplanon?

- Yes
- No, I'd like help getting trained
- No, I'm not a clinician
- No, I'm a clinician but not interested

Method of Birth Control	How to use it	How well it works	Benefits	Risks	% satisfied	
Nexplanon Implant 	Placed under skin of arm by a clinician. Works for 3 years.		>99%	<ul style="list-style-type: none"> <li>• Nothing to do or remember</li> <li>• Light or no periods</li> <li>• May decrease acne</li> <li>• No increased risk of clots</li> </ul>	• Irregular periods	79%
Mirena IUD 	Placed in uterus by clinician. Works for 5 years.		>99%	<ul style="list-style-type: none"> <li>• Nothing to do or remember</li> <li>• Light or no periods</li> <li>• No increased risk of clots</li> </ul>	• Irregular periods	86%
ParaGard IUD	Placed in uterus by clinician. Works for 12 years.		>99%	<ul style="list-style-type: none"> <li>• Nothing to do or remember</li> <li>• No hormones</li> <li>• Periods remain regular</li> <li>• Effective immediately</li> <li>• No increased risk of clots</li> </ul>	• May cause heavier periods and cramping	80%
Depo Provera shot 	Given every 3 months.		97%	<ul style="list-style-type: none"> <li>• Light or no periods</li> <li>• May decrease acne</li> <li>• No increased risk of clots</li> </ul>	<ul style="list-style-type: none"> <li>• Irregular periods</li> <li>• May cause weight gain</li> </ul>	54%
NuvaRing 	You place in vagina; replace monthly.		92%	<ul style="list-style-type: none"> <li>• Lighter periods</li> <li>• May decrease acne</li> </ul>	• Blood clots	53%
Evra Patch 	You place on skin; replace weekly.		92%	<ul style="list-style-type: none"> <li>• Lighter periods</li> <li>• May decrease acne</li> </ul>	• Blood clots	44%
Combined Pill 	Swallow at the same time daily.		92%	<ul style="list-style-type: none"> <li>• Lighter periods</li> <li>• May decrease acne</li> </ul>	• Blood clots	54%
Progestin-only mini-pill 	Swallow at the same time daily.	92%	<ul style="list-style-type: none"> <li>• Lighter periods</li> <li>• No increased risk of clots</li> </ul>	• Irregular periods	54%	
Condoms 	Must use every time you have sex.	85%	<ul style="list-style-type: none"> <li>• Protects from infections and HIV</li> </ul>	• Allergy to latex	43%	

# References

- [Counseling of female veterans about risks of medication-induced birth defects.](#) PMID: 23807071
- [Provision of potentially teratogenic medications to female veterans of childbearing age.](#) PMID: 20706159
- [Clinical decision support to promote safe prescribing to women of reproductive age: a cluster-randomized trial.](#) PMID: 22297687
- [Counseling about medication-induced birth defects with clinical decision support in primary care.](#) PMID: 23930947
- [Women's perspectives on counseling about risks for medication-induced birth defects.](#) PMID: 19637252
- [Prescription of teratogenic medications in United States ambulatory practices.](#) PMID: 16271908
- [Documentation of contraception and pregnancy when prescribing potentially teratogenic medications for reproductive-age women.](#) PMID: 17876020
- [Opportunities missed: improving the rate of contraceptive counseling or provision when prescribing reproductive-aged women potentially teratogenic medications in a family medicine resident clinic.](#) PMID: 21920192
- [Providing contraception for women taking potentially teratogenic medications: a survey of internal medicine physicians' knowledge, attitudes and barriers.](#) PMID: 20087677
- [Promoting safe prescribing in primary care with a contraceptive vital sign: a cluster-randomized controlled trial.](#) PMID: 23149528

# Thank You!



## Questions?

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# Hepatic enzyme inducers



- Decrease effectiveness of hormonal contraceptives (including implants)
  - Carbamazepine
  - Barbiturates
  - Phenobarbital
  - Primidone
  - Effavirenz
  - St. John's Wort
- DMPA likely still ok
- ParaGard<sup>®</sup> "copper T" still works really well