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# Maternal Exposure to Venlafaxine (Effexor®) and Risk for Birth Defects

Kara Duwe, Sonja Rasmussen, Carol Louik, Carla van Bennekom,  
Tiffany Colarusso, Jennita Reefhuis



August 17, 2011

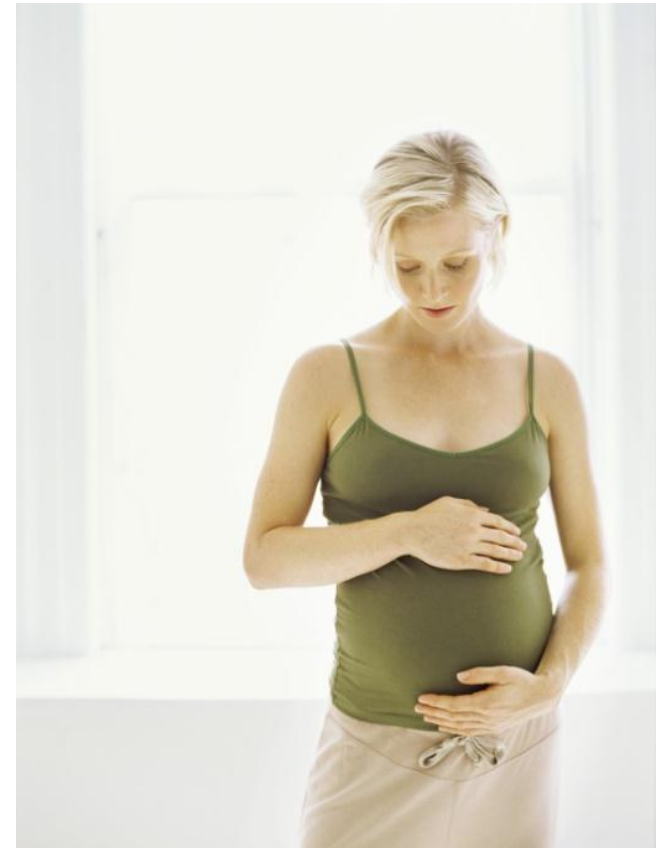
# Disclaimer



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- **The research described in this presentation was supported by funding from the U.S. Centers for Disease Control and Prevention.**
- **The authors have no conflicts of interest to disclose.**

- **Prevalence of depressive disorders during pregnancy: ~14-23%\***
- **Antidepressants are a common exposure during pregnancy: ~4.5%\*\***



\*Yonkers et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. 2009

\*\* Alwan et al. Patterns of Antidepressant Medication Use Among Pregnant Women in a United States Population. Journal of Clinical Pharmacology. 2011;51:264-270.

# Venlafaxine



- **Venlafaxine (Effexor®):**
  - **Serotonin-norepinephrine reuptake inhibitor (SNRI)**
  - **Introduced in 1994**
  - **Used to treat major depression and anxiety disorders**
- **Limited information available on the safety of venlafaxine during pregnancy**
  - **FDA Use-In Pregnancy Guide: Class C**

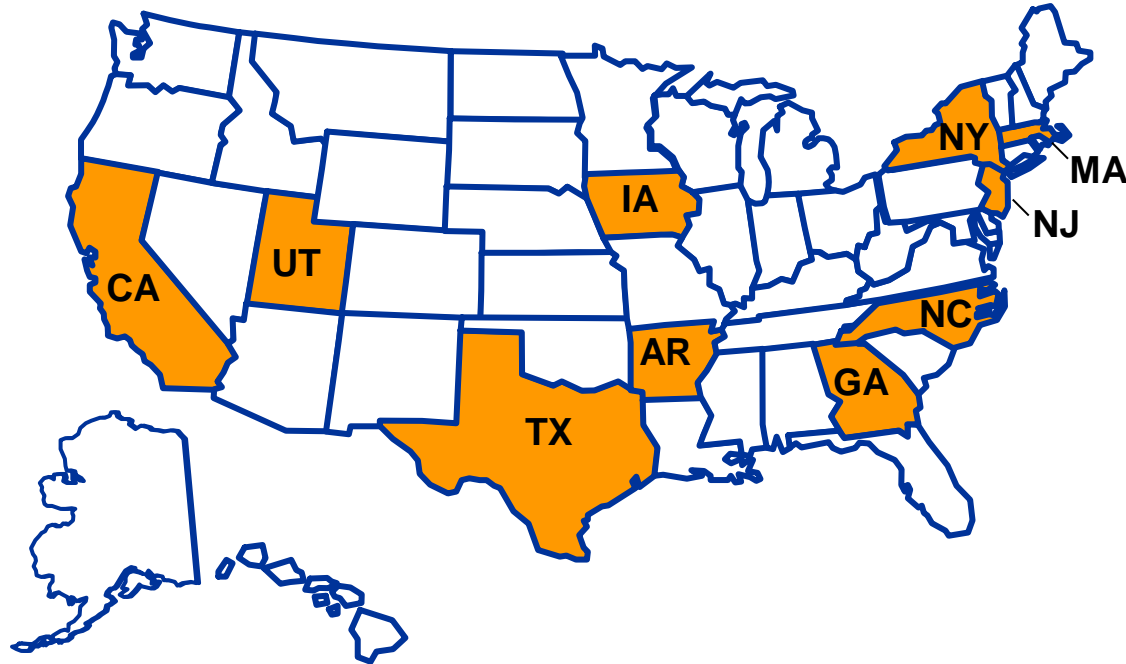


- **One in every 33 U.S. babies born with a birth defect**
- **Leading cause of infant mortality in the U.S., accounting for 1 in 5 infant deaths**
- **Increased risk for many lifelong physical, cognitive, and social challenges**



- **To determine whether reported use of venlafaxine during early pregnancy is associated with any specific birth defect or class of defects**





- **National Birth Defects Prevention Study: Ongoing, population-based, case-control study of major birth defects**

## ● Case Infants:

- Live births (all sites), fetal deaths  $\geq 20$  wk gestation (AR, CA, GA, IA, MA, & TX), & elective terminations (AR, CA, GA, IA, & TX)
- Known chromosomal abnormalities & single-gene disorders excluded
- Reviewed and classified by clinical geneticists
- Clinical information on infants with heart defects reviewed by clinicians with expertise in pediatric cardiology

## ● Control Infants:

- Live born infants without birth defects randomly selected from hospital deliveries or birth certificate records





- **Detailed maternal interview collects information on various exposures before and during pregnancy**
  - **Conducted between 6 weeks and 2 years after the estimated date of delivery**
  - **Asked what medications were taken, when they started and stopped taking the medications, and how often they were used**



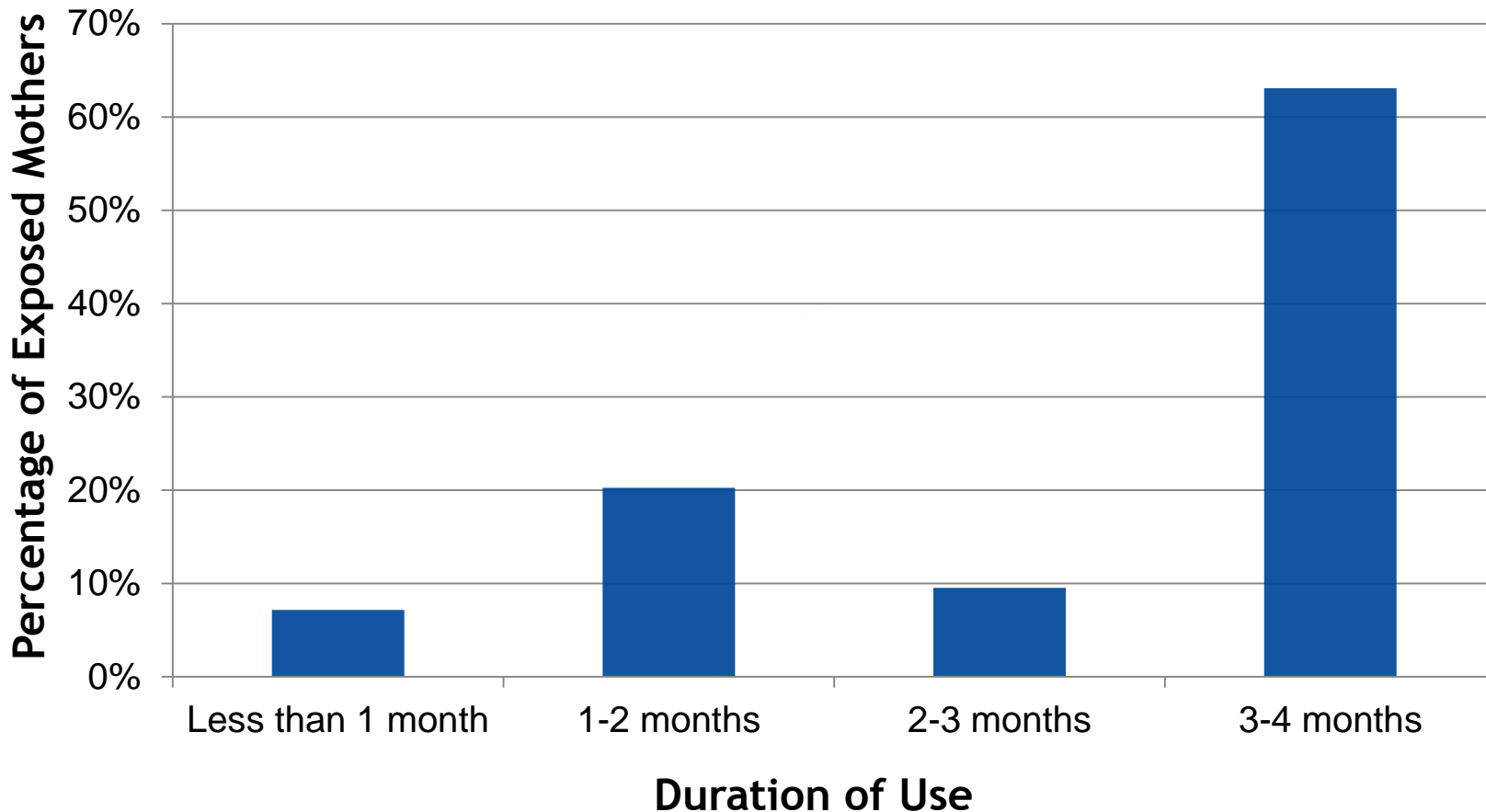
- **Births from October 1, 1997-December 31, 2007**
- **Outcome: Birth defect categories  $\geq 400$  cases**
- **Exposure : Any venlafaxine exposure from one month before pregnancy through the 3<sup>rd</sup> month of pregnancy**
- **Exclusions:**
  - **Mothers with pre-pregnancy Type 1 or Type 2 diabetes (n=477 cases, 51 controls)**
  - **Mothers exposed to other antidepressant medications (n=783 cases, 269 controls)**
  - **Mothers exposed outside the window of interest or with missing information on the timing of exposure (n=4 cases, 0 controls)**

- **Estimated crude and adjusted odds ratios (OR) and 95% Fisher's Exact confidence intervals (CI)**
- **Characteristics adjusted for in analyses:**
  - **Age (<30, ≥ 30 yrs)**
  - **Race (white, non-white)**



- **Of the 27,448 NBDPS mothers included, 85 (0.31%) reported using venlafaxine during early pregnancy**
  - **0.17% (14/8,112) of control mothers reported any use**
  - **0.37% (71/19,336) of case mothers reported any use**
  
- **Exposure more common among mothers of white race/ethnicity, with a higher education level (> H.S.), who reported any folic acid use B1-P1**

## Reported Duration of Venlafaxine Use During Early Pregnancy (B1-P3)<sup>‡</sup>



<sup>‡</sup> B1-P3 describes the time period of 1 month preconception through month 3 of pregnancy

**PRELIMINARY DATA**

# Maternal Use of Venlafaxine and Non-Cardiac Birth Defects



Birth Defects	No. of Infants	Any Exposure (B1-P3)	Expected Exposed	Adjusted OR (Exact 95% CI)
Controls	8019	14		1.0 (ref)
Anencephaly	415	4	0.7	6.1 (1.4-19.5)
Spina bifida	881	3	1.5	2.1 (0.4-7.4)
Anotia/Microtia	470	1	0.8	§
Cleft Lip +/- Palate	2140	6	3.7	1.6 (0.5-4.3)
Cleft Palate	1124	6	2.0	2.9 (0.9-8.0)
Esophageal Atresia	496	0	0.9	§
Anorectal Atresia	741	1	1.3	§
Hypospadias	1570	7	2.7	2.5 (0.7-8.3)
Limb defects	845	3	1.5	2.1 (0.4-7.6)
Craniosynostosis	992	3	1.7	1.5 (0.3-5.5)
Diaphragmatic Hernia	592	1	1.0	§
Gastroschisis	904	6	1.6	5.3 (1.5-16.9)

§ Odds ratios were not calculated due to small numbers ( $\leq 2$  cases exposed to venlafaxine during early pregnancy).

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Cardiac Birth Defects	No. of Infants	Any Exposure (B1-P3)	Expected Exposed	Adjusted OR (Exact 95% CI)
Controls	8019	14		1.0 (ref)
Conotruncal defects	1760	5	3.1	1.6 (0.5-7.4)
d-Transposition of the Great Arteries	546	2	1.0	§
Tetralogy of Fallot	801	1	1.4	§
Right ventricular outflow tract obstructions	1269	5	2.2	2.2 (0.6-6.6)
Pulmonary valve stenosis	1001	5	1.7	2.7 (0.8-7.9)
Left ventricular outflow tract obstructions	1466	8	2.6	2.9 (1.0-7.4)
Hypoplastic left heart syndrome	438	2	0.8	§
Coarctation of the aorta	774	5	1.4	3.4 (0.9-10.0)
Septal defects	3631	15	6.3	2.4 (1.1-5.5)
VSD perimembranous	1418	4	2.5	1.6 (0.4-5.1)
ASD secundum or ASD NOS	2179	8	3.8	2.3 (0.8-5.8)
VSD-ASD Association	572	2	1.0	§

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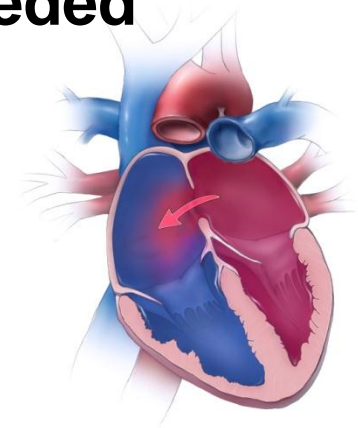


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PRELIMINARY DATA

- **Data suggest associations between prenatal use of venlafaxine and some birth defects**
  - **Some associations might be chance findings**
  - **Confirmation in other studies is needed**



# Comparison with Previous Findings



- **Einarson 2001**

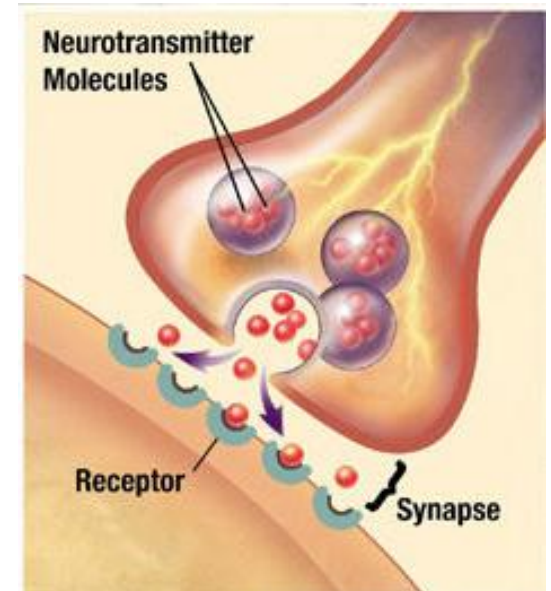
- **No differences between exposed women and comparison groups**
- **150 exposed; 2 birth defect outcomes**

- **Animal studies**

- **Da-Silva 1999: adverse effects on rat fetuses**
- **Manufacturer 2007: no teratogenic effects on rats and rabbits**



- **Studies have suggested that neurotransmitters may act as morphogens (signaling molecules during embryogenesis)**
  - **Serotonin: morphogen in craniofacial and cardiac development**
  - **Consistent with findings for congenital heart defects**



- **Small numbers of mothers exposed to venlafaxine during early pregnancy**
- **No dose information**
- **Self-reported data could lead to exposure misclassification or recall bias**
- **Unable to assess confounding by indication**



- **Large, population-based study**
  - **Consistent case definitions classified by clinical geneticists**
  - **Clinical information on infants with heart defects reviewed by clinicians with expertise in pediatric cardiology**
- **Venlafaxine exposure separate from other antidepressant medications**



# Acknowledgements



- **Collaborators: Sonja Rasmussen, Tiffany Colarusso, Carol Louik, Carla van Bennekom, Jennita Reefhuis**
- **Participating families, interviewers, and collaborators at all sites who contribute to the National Birth Defects Prevention Study**



Extra slides...



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# Gastroschisis- Stratified by Age



<b>Gastroschisis</b>	<b>Exposed Cases</b>	<b>Exposed Controls</b>	<b>Crude OR (95% Exact CI)</b>
<30 years	5	6	4.9 (1.2-19.1)
≥ 30 years	1	8	6.6 (0.1-50.6)

# Demographic Table



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	CASE MOTHERS					CONTROL MOTHERS				
	Exposed (n=71)		Unexposed (n=19,265)		P-value	Exposed (n=14)		Unexposed (n=8098)		P value
	n	%	n	%		n	%	n	%	
<b>Age</b>										
<30 yrs	38	53.5	11639	60.4	0.24	6	42.9	4949	61.1	0.16
>= 30 yrs	33	46.5	7626	39.6		8	57.1	3149	38.9	
<b>Education</b>										
<=HS	16	22.5	8417	44.1	<0.01	0	0.0	3323	41.5	<0.01
>HS	55	77.5	10683	55.9		14	100.0	4671	58.4	
<b>Race</b>										
NH White	66	94.3	11256	59.1	<0.01	10	71.4	4671	58.4	0.33
Other	4	5.7	7755	40.7		4	28.6	3305	41.3	
<b>Obesity</b>										
Yes	17	24.3	3352	17.6	0.21	5	35.7	1261	15.8	0.05
No	53	75.7	14853	77.9		9	64.3	6405	80.0	
<b>Smoking (B1-P3)<sup>†</sup></b>										
Any	16	22.9	3819	20.0	0.56	3	21.4	1437	18.0	0.74
None	54	77.1	15226	79.9		11	78.6	6563	82.0	
<b>Folic Acid Use (B1-P1)<sup>§</sup></b>										
Yes	54	77.1	9584	50.3	<0.01	8	57.1	4076	50.9	0.64
No	16	22.9	9474	49.7		6	42.9	3929	49.1	
<b>Parity</b>										
0	25	35.7	8139	42.7	0.24	5	35.7	3229	44.4	0.72
>0	45	64.3	10913	57.3		9	64.3	4774	59.6	

# Exposure Over Time



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Infant Year of Birth	CASE MOTHERS				CONTROL MOTHERS			
	Exposed (n=70)		Unexposed (n=19,058)		Exposed (n=14)		Unexposed (n=8005)	
	n	%	n	%	n	%	n	%
1997	0	0	207	1.1	0	0	99	1.2
1998	2	2.9	1634	8.6	0	0	730	9.1
1999	1	1.4	1955	10.3	0	0	825	10.3
2000	3	4.3	2090	11.0	1	7.1	857	10.7
2001	2	2.9	1972	10.3	0	0	776	9.7
2002	10	14.3	1711	9.0	1	7.1	682	8.5
2003	6	8.6	1765	9.3	0	0	844	10.5
2004	15	21.4	2214	11.6	3	21.4	844	10.5
2005	13	18.6	2083	10.9	3	21.4	787	9.8
2006	8	11.4	1681	8.8	2	14.3	800	10.0
2007	10	14.3	1745	9.2	4	28.6	761	9.5

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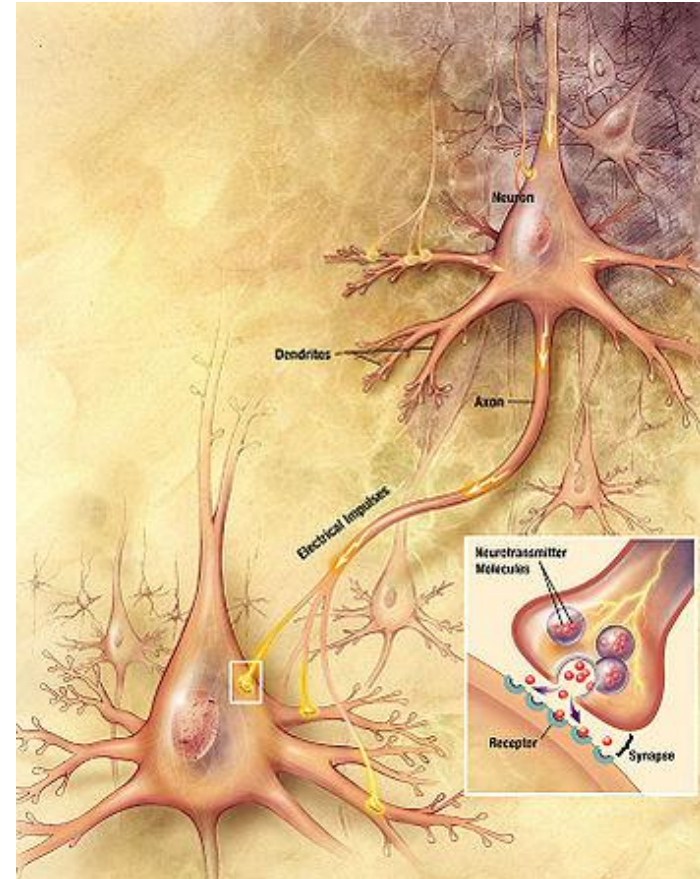


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## ● Mechanism of Action

- Blocks transporter “reuptake” proteins for key neurotransmitters
  - Serotonin
  - Norepinephrine
- High doses can affect dopamine reuptake



- **Einarson et al (2001)**
  - **Prospective cohort (n=150): Canada**
  - **Exposure: use of venlafaxine during pregnancy (maternal interview)**
  - **No significant differences between exposed women and comparison groups**
  
- **SSRIs : increased risk for some birth defects**
  - **Congenital heart defects: VSDs, ASDs, RVOTO**
  - **Anencephaly, craniosynostosis, omphalocele**