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

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Disclaimer

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- The authors have no conflicts of interest to disclose.

Depression during Pregnancy

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- **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

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- **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**

Birth Defects

- 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

Study Objective

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

Methods- Data Collection

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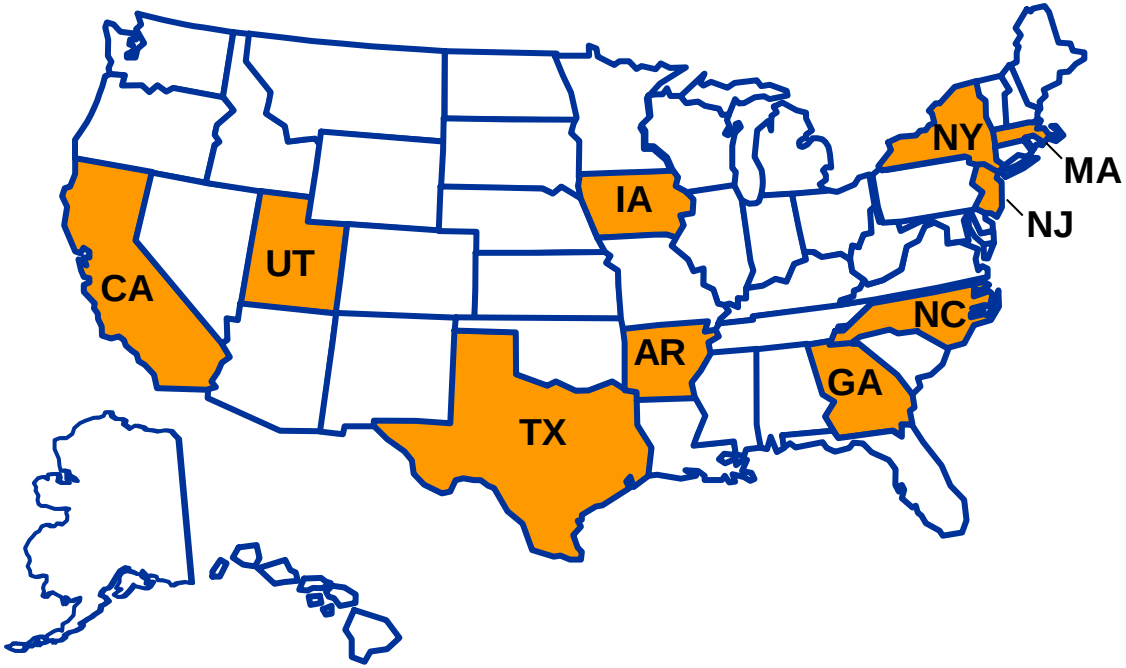

- **National Birth Defects Prevention Study: Ongoing, population-based, case-control study of major birth defects**

Ascertainment of Cases & Controls

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- **Case Infants:**
  - Live births (all sites), fetal deaths ≥ 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

Methods

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- **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**

Methods

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- Births from October 1, 1997-December 31, 2007
- Outcome: Birth defect categories ≥400 cases
- Exposure : Any venlafaxine exposure from one month before pregnancy through the 3rd 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)

Statistical Analyses

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- 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)

Preliminary Results

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- 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

PRELIMINARY DATA

Results

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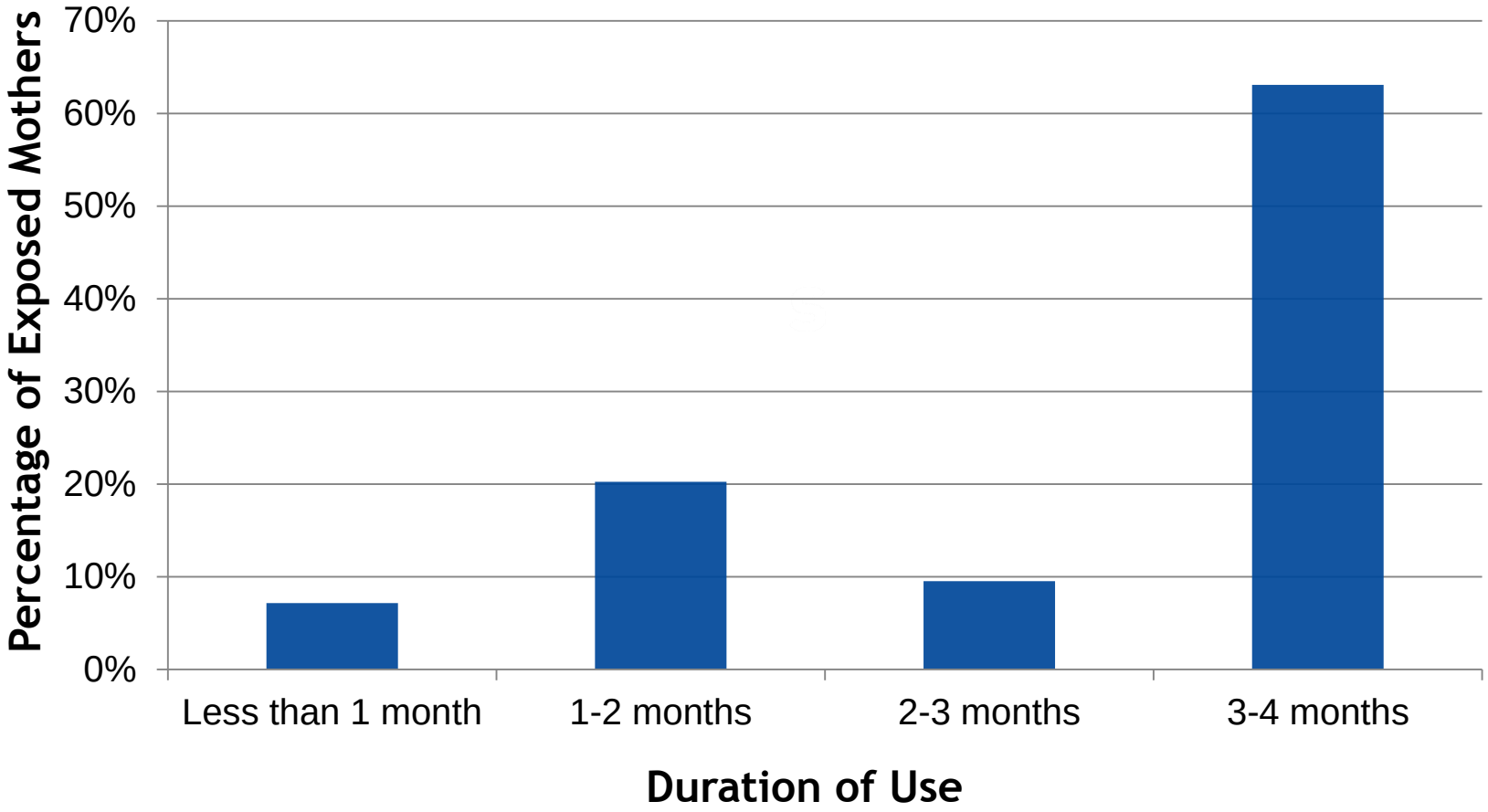
Reported Duration of Venlafaxine Use During Early Pregnancy (B1-P3)‡



‡ 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

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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 (≤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)
Contruncal 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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Discussion

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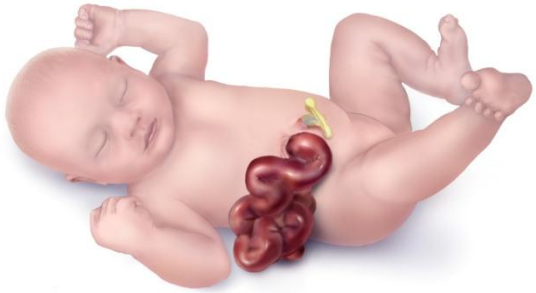
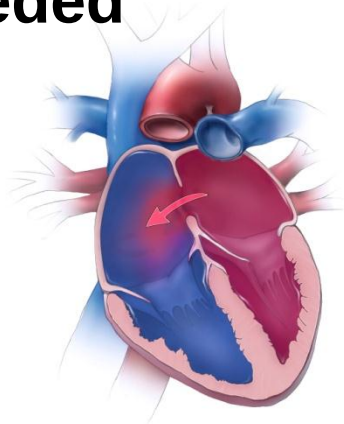
- **Data suggest associations between prenatal use of venlafaxine and some birth defects**
  - **Some associations might be chance findings**
  - **Confirmation in other studies is needed**





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Comparison with Previous Findings

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- **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**

Discussion- Biologic Plausibility

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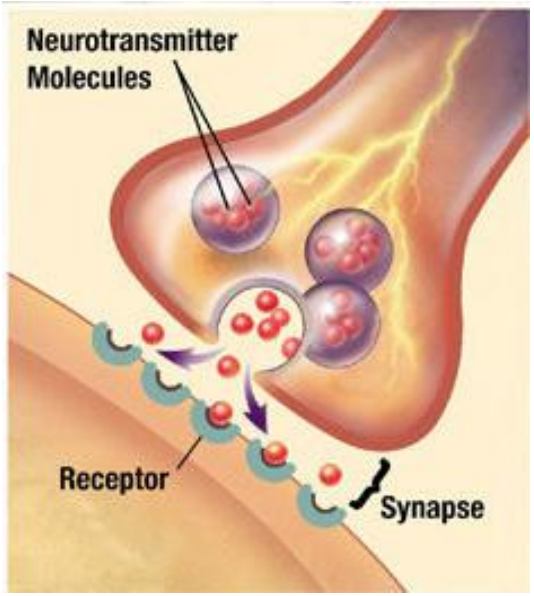
- **Studies have suggested that neurotransmitters may act as morphogens (signaling molecules during embryogenesis)**
  - **Serotonin: morphogen in craniofacial and cardiac development**
  - **Consistent with findings for congenital heart defects**



Limitations

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- 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

Strengths

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- **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

Gastroschisis	Exposed Cases	Exposed Controls	Crude OR (95% Exact CI)
<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**	**%**	
Age										
<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	
Education										
<=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	
Race										
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	
Obesity										
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	
Smoking (B1-P3)†										
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	
Folic Acid Use (B1-P1)§										
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	
Parity										
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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	CASE MOTHERS				CONTROL MOTHERS			
	Exposed (n=70)		Unexposed (n=19,058)		Exposed (n=14)		Unexposed (n=8005)	
	n	%	n	%	n	%	n	%
Infant Year of Birth								
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

Exposure Over Time

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Background Information- SNRIs

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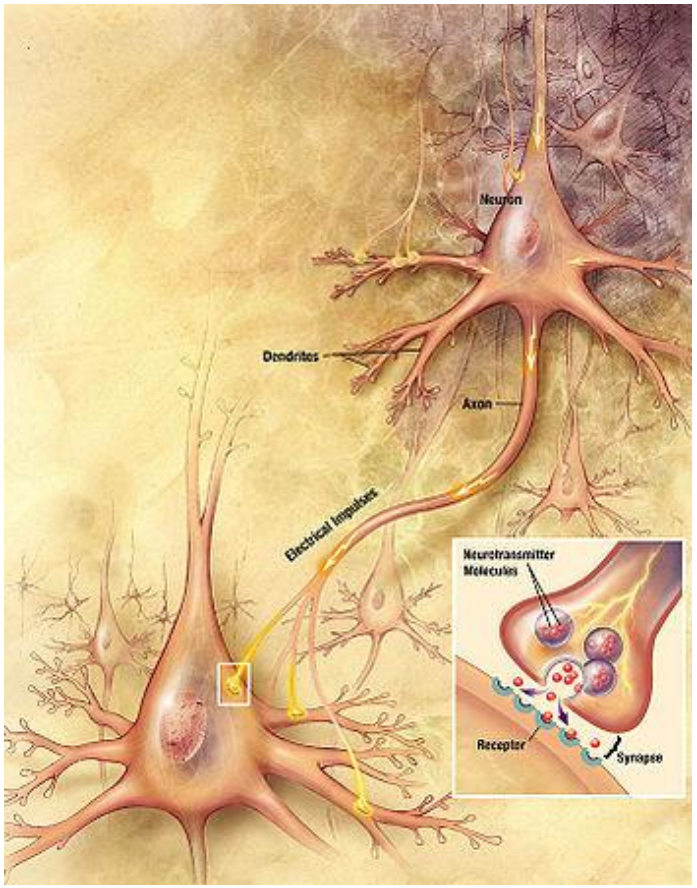
- Mechanism of Action
  - Blocks transporter “reuptake” proteins for key neurotransmitters
    - Serotonin
    - Norepinephrine
  - High doses can affect dopamine reuptake



Safety of Use during Pregnancy

- 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